PROGRAM BOOK

ICIA 2021 AHVAZ

15th Virtual nternational Congress of
Immunology and Allergy

27-29 January 2021 | AJUMS | Ahvaz, Iran

پانزدهمین کنگره بین‌المللی ایمونولوژی و آلرژی

اهـواز - ۸ تا ۱۰ بهمـن ۱۳۹۹

Ahvaz Jundishapur
University of Medical Sciences

دانش و فضیلت مافوق بازو و شمشیر است

عبارت سر در ورودی کتابخانه‌ی دانشگاه کهن جندی شاپور(۲۷۱ میلادی)

The logo sentence above the library entrance of
the ancient Jundishapur University (271A.D.)

Knowledge and Virtue are Superior to Fist and Sword

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اهواز، دانشگاه علوم‌پزشکی جندی‌شاپور اهواز | دانشکده پزشکی
Faculty of Medicine , Ahvaz Jundishapur University
of Medical Siences, Ahvaz, Iran

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Chairman Welcome message

In the Name of GOD

Ahvaz Jundishapur University of Medical Sciences is one of the oldest universities in the world, which has been established in 1956. Initially, two faculties of agriculture and medicine were built, and gradually this university expanded to its present form. Ahvaz Jundishapur University has always tried to contribute to the development of medical knowledge and the forward scientific movements in the country. We are proud to host prominent scientists and intellectuals at home and abroad at the 15th International Congress of Immunology and Allergy, 2021. Undoubtedly, the gathering of educated researchers with young students and researchers will be a good opportunity to exchange updated knowledge and scientific-research experiences.

Fourteen sessions of this congress are a valuable scientific heritage that has a significant quota in the development of immunology in the world. This year, the congress has been defined in 20 panels, with different themes. However, two new panels entitled “Immuno-pathogenesis and diagnosis of Covid-19” and “Covid-19 treatment”, are included in the list of panels, highlighting the importance of the position of immunology in overcoming the challenges posed by the recent epidemic.

Finally, I would like to thank my colleagues in the scientific and executive team, especially Dr. Ali Khodadadi (Head of Scientific Committee) who have worked tirelessly to hold the Congress as well as possible.

Dr. Farhad Abolnezhadian
Chairman of the 15th International Congress of
Immunology and Allergy, 2021

President of ISIA Welcome Message

As president of the "Iranian Society for Immunology and Allergy" (ISIA), it is my pleasure to extend this invitation to you to join us in Ahvaz in January 2021 at the "15th international Congress of Immunology and Allergy" (ICIA2021). Being held every two years and regularly attracting over 1400 delegates, ICIA2021 will begin to work on 27th January. ISIA together with ICIA's patrons will work to create a memorable scientific event for participants. The opportunity of exploring the most recent and innovative advances in the field of immunology and allergy from bench to bedside will motivate all attending's with different interests in almost all the fields of modern immunology. Offering a fine balance between basic and applied/translational researchers, we ensure you will totally be satisfied with this scientific session. Like all previous ICIAs, ISIA will follow its missions of fostering young and not so young researchers as scientists. I do hope that you will be able to join us at ICIA2021 in Ahvaz and I look forward to seeing you there.

Sincerely,

Mohammad Vodjgani, Ph.D.
President of the Iranian Society for Immunology and Allergy (ISIA)

Head of Scientific Committee Welcome Message

Dear Colleagues and Friends

It is with a great pleasure that we welcome you to join our Virtual "15th International Congress of Immunology and Allergy" (ICIA 2021) in Ahvaz, Iran, from 27 to 29, January. 2021. Holding such an invaluable academic and scientific meeting provides a good opportunity for sharing ideas and experiences with the most outstanding domestic and international scholars to motivate students and graduates of immunology and all other related fields on their scientific endeavor. Moreover, with the participation of several scientists and experts in clinical immunology and allergy covering different dimensions such as diagnosis, prevention, and treatment in the field of immunology. Along with contributions from scholars in the innate and adaptive immunity, diseases, and dysregulation of the immune system, immune disorders including allergy/asthma as well as autoimmunity and clinical sciences will help sharing information and strengthen the relationship between basic and clinical sciences, and immune interventions with an emphasis on immunology-based therapy and COVID19 vaccines.

Keynote speeches of different panels, presentation of abstracts, advanced courses, and workshops will form the core of ICIA-2021, which will be the center of attention of all scholars, experts, and students attracted to the field of immunology. Thus, ICIA-2021 strives to take advantage of valuable experiences and ideas to make this meeting more fruitful.

I hope that with the scientific cooperation of nationwide and international medical universities and research centers, together with participation of companies specialized in immunological and laboratory products, pharmaceutical companies and other scientific organizations, ICIA-2021 becomes a memorable meeting for us all.

Sincerely,

Ali Khodadadi, Ph.D.
Head of Scientific Committee of the ICIA-2021 Congress

Head of Executive Committee Welcome Message

Dear Colleagues and Friends

I am delighted to warmly welcome you to attend 15th ICIA, held on January 27-29, 2021, in Ahvaz-Iran. The congress is organized jointly by Iranian Society of Immunology and Allergy (ISIA) and Ahvaz Jundishapur University of Medical Sciences (AJUMS) accompanied with other national and international outstanding Medical Universities and Scientific Institutes. As the Executive manager, I would like to express my sincere welcome to all of the distinguished guests and participants to ICIA2021. With the purpose of bringing together leading academic scientists, researchers and scholars to exchange and share their experiences and research results on all aspects of Immunology and promoting the international communication and cooperation, it is our best pleasure to hold the ICIA2021, which covers various fields of immunology. We again invite you to join us at ICIA2021 to have memorable scientific experiences.

Golamreza Sarizadeh, Ph.D.
Head of Executive Committee of the Congress

15th International Congress of Immunology and Allergy

ICIA 2021 AHVAZ Virtual

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

Congress Chairman

Dr. Farhad Abolnezhadian

Department of Pediatrics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Head of the Scientific Committee

Dr. Ali Khodadadi

Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Head of the Executive Committee

Dr. Gholamreza Sarizadeh

Head of Resource Development Deputy
Ahvaz Jundishapur University of Medical Sciences

Congress Panels Committee Chairman

Dr. Mehri Ghafourian

Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Head of the International Committee

Dr. Ataollah Ghadiri

Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Coordinator of the Congress Workshops

Dr. Afshin Amari

Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Coordinator of the Executive Committee

Dr. Ali Asadirad

Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences

Director of International Affairs, Member of the Executive Committee

Dr. Morteza Khafaei

Health Research Center, Ahvaz Jundishapur University of Medical Sciences

Head of Research and Technology Deputy , Member of the Executive Committee

Dr. Mehdi Ahmadi Moghadam

Department of Environmental Health, Ahvaz Jundishapur University of Medical sciences

Head of Education Deputy , Member of the Executive Committee

Dr. Mohammadreza Fathi

Department of Pediatrics, Ahvaz Jundishapur University of Medical Sciences

IRAN ICIA 2021 AHVAZ

Strategic Committee of ICIA 2021

Dr. Farhad Abolnezhadian
Chairman of the Congress

Dr. Mohammad Vodjgani
President of ISIA

Dr. Ali Khodadadi
Head of Scientific Committee of the Congress

Dr. Gholamreza Sarizadeh
Head of Executive Committee of the Congress

Dr. Mehri Gafourian Broujerdnia
Congress Panel Committee Chairman

Dr. Ataollah Gadiri
Head of International Committee of the Congress

Dr. Afshin Amari
Coordinator of ICIA2021 Workshops

Dr. Ali Asadirad
Coordinator of the Executive Committees

Dr. Morteza Khafaei
Director of International Affairs, Member of the Executive Committee

Dr. Mehdi Ahmadi Moghadam
Head of Research and Technology Deputy, Member of the Executive Committee

Dr. Mohammadreza Fathi
Head of Education Deputy , Member of the Executive Committee

Scientific Committee of ICIA2021 (International)

Ahmad Jalili
Akihiro Shimosaka
Ali Harandi
Alireza Ranjbar
Anne puel
Arezoo Jamali
Arjan Griffioen
Bhaskar Saha
Brian Till
Christian Buchholz
Christine Brown
Dieter Kabelitz
Hans-Uwe Simon
Karsten Krüger
Michael Stear
Behnaz Bayat
Reza nasiri

Scientific Committee of ICIA2021 (National)

Abbas Ali Amini
Abbas Azadmehr,
Abbas Hajifathali
Abdolreza Esmaeilzadeh
Zahrasadat Faghih
Aboulghasem Ajami
Adel Mohammadzadeh
Mohammad Shafi Mojadadi
Afsaneh Aghaie
Afshin Amari
Ahad Mokhtarzadeh
Mahdieh Molanouri Shamsi
Ahmad Zavaran hoseini
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Ali Anisian
Ali Asadirad
Ali Khodadadi
Ali Mohammad Varzi
Ali Reza Andalib
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Amin Reza Nikpoor
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Elham Ashoori
Elham Masoumi
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Ali Memarian
Mehrnaz Mesdaghi
Mehdi Mirsaeidi
Hamid Reza Mirzaei
Seyed Mohammad Moazzeni
Mohammad Hassan Zuhair
Mohammad mahdi Mohammadi
Vahid Mohammadi Shahrokhi
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Farhad Jadidi-Niaragh
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Reza Jafari Shakib
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Leila Jafarzadeh
Seyed Amir Jalali
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Farshid Yeghaneh
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Davood Rostamzadeh
Farshid Saadat
Ali Akbar Saboor Yaraghi
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Jafar Salimian
Siamak Sandoghchian Shotorbani
Mojtaba Sankian
Mandana Sattari
Farhad Seif
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Mohammed Gharagozlou
Tohid Gharibi
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Golamreza Khamisipur
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Khalil HajiAsgarzadeh
laya kafami
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Leili Aghebatimaleki
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Nahid Rezaei
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Maryam Keshavarz
Maryam Nourizadeh

Nafiseh Pakravan
Maryam Tavakoli
Maryam Zadsar
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Marzieh Ebrahimi
Masoud Nikbakht
Masoud Soleimani
Massoumeh Ebtekar
Mehdi Mahdavi
Mehdi Yousefi
Mehri Ghafurian
Mohammad Fereidouni
Mohammad Hossein Alimohammadian
Mohammad Javad Fattahi
Mohammad Kazemi Arababadi
Mohammad Mahdi Eftekharian
Nasrollah Erfani
Mohammad Mehdi Amiri
Mohammad Reza Abbaszadegan
Mohammad Reza Haghshenas
Mostafa Haji molla hoseini
Mohammad Taher Tahouri
Mohammad Vojgani
Mohammad-Ali Assarehzadegan
Mohammadreza Ataollahi,
Mohsen Abdolmaleki
Mohsen Abolhassani
Mojdeh Hakemi Vala
Mojgan Shayegan
Abdolkarim Sheikhi
MehdiS hekarabi
Fazel Shokri
Monireh Hajimoradi
Nafiseh Esmaeil
Narges Arandi
Narges Eslami
Nariman Mosaffa
Ali Mostafaie

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Sara Asadi Asl
Sara Hashem pur
Sara Soudi
Sasan Moogahi
Sedigeh Amini
Sepideh Darougar
Seyed Alireza Esmaeili
Seyed Hmidollah Ghafari
Seyed Reza Bani Hashemi
SeyedMahmoud Hashemi
Hadi Hassannia
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Samira Rajaei
Shahrnaz Armin
Shokrollah Farrokhi
Sima Balouchi Anaraki
Sima Rafati
Sima Shokri
Soheila Ajdary

Soheyla Alyasin
Soosan Ardestani
Tohid Kazemi
Tooba Ghazanfari
Vahid Yousefi
Yaghub Yazdani
Zahra Amirghofran
Zahra Mojtahedi

Scientific Committee of ICIA2021 Workshops

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Dr. Kaveh Baghaei
Dr. Farshid Noorbakhsh
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Executive Committee of ICIA2021

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Heads of Executive Committee of the Congress
Dr. Ali khodadadi
Dr. Ali Asadirad
Dr. Mehri Ghafurian
Dr. Afshin Amari
Dr. Mohammad Hassan Pipelzadeh
Dr. Ataollah Ghadiri
Dr. AbdolHossein Shakournia
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Dr. Mohammad Badavy
Dr. Mohammadreza Fathi
Dr. Mehdi Ahmadi Moghadam
Khadijeh Sajadi Mehr
Mousa Sharifat
Mohammad Ghasemi

Students participate in the Executive Committee of ICIA2021

Abodolla Mousavi
Afshin Derakhshani
Ali Farhadi
Ali Saeidi Broujeni
Behnaz Rami
Emad Imani
Farzad Nazari
Hadis Alidadi
Ladan Bajelan
Mahvash Sadeghi
Marzeah Shamshiri
Mehdi Abbaspur
Mohadeseh Sheikhi
Mohammad Mahmoudi
Mohammad Zaer
Mojtaba Shohan
Moosa Sharifat
Morteza Hashempour
Nafiseh Keshavarzian
Nazanin Judaki
Negar Hoseinkhani
Nilufar Mashhadi
Pourya Gieasi
Reihaneh Rsouli
Rezaei Tazangi Fatemeh
Roghayeh Nouri
Sajjad Dehnavi
Salar Pshangzadeh
Samaneh Ebrahimi
Samira Najafi
Samira Shojapurian
sanaz Tayebi
Sara Hoseini
Sara Iranparast
Sepideh Saljugi
Seyed Taleb Hoseini
Shahoo Khayati
Sheida Farrokhi
Sheyda Houshmandfar
Somayeh Igder

ICIA 2021 AHVAZ 15th Virtual International Congress of Immunology and Allergy

27-29 January /AJUMS/Ahvaz/Iran

Knowledge and Virtue are Superior to Fist and Sword

Invited speakers

27th 9:00-9:40

Nima Rezaei

Diagnostic Approach to patients with Inborn Errors of Immunity

27th 9:50-10:30

Akihiro Shimosaka

NK cell and cancer immunotherapy

27th 14:00-14:40

Hans-Uwe Simon

Molecular mechanism of neutrophil extracellular traps

27th 14:50-15:30

Ali Harandi

Lessons Learned from COVID-19 Vaccines

28th 9:00-9:40

Brian Till

The clinical application of CAR T cell therapy for B cell non-Hodgkin lymphomas

28th 9:50-10:30

M.J. Stear and K. Donskow-Lysoniewska

The influence of galectin 3, galectin 9 and parasite galectin on mast cell degranulation

28th 14:00-14:40

Christian Buchholz
Annika Frank

Targeted lentiviral vector for invivo gene delivery in CAR-mediated immunotherapy

28th 14:50-15:30

Ahmad Jalili

Novel insights into the pathophysiology & treatment of atopic dermatitis

29th 9:00-9:40

Christine Brown

CAR T cell therapy in solid tumors

29th 9:50-10:30

Alireza Ranjbar

Immunometabolism in obesity and its clinical relevance

29th 14:00-14:40

Dieter Kabelitz

Perspectives of human gamma/delta T-cells for immunotherapy of cancer

28th 11:00-13:00

Anne Puel

Genetic evaluation of PID patients with fungal infections

28th 11:00-13:00

Arjan Griffioen

An new strategy against cancer without side effects; vaccination against the tumor vasculature

28th 11:00-13:00

Krüger Karsten

Effects of an Active Lifestyle on ("Healthy") Immune Aging

27th 11:00-13:00

Reza-Nassiri

Allergy and immunotherapy of Allergy

28th 11:00-13:00

Bhaskar Saha

Leishmania

29th 11:00-13:00

Behnaz-Bayat

HPA and HNA allo-antibodies and Endothelial cells

ACTO

IUIS

ICIA 2021 AHVAZ
15th International Congress of Immunology and Allergy
27-29 January 2021

Main speakers

Nima Rezaei
Tehran university of medical science,Iran

Diagnostic Approach to patients with Inborn Errors of Immunity

Hans-Uwe Simon
Institute of Pharmacology, University of Bern, Bern, Switzerland

Molecular mechanism of neutrophil extracellular traps

Brian Till
Seattle Cancer Care Alliance, University of Washington Medical Center

The clinical application of CAR T cell therapy for B cell non-Hodgkin lymphomas

Christian Buchholz
Head of Molecular Biotechnology and Gene Therapy at PEI in Langen, Germany

Targeted lentiviral vector for invivo gene delivery in CAR-mediated immunotherapy

Christine Brown
Beckman Research Institute of the City of Hope, Duarte, CA, USA

CAR T cell therapy in solid tumors

Dieter Kabelitz
Institute of Immunology, University of Kiel, German

Perspectives of human gamma/delta T-cells for immunotherapy of cancer

Akihiro Shimosaka
chairman of Asian Cellular Therapy Organization (ACTO)

NK cell and cancer immunotherapy

Ali Harandi
Institute of Biomedicine, University of Gothenburg, Sweden

Lessons Learned from Vaccines for Ebola and COVID-19

M.J. Stear and K. Donskow-Lysoniewska
La Trobe Univ, Dept Anim Plant & Soil Sci, AgriBio, Ctr AgriBiosci, Melbourne, Vic, Australia

The influence of galectin 3, galectin 9 and parasite galectin on mast cell degranulation

Ahmad Jalili
Dermatology and Skin Care, Bürgenstock Medical Center, Lucerne, Switzerland

Novel insights into the pathophysiology & treatment of atopic dermatitis

Alireza Ranjbar
Institute of Interventional Allergology and Immunology, Bonn/Cologne, Germany

Immunometabolism in obesity and its clinical relevance

DAY 1
Wednesday, 27 January,2021

Main Board

8:00 9:00	**Opening Ceremony**
9:00 9:40	**Nima Rezaei** Diagnostic Approach to patients with Inborn Errors of Immunity
9:50 10:30	**Akihiro Shimosaka** NK cell and cancer immunotherapy
1o:30 11:00	**Break & poster visiting**

Panel 1

COVID-19 Immunology and Immunopathology

Keynote Speaker

11:00 13:00							
Tooba-Ghazanfari Association of immunological and inflammatory factors with disease severity in COVID-19	**Hamid Reza-Abtahi** Hemoperfusion and removal of cytokines in COVID-19 immunopathology	**Mohammad Reza-Salehi** The role of inflammatory factors in the clinical management of COVID-19	**Abdolrahman-Rostamian** Corticosteroids mechanism in the treatment of COVID-19	**Alijan-Tabraee** Viral mutations and disease diagnosis in COVID-19	**Maryam-Mahluji Rad** Cellular immune responses in COVID-19	**Ali-Mostafaee** Intrinsic and inflammatory immune responses in COVID-19	**Reza- Jafari** Psychoneuroimmunological aspects of COVID-19

Oral presentation

Sara Iranparast Evaluation of the frequency of HLA- A*02 and -A*30 alleles in moderate and severe COVID-19 patients in Khuzestan province, Iran	**Faezeh Maghsood** Differential antibody response to SARS-CoV2 antigens in convalescent and deceased Iranian COVID 19 patients	**Fatemeh Keshavarz** Patients with Covid 19 have significantly reduced CH 50 activity compared with healthy individuals	**Shokrollah Farrokhi** Association between allergic diseases and COVID-19 in 400 Iranian patients	**Mehdi Shahbazi** Reduced frequency of T helper 17 and T helper 1 cells and their association with critical coronavirus disease-2019	**mohammad mirzakhani** Exhaustion Markers in CD8 T Cells of COVID-19 Patients: TIM-3 and CD39, but not PD-1	**Saeid Taghiloo** Apoptosis and immunophenotyping of peripheral blood lymphocytes in Iranian COVID-19 patients; clinical and laboratory characteristics

13:00 14:00	**Break & poster visiting**

DAY 1
Wednesday, 27 January,2021

panel 2

Cancer Immunology

Keynote Speaker

Abolghasem Ajami **Innate lymphoid Cells in tumor immunology**	**Fereshteh Mehdipour** **Regulatory roles of B cells in Solid malignancies**	**Mahboobeh Razmkhah** **Dual role of mesenchymal stem cells in the tumor microenvironment**	**Amin Ramezani** **New advancement in production of biological modifies in cancer**

.1:00
13:00

Oral presentation

Atri Ghods **The heterogeneity of human lymphocytes expressing intracellular and membranous forms of TNF-α in breast tumor draining lymph nodes**	**Marzie Norouzian** **HNSCC progression from non-invasive early stages to invasive advanced stages is associated with a shift from Th1/Tc2 patterns to Th2/Tc2 response**	**hosein Hakim** **Suppression of granzyme B production in B cells by tumor cells in a co-culture system**	**Simin Ahmadvand** **Prognostic power of PD-1 and PD-L1 in tongue and larynx squamous cell carcinoma: introducing a new scoring system**	
Mohammad Reza Haghshenas **Increase in Helios-expressing regulatory T cells in lymph nodes of breast cancer mice treated with Everolimus**	**Saeid Taghiloo** **The effects of PI3K/Akt/mTOR signaling pathway inhibitors on immune evasion mechanisms of Acute Myeloid Leukemia**	**Sima Balouchi Anaraki** **A murine monoclonal antibody against myosin heavy chain-9 expressed in pancreatic cancer**	**Mohsen Soltanshahi** **Ibrutinib and everolimus modulate the expression of immune checkpoint molecules through STAT3-mediated suppression of breast cancer cells**	**Reza Darvishvand** **The frequency of natural killer (NK) cell subsets in peripheral blood of the patients with breast cancer: a reflection of the disease.**

.3:00
14:00

Break & poster visiting

DAY 1
Wednesday, 27 January,2021

Panel 3
Oral & Mucosal Immunology

Keynote Speaker

Mandana-Sattari

Special Immunologic Characteristics of Gingiva

Oral presentation

11:00 13:00	**Mahsa Bazargan** **Chemokine mission in oral cavity health and periodontal disease**	**Mahya ramezani** **Comparing the gingival expression of MMP-1, MMP-9 (matrix metalloproteinase) and HBD-3 (human beta defensing-3) in healthy individuals and patients with moderate to severe chronic periodontitis.**	**Danial Touzandehjani** **Correlation between gingival expression of IL-33, ST2 and LL37 and periodontal diseases**
	nikoo hossein khan nazer **Immunomodulatory properties of osteogenic differentiated dental pulp stem cells**	**Marjan Golabi** **Assessment the expression of CXCL13, and CCL28 chemokines in gastric biopsy specimens of infected individuals with Helicobacter pylori**	**Farzaneh kheiri** **The role of tolerogenic dendritic cells subsets in the screening of celiac disease**
13:00 14:00	**Break & poster visiting**		

DAY 1
Wednesday, 27 January,2021

Panel 4

Stem Cell & Immune cell therapy

Keynote Speaker

Oral presentation

11:00 13:00	**Arezoo Jamali** **Highly Efficient and Selective CAR-gene Transfer Using CD4- and CD8-Targeted Lentiviral Vectors**	**Elham Masoumi** **Manufacturing Process of Chimeric Antigen Receptor T Cells Disposes Them to Expression of A2a Receptor, an Inhibitory Molecule**	**Abdolamir Allameh** **Hepatic differentiation of human bone marrow mesenchymal stem cells is associated with changes in selected cellular cytokines**	**Mehnoosh Ashja Arvan** **Impact of IFN-β and LIF overexpression in human adipose-derived stem cells (hADSCs) properties**
	Anwar Fathollahi **Intranasal administration of mesenchymal stem cells derived exosomes reduced the disease severity of experimental autoimmune encephalomyelitis in a mouse model**	**Hadi Esmaeili Gouvarchin ghaleh** **Immunomodulatory functions of Mesenchymal Stem Cells treated with Tretinoin altered the Clinical and,..**	**fahime lavi** **Assessment of proliferativeand anti-apoptotic and immunomodulatory activity of crocin and crocetin on adipose-derived ,...**	**Sara Hosseini** **The Impacts of Lupus Mice MSC on Healthy and Lupus Balb/c Mice Model**
13:00 14:00	**Break & poster visiting**			

DAY 1
Wednesday, 27 January,2021

Panel 5

Allergy and immunotherapy of Allergy

Keynote Speaker

Alireza-Ranjbar | **Reza-Nassiri**

11:00 – 13:00 Oral presentation

haleh Abdoli sereshki The most allergenic pollen grains in Tehran: an update study	**seyed mohammadreza Bolandi** Aangiogenesis inhibitory effect of Bevacizumab: A new strategy to cure asthmatic rats	**haleh Abdoli sereshki** Immunochemical Characterization of Privet Pollen Allergens	**mohammad hossein shams** Immunochemical Characterization of Populus nigra Pollen Allergens	**Niloofar Daneshfar** Chemerin Receptor 23 (ChemR23) gene polymorphisms and risk of allergic rhinitis
mostafa atashbasteh Expression of plasma-derived exosomal miR-125b is associated with inflammatory markers in severe asthma patients	**Shokrollah Farrokhi** Association Between Chronic Rhinosinusitis and Allergic Diseases in Adults: A GA2LEN Study	**Mahvash Sadeghi** Induction of regulatory T cell response by DC-aptamer-modified gold nanoparticles coated with ovalbumin in allergic mice model through sublingual immunotherapy	**Ali Farhadi** OVA immunodominant T cell epitope encoding DNA vaccine inhibits eosinophilic infiltration in a mouse model of Allergic rhinitis	

13:00 – 14:00 **Break & poster visiting**

DAY 1
Wednesday, 27 January,2021

Main Panel

14:00 – 14:40 — Hans-Uwe Simon
Molecular mechanism of neutrophil extracellular traps

14:50 – 15:30 — Ali Harandi
Lessons Learned from COVID-19 Vaccines

15:30 – 16:00 — Break & poster visiting

Panel 1

Treatment of COVID 19

keynote

16:00 – 18:00

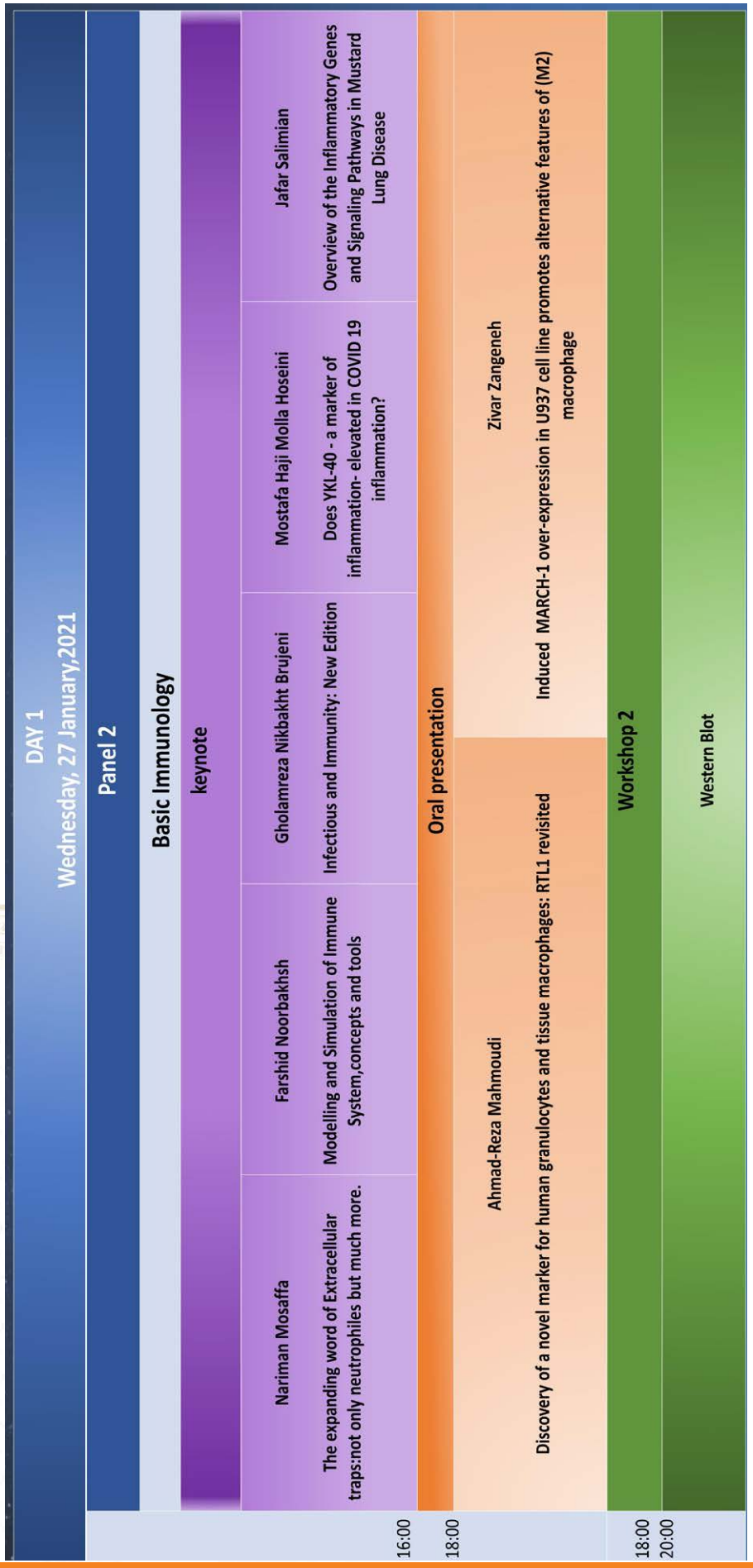
Mehdi Mirsaeidi Challenges in covid treatment	Arda kiani cytokine storm	Abdolreza Esmaeilzadeh Immune-based therapy for COVID-19

Oral presentation

Sara Iranparast Protein E-Peptide Driven Vaccine for Novel Coronavirus: Immunoinformatics	Faezeh Maghsood Development of novel neutralizing monoclonal antibodies against SARS-CoV-2	Ava Resae Therapeutic Effects of Mesenchymal Stem Cell (MSC) Therapy on Covid-19 Respiratory Symptoms	Mostafa Akbariqomi Adjuvant use of melatonin as a potent anti-inflammatory to improve clinical outcomes in COVID-19 patients
Sajad Dehnavi Effects of curcumin on serum levels of inflammatory cytokines in COVID-19 patients	Mohammad Barary Hydroxychloroquine and azithromycin: As a double edge sword for COVID-19?	Hamed Valizadeh The Nanocurcumin effects on the Treg cell frequency and FoxP3 expression in mild and severe 2019-novel coronavirus patients	Safa Tahmasebi Investigation of Nanocurcumin effects on cytokine profile of the Th17 cell in mild and severe COVID-19 patients Compared to the placebo group

Workshop 1

18:00 – 20:00 — Application of nanotechnology in immunotherapies


DAY 1
Wednesday, 27 January,2021
Panel 2
Basic Immunology
keynote
Nariman Mosaffa
The expanding word of Extracellular traps:not only neutrophiles but much more.
Farshid Noorbakhsh
Modelling and Simulation of Immune System,concepts and tools
Gholamreza Nikbakht Brujeni
Infectious and Immunity: New Edition
Mostafa Haji Molla Hoseini
Does YKL-40 - a marker of inflammation- elevated in COVID 19 inflammation?
Jafar Salimian
Overview of the Inflammatory Genes and Signaling Pathways in Mustard Lung Disease
Oral presentation
Ahmad-Reza Mahmoudi
Discovery of a novel marker for human granulocytes and tissue macrophages: RTL1 revisited
Zivar Zangeneh
Induced MARCH-1 over-expression in U937 cell line promotes alternative features of (M2) macrophage
Workshop 2
Western Blot
16:00
18:00
18:00
20:00

DAY 1
Wednesday, 27 January,2021

Panel 3

Reproductive immunology

keynote

Maryam Tavakoli & Mahdi Yousefi

Thyroid autoimmunity and pregnancy loss

16:00 – 18:00 Oral presentation

Reyhane Rahnema Thyroid Peroxidase In Human Endometrium And Placenta: A Potential Target For Anti-TPO Antibodies	**Houshang Nemati** Effect of autoimmune thyroiditis on women infertility	**Fatemeh Rezayat** An Invisible Pattern of Autoantibodies in the of Women with Recurrent Spontaneous Abortion	**Kimia Zarnani** Decidualization-incompatible mating in CBA/J x DBA/2 model: Does quality of seminal plasma play a role?	**Kayhan Zarnani** It is defective decidualization not aberrant immune system that triggers abortion in CBA/J x DBA/2 mating	**Mahvash Zargar** Evaluating Chronic Endometritis in Women with Recurrent Implantation Failure and,..	**Sara Khorami-sarvestani** Proteome Analogy in the first-trimester and Term Human Placentas	**Hasan Namdar-Ahmadabad** Effect of Maternal LPS Exposure during Pregnancy on Expression ,..
Forough Parhizkar Preeclampsia-exosomes: Their role in Th17/Treg axis imbalance in healthy pregnant women	**Iman Naamipouran** Effect of Different Concentrations of Leukemia Inhibitory Factor on Gene Expression ,..	**Sahel Heidari** Expression levels of monocyte chemoattractant protein-1, hepatocyte growth factor,..	**Zeinab Shojaei** Evaluation of Toll-Like Receptors 6-10 Gene expression Levels in Endometriosis	**Fateme Zare** Contraceptive and molecular function of a novel recombinant vaccine based human leukemia ,..	**Abdolah Mousavi-Salehi** Evaluation of CD3 CD56 NKT cell percentage and function and,..	**Motahareh Ehsani** Evaluating the Frequency of CD8+HLA-G+ T cell in primary Unexplained Infertile Females	**Mohammad Barary** Ameliorative effect of Alpinia officinarum Hance extract on nonylphenol-induced reproductive toxicity in male rats

Workshop 3

18:00 – 20:00

Stem cells (Classification, Properties, Separation methods, Therapeutic application)

DAY 1
Wednesday, 27 January,2021

Panel 4

Tolerance and Autoimmunity

keynote

Abdollah-Jafarzadeh

Autoimmunity and COVID-19

16:00
18:00

Oral presentation

Seyed Alireza Esmaeili Inhibitory effects of tolerogenic probiotics on migratory potential of lupus patients – derived DCs	Atefeh Alaei The ex vivo effects of Lactobacillus delbrueckii and Lactobacillus rhamnosus on inflammatory,..	zahra javanmardi Generation of lupus M1 and M2 macrophages differentiated by tolerogenic probiotics	Parisa Ahmadi investigation of Lactobacillus rhamnosus and Lactobacillus delbrueckii effects on,..	elahe parkan Beneficial effects s of combined prednisolone and theophylline in improving,..	Maryam Mohammadi Effect of hydroalcoholic extract of Ferula assa-foetida L. resin on,...	sahar samemaleki Effect of Platelet Rich Plasma and Autologous Conditioned Serum,...	maryam roozbehkia Effects Of β-D-mannuronic Acid On TLR2 And TLR4 Expression And Downstream Signalling In Monocyte,..	
Zahra Amiri Therapeutic treatment with Curcumin decreases the severity of experimental autoimmune encephalomyelitis,..	shadi moradi Assessment of expression profile of microRNAs in multiple sclerosis patients treated with fingolimod	Paria bayati Differential expression of miR-27a and miR-138a in patients with systemic sclerosis	Shima Rahmani The expression analyses of RMRP, and RORC in RRMS patients treated with different drugs versus naïve patients and healthy controls	Shima Shapoori Alteration of Sema3A, Sema7A and their receptors gene expression in treated multiple sclerosis patients	Mohammad javad tavassolifar Redox imbalance in CD4+ T cells of relapsing-remitting multiple sclerosis patients	Mobina Belalzadeh Evaluation of TLR2,TLR4,TLR9 expression with Angiopoietin 4 proteins,..	Saeede Nikpasand Reduction of Circulating CD19 / CD24hi / CD38hi Breg cells could result in Psoriasis pathogenesis.	Zohreh Babaloo Evaluation of SOCS1 methylation in patients with Behcet's disease

Workshop 4

18:00
20:00

Training theoretical and practical principles of immunohistochemistry

DAY 1
Wednesday, 27 January,2021

Panel 5

Immuno-genetic & Bioinformatics

keynote

Elham-Ashoori KIR variation in Iranians combines high haplotype and allotype diversity with an abundance of functional inhibitory receptors	**Amir Ali-Hamidieh** Recent Advances in Immune Cell Therapies: Hope and Fear	**Seyed Hamidollah-Ghaffari** Use of Ig/TCR gene rearrangements for detection of Minimal residual disease in patients with Acute Lymphoblastic Leukemia

Oral presentation

16:00 18:00	**Ghasem Solgi** HLA class II alleles may predict the severity of COVID-19 disease	**Ashkan Rasouli saravani** Relevance of autoantibody profile with HLA-DRB1 and -DQB1 alleles in a group of Iranian systemic lupus erythematosus patients	**Ali Khorasanizadeh** Association of IL-10 genetic polymorphisms (592 A/C and 819T/C) with the susceptibility to Acute Lymphocytic Leukemia in Children of Southwestern Iran	**Mojdeh Matloubi** The impact of interleukin (IL)-33 gene polymorphisms on asthma incidence in the Iranian population	**Sepide Namdari** Increased frequency of KIR2DS4 del/del among AA genotype carriers with B cell acute lymphoblastic leukemia in southwestern Iranian population	**marjan hematian larki** Killer cell immunoglobulin-like receptors (KIRs) gene diversity in Iranian patients with breast Cancer

Workshop 5

18:00
20:00

Phage display

DAY 2 Thursday, 28 January,2021				
9:00 9:40	**Main Panel** **Brian Till** **The clinical application of CAR T cell therapy for B cell non-Hodgkin lymphomas**			
9:50 10:30	**M.J. Stear and K. Donskow-Lysoniewska** **The influence of galectin 3, galectin 9 and parasite galectin on mast cell degranulation**			
1o:30 11:00	**Break & poster visiting**			
11:00 13:00	**Panel 1** **Vaccine & COVID-19 Vaccine** **Keynote Speaker**			
	Seyed Reza-Bani Hashemi **Research and development on the COVID-19 vaccine**	**Sima-Rafati** **Leishmania tarentolae an efficient key for vaccine production and Immunotherapy**	**Alireza-Biglari** **Vector-based vaccines in COVID-19**	
	Oral presentation			
	Atefeh Sadeghi Shermeh **Evaluation of protection induced by in vitro maturated MoDCs presenting CD8+ T cell stimulating peptides after a heterologous vaccination regimen in BALB/c model against Leishmania major**	**Parisa Amirkalvanagh** **NanoInterleukin-29-adjuvanted genetic vaccine improves cell-mediated immune responses against Herpes Simplex Virus Type I**	**Abolfazl Rahmani** **Development of a novel chimeric multi-epitope vaccine via cancer-testis antigens against colorectal cancer using immunoinformatics and reverse vaccinology approaches**	**Nafiseh Keshavarzian** **Evaluation of Leishmanization Using Iranian Lizard Leishmania Mixed with CpG-ODN as a Candidate Vaccine against Experimental Murine Leishmaniasis**
13:00 14:00	**Break & poster visiting**			

DAY 2
Thursday, 28 January,2021

panel 2

Immunology of Infectious Disease

Keynote Speaker

Payam tabarsi	Bhaskar Saha	Akihiro Shimosaka
TB/HIV:challenges and solution	Leishmania	NK cell Antivirus Activity

Oral presentation

11:00 13:00	vahab jamali Bioinformatics study of the most relevant signaling pathways of two human coronavirus microRNAs in cancer incidence	Ali Ranaie Prevalence of β-lactamase producing Acinetobacter baumannii in Iran	Arshid Yousefi Avarvand Immunogenicity of HspX/EsxS fusion protein of Mycobacterium tuberculosis along with ISCOMATRIX and PLUSCOM nano-adjuvants after subcutaneous administration in animal model	Forough Golsaz-Shirazi Influence of PRR ligands on induction of innate immunity and control of HBV infection	hamzeh sarvnaz Optimization of hepatitis B infection in cell culture using serum and cell culture derived viral inoculums
	Pooria Fazeli Correlation between IL-28 polymorphism and spontaneous clearance in HCV patients: systematic review and meta-analysis	Mousa Mohammadnia-Afrouzi Exhaustion markers in CD4+ T cells of COVID-19 patients: TIM-3 is more important than CD39 and PD-1	Atefeh Najmadini Evaluation of Peripheral Cytotoxic T cell percentage in relations to EBV viral Load in MS patients	Zahra Kamiab Toll like receptor 3 and 9 are up-regulated in the hospitalized COVID-19 infected patients	Arghavan Asghari Evaluation of HBx, BRCA1, and RAD51 expression in hepatitis B patients
13:00 14:00	**Break & poster visiting**				

DAY 2
Thursday, 28 January,2021

Panel 3

Immunology of aging , nutrition and exercise

Keynote Speaker

Mahdieh Molanouri Shamsi Modulatory Effects of Physical Exercise on Immune Responses in Relation to Vaccination of Older Adults	**Ali Akbar Saboor Yaraghi** Micronutrients and Immune Function	**Prof.Krüger Karsten** Effects of an Active Lifestyle on ("Healthy") Immune Aging

Oral presentation

11:00
13:00

Karim Parastouei Effect of Vitamin A, Vitamin D and their combination on gene expression of CD4+ T cells cytokines and transcription factors in experimental model of Multiple Sclerosis in C57-BL/6 mouse	**Hadi Bazyar** Anti-inflammatory and antioxidant effects of synbiotics in type-2 diabetes mellitus patients with periodontal disease under nonsurgical-periodontal-therapy. A double-blind, placebo-controlled trial	**Nafiseh Esmaeil** Combined All-Extremity High-Intensity Interval Training Regulates Immunometabolic Responses through Toll-Like Receptor 4 Adaptors and A20 Downregulation in Obese Young Females	**Mona Oraei** Study on the effects of vitamin D on the gene expression and DNA methylation of FOXP3 gene in the splenocytes of C57BL/6 mice	
Sepideh Maralbashi The effect of docosahexaenoic acid (DHA) on the cellular and exosomal expression of mammalian target of rapamycin (mTOR) and related microRNAs in breast cancer cell lines	**Damoon Ashtary-Larky** Is inflammatory and metabolic response to an acute session of resistance training different among trained and untrained individuals?	**Mahdi Ghasemiartiyan** The amount of interleukin-6 in the serum of strength athletes and endurance athletes compared to non-athlete people	**Zeinab sadat Moosavifard** Fasting and the Immune System	**Mojtaba Mollaei** The intrinsic and extrinsic elements regulating inflammation

13:00
14:00 **Break & poster visiting**

DAY 2
Thursday, 28 January,2021

Panel 4

Cancer Immunotherapy

Keynote Speaker

11:00 13:00	Arjan Griffioen An new strategy against cancer without side effects; vaccination against the tumor vasculature	Nowrouz Delirezh DC-based Cancer Immunotherapy	Davar Amani Tumor-derived Exosomes: a promising approach for cancer immunotherapy	
	Parviz Kookhaei Berberine and cancer therapy: a focus on CLL	Hossein Asgarian-Omran Immune check point blockade (ICB) strategy in the treatment of chronic lymphocytic leukemia	Arezoo Jamali Highly Efficient Generation of Transgenically Augmented CAR NK Cells Overexpressing CXCR4	Hamid Reza Mirzaei CAR T cells hit the tumor microenvironment: teaching an old dog a new tricks

Oral presentation

Leila Jafarzadeh Construction and Functional Characterization of a Fully Human Anti-mesothelin Chimeric Antigen Receptor (CAR) Expressing T Cell	Elham Masoumi Targeted knock-down of A2a Receptor Enhances the function of anti-mesothelin CAR T cells.	Vahid Khaki Establishment of a murine model of breast cancer expressing human epidermal growth factor receptor 2 (4T1-HER2)
Mehdi Mohammadi A novel anti-HER2 bispecific antibody with potent in vitro and in vivo tumor inhibitory effects	Shakiba Jafarkhan PD-1 and Tim-3 blocking dose not improve the apoptosis of leukemic cells by peripheral blood CD8+ T cells in chronic lymphocytic leukemia	Ahmad Reza Mahmoudi PLAC1: a potential biomarker for targeted immunotherapy of melanoma

13:00 14:00 **Break & poster visiting**

DAY 2
Thursday, 28 January,2021

panel 5

Immunodeficiency

Keynote Speaker

	Zahra Chavoshzadeh Introduction and Patient Presentation	prof Anne Paul Genetic evaluation of PID patients with fungal infections	Somayeh Sharifynia Diagnostic methods in patients with fungal infections	Davood mansouri Treatment of fungal infections in patients with primary immunodeficiency

11:00 13:00 Oral presentation

Fereshte Salami CTLA-4 Expression in Stimulated Lymphocyte from Common Variable Immunodeficiency Patients with Enteropathy and with No Known Monogenic Disease	Farzad Nazari Evaluation of Radiation Sensitivity in Patients with Hyper IgM Syndrome	yasser bagheri Evaluation of effective factors on IL-10 signaling in B cells in selective IgA deficient patients	Faezeh Abasirad Increased Expression of B Lymphocyte Induced Maturation Protein 1 (BLIMP1) in Patients with Common Variable Immunodeficiency (CVID)	Mahsa Taghavi Farahabadi The Effects of Mesenchymal Stem Cells Conditioned Media and Exosomes on the function of neutrophils from chronic granulomatous disease patients

13:00 14:00 Break & poster visiting

DAY 2 Thursday, 28 January,2021				
	Main Panel			
14:00 14:40	Christian Buchholz Targeted lentiviral vector for in vivo gene delivery in CAR-mediated immunotherapy			
14:50 15:30	Ahmad Jalili Novel insights into the pathophysiology & treatment of atopic dermatitis			
15:30 16:00	Break & poster visiting			
	Workshop 1	Workshop 2	Workshop 3	Workshop 4
16:00 18:00	Basic,Methods and Application of Flow Cytometry	CRISPR advanced Training Course and Operation	Introduction of theoretical and practical standard approaches for RT-PCR method in basic science research	DNA Aptamer
	Workshop 1	Workshop 2	Workshop 3	Workshop 4
18:00 20:00	Magnetic Activated Cell Sorting	Immunogenetics and Pyrosequencing	Introductory bioinformatics, an overview of NCBI databases	miRNAs: Introduction, Biogenesis, Function and Quantitative detection by Real time PCR

DAY 3
Friday, 29 January,2021

9:00 9:40	**Main Panel** **Christine Brown** **CAR T cell therapy in solid tumors**						
9:50 10:30	**Alireza Ranjbar** **Immunometabolism in obesity and its clinical relevance**						
1o:30 11:00	**Break & poster visiting**						
11:00 13:00	**Panel 1** **Research & Development** **Keynote Speaker**						
	Majid Khosh Mirsafa **Current perspectives of clinical laboratory immunology in medical era**		**Mojtaba-Sankian** **Open innovation platform promotes university-industry alliances for R&D**		**Mohammad Javad-Rasaee** **The impact of scientific authority on development and advancment of strategic technologies**		
	Oral presentation						
	Amir Valizadeh **miR-622 serves as a tumor-suppressive and impairs motility through inhibiting metastatic genes in prostate cancer**	**Raoufeh Ahmadi fesharaki** **Identification of fully human single chain Fragment variable Antibody against Interleukin-6 using Phage Display**	**Mohammadrasul Zareinejad** **Characterization of 6D6 hybridoma clone producing Monoclonal Antibody reactive with Bladder Cancer Cell lines**	**Sorour Shojaeian** **Quantum Dot-labeled Tags Improve Minimal Detection Limit of CA125 in Ovarian Cancer Cells and Tissues**	**Masoud Hassanzadeh Makoui** **Production and immunohistochemical characterization of mouse monoclonal antibodies specific for the human tumor-associated antigen Ki67**	**Somayeh Ghotloo** **Efficient neutralization of tetanus toxin by a single chimeric monoclonal antibody**	**Fatemeh moaddab** **Expression analysis of beta-secretase 1 (BACE1) enzyme in peripheral blood of patients with Alzheimer's disease**
	Sajjad Eslamkhah **Evaluation of two genomic DNA extraction method from fecal samples of patients with colorectal cancer**	**Sara Adibfar** **Coinhibition of CD73 and EZH2 molecules suppresses the growth and development of 4T1 breast cancer cells, in vitro**	**Sahar Khosravi** **Effect of Dimethyl fumarate Loaded-PLGA Nanoparticles on Expression of IL-1, IL-6, TNF-α Genes in Murine Splenocytes**	**Omid Yeganeh** **Protection against Acinetobacter baumannii infection by novel anti outer membrane protein A (Omp A) monoclonal antibody (MAb)**	**parnian Navabi** **Design and optimization of a chimeric single-chain fragment variable (scFv) antibody against IL2Rα (CD25)**	**Fereshte Ghafari** **The effect of targeted DMF loaded-PLGA nanoparticles on the pattern of cytokine expression in dendritic cells**	
13:00 14:00	**Break & poster visiting**						

DAY 3
Friday, 29 January,2021

Panel 2

Immunomodulation & Immunoregulation

Keynote Speaker

Tooba Ghazanfari

Immunoregulation: The Horizon ahead in Diagnonsis and Treatment of Diseases

Farshid Nourbakhsh

Immunoregulation from a System and Computational Biology Perspective

Oral presentation

11:00 13:00	**Mohsen Naseri** **Enhancement of the Immunomodulatory Properties of Dental Pulp Stem Cells by Crocin through Up-expression of HLA-G5 and STAT3 Genes**	**Mohsen Naseri** **Comparison of modulation of microRNAs for human dental pulp stem Cells and human adipose derived mesenchymal stem cells by Crocin.**	**Sheida Farrokhi** **Immunomodulatory Potential of Murine Adipose-Derived Mesenchymal Stem Cells is enhanced Following Culture on Chitosan Film**	**Malaksima Ayadilord** **Immunomodulatory effects of phytosomal curcumin are associated with downregulating miR-155 and miR-126a in dental pulp stem cells**	
	Samad Farashi Bonab **Evaluation of effect of long-term usage of acetaminophen on the gene expression levels of arginase and cyclooxygenase in leukocytes**	**Maryam Mohammadi** **The Effect of hydroalcoholic extract of Ferula assa-foetida L. oleo-gum-resin on serum levels of IL-6 and TNF-α cytokines and oxidative stress parameters in animal model of rheumatoid arthritis**	**Nabiollah Mohammadi** **CTLA-4 FC improves the potency of insulin-producing cells differentiated from mouse bone marrow mesenchymal stem cells**	**Mansoore Saharkhiz** **Crocin improves the immunomodulatory capacity of dental pulp stem cells via up-regulation of CD200 glycoprotein**	**SeyedeSara Hassani** **Evaluation of the regulatory axis of long non-coding RNA NEAT1/miR199a-5p/heat shock protein A5 gene expression in patients with diabetic neuropathy**
13:00 14:00	**Break & poster visiting**				

DAY 3
Friday, 29 January,2021

Panel 3

Immunohematology & Transplantation

Keynote Speaker

Yadollah-Shakiba Immunological evaluations in solid organ Transplantation	**Behnaz-Bayat** HPA and HNA allo-antibodies and Endothelial cells

Oral presentation

11:00 13:00	**Afsaneh Aghaie** Special Anti-Hepatitis Antibody Content of IVIGs Made of Iranian Plasma	**Alireza Ghavami** Association between Prognosis factors together and Response to Therapy and ABO blood groups in Acute Lymphoblastic Leukemia	**Fatemeh Khorshidi** Extraction and purification of α–Defensin from leukocytes trapped on leukoreduction filters by cation exchange chromatography	**Seyedeh Farzaneh Jalali** The new approach for stabilization the reactivity of coombs control cells by fixation of RBC membrane	**Mozhdeh Karimi** Frequency of dendritic cell subsets and ILT3, ILT4 gene expression in two different immunosuppressive protocols in kidney transplant recipients	**Seyede Najibe Nasiri** Enhancing effects of PNU-74654 on the antiproliferative effects of 5-FU in breast cancer via the inhibition Wnt pathway
	Mohammad Mirzakhani Reduced CD4+ CD25++ CD45RA-Foxp3hi Activated Regulatory T Cells and its Association with Acute Rejection in Patients with Kidney Transplantation	**Alireza Mardomi** PD-L1 overexpression protects the mesenchymal stem cell-derived cardiomyocyte-like cells against alloreactive immune responses in mice	**Shima Afzali** Investigating the role of BAFF and its receptors in renal transplant recipients with chronic antibody-mediated rejection	**Seyed Ehsan Asadi** Evidence for a rebalanced hemostatic system in pediatric liver transplantation: A prospective cohort study	**Saeedeh Salehi** Transitional immature regulatory B cells and regulatory cytokines can discriminate chronic antibody-mediated rejection from stable graft function	
13:00 14:00	**Break & poster visiting**					

DAY 3
Friday, 29 January,2021

Panel 4

Psychoneuroimmunology &Immuno-endocrinology

Keynote Speaker

11:00	Ahmad Ali-Noorbala Psychoneuroimmunology of depression	Mojdeh-Ghabaee Pathophysiology of autoimmune encephalitis	Sara-Hashempour Psychoneuroimmunology of psychosis

13:00 Oral presentation

Elnaz khosh Immunologic Effect of Tissue-Plasminogen Activator (t-PA) on Interleukin-10 (IL-10) in Acute Ischemic Stroke Patients	maryam zare rafie IL-38; as an early predictor marker for the ischemic stroke prognosis	Morteza Jafarinia Assessment of plasma Osteopontin level in relapsing- remitting multiple sclerosis patients	Azita Mohammadzadeh Evaluation of the Immunological Factor Hepcidin in Ischemic Stroke Patients Receiving the tissue-Plasminogen Activator (t-PA)

13:00 – 14:00 **Break & poster visiting**

DAY 3
Friday, 29 January,2021

Panel 5

Immunopharmacology & Medicinal Plants

Keynote Speaker

11:00 13:00	Mojdeh Hakemi-Vala Design and screening of melittin-derived peptides and evaluation of their antibacterial and toxicity activity in cell culture	Somayeh Ghotloo Anti-tumor effects of the aqueous seed extract of Trachyspermum ammi (L.) sprague on human cancer cell lines	Mojgan Tansaz Introduction of traditional Iranian medicine and its therapeutic approach in Covid-19 disease

Oral presentation

Ali Saeedi-Borujeni Tranilast:A NLRP3 Inflammasome Inhibitor Drug for COVID-19	Fatemeh Mashhadi Immunomodulatory Activities of Extracts and Essential Oils of Two Oregano Species (Origanum Vulgare L. and Origanum Majorana L.)	Somayeh Ghotloo Anti-tumor effects of the aqueous seed extract of Trachyspermum ammi (L.) sprague on human cancer cell lines	Maryam Mohammadlou Impact of Berberine on anti-apoptotic Bcl-2 protein expression in patient with B-Chronic Lymphocytic Leukemia	Amin Dakhili Ardestani Evaluation of chemical content, antioxidant, anti-inflammatory and anti-proliferative effects of Ferula assa foeitida gum essential oil on MDA-MB-468 breast cancer cell line

13:00 14:00 — Break & poster visiting

DAY 3 Friday, 29 January,2021				
14:00 14:40	Main Panel Dieter Kabelitz Perspectives of human gamma/delta T-cells for immunotherapy of cancer			
14:50 16:00	Closing Ceremony			
16:00 18:00	Workshop 1 How to publish an article in reputable journals	Workshop 2 Introduction to lymphocyte proliferation assessment methods with emphasis on CFSE method and its flow cytometric analysis in Flowo-jo software	Workshop 3 Theoretical and practical aspects of purification, production and characterization of immunogens	Workshop 4 Analyzing real-time PCR data
18:00 20:00	Workshop 1 Preparation of CAR T cells	Workshop 2 Key points in multi-color flow cytometry panel design	Workshop 3 Basics of working with Viral vectors	Workshop 4 Introduction and presentation of different statistical graphs with Excel and Graph Pad Prism software

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

Panels Posters

ICIA 2021 AHVAZ
27-29 January /AJUMS/Ahvaz/Iran
Knowledge and Virtue are Superior to Fist and Sword

15th Virtual International Congress of Immunology and Allergy

Immunology and Immunopathology of COVID-19 Panel

Chairman

Tooba Ghazanfari

Some topics presented in this panel:

- Association of immunological and inflammatory factors with disease severity in COVID-19
- Hemoperfusion and removal of cytokines in COVID-19 immunopathology
- Cellular immune responses in COVID-19
- Psychoneuroimmunological aspects of COVID-19
- Corticosteroids mechanism in the treatment of COVID-19
- The role of inflammatory factors in the clinical management of COVID-19

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Hamid Reza Abtahi

Mohamad Reza Salehi

Abdolrahman Rostamian

Maryam Mahluji Rad

Ali Mostafaie

Alijan Tabraei

Reza Jafari

Keynote Speaker

Tooba Ghazanfari	Hamid Reza Abtahi	Mohammad Reza Salehi	Abdolrahman Rostamian
Alijan Tabraee	Maryam Mahluji Rad	Ali Mostafaee	Reza Jafari

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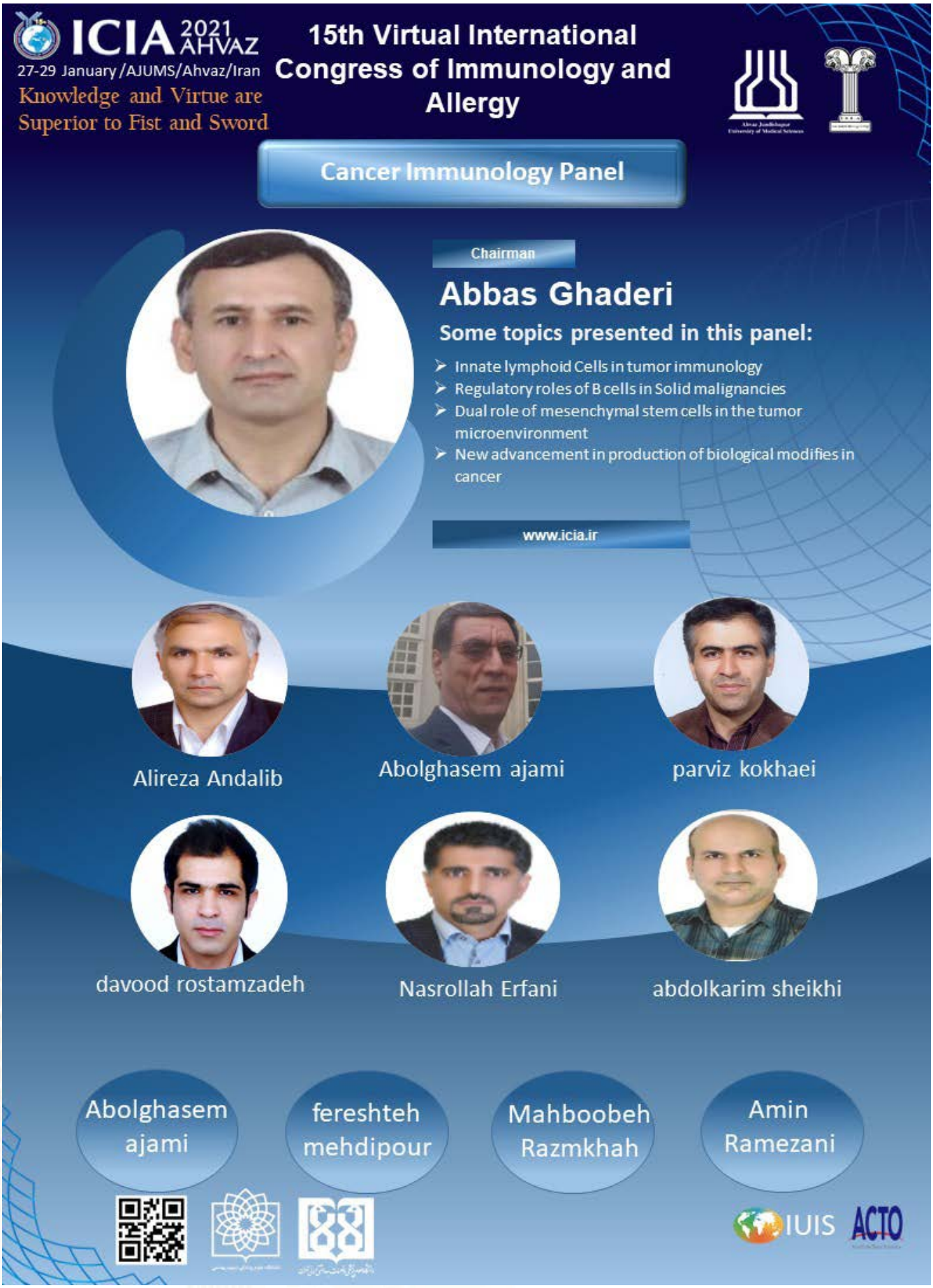
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15th Virtual International Congress of Immunology and Allergy
Cancer Immunology Panel
Chairman
Abbas Ghaderi
Some topics presented in this panel:
Innate lymphoid Cells in tumor immunology
Regulatory roles of B cells in Solid malignancies
Dual role of mesenchymal stem cells in the tumor microenvironment
New advancement in production of biological modifies in cancer
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Alireza Andalib
Abolghasem ajami
parviz kokhaei
davood rostamzadeh
Nasrollah Erfani
abdolkarim sheikhi
Abolghasem ajami
fereshteh mehdipour
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15th Virtual International Congress of Immunology and Allergy

Oral and Mucosal Immunology Panel

Chairman

Mandana Sattari

Some topics presented in this panel:

- Special Immunologic Characteristics of Gingiva
- Chemokine mission in oral cavity health and periodontal disease
- Immunomodulatory properties of osteogenic differentiated dental pulp stem cells
- Correlation between gingival expression of IL-33, ST2 and LL37 and periodontal diseases
- The role of tolerogenic dendritic cells subsets in the screening of celiac disease

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Maryam Baharvand

Feryal Taleghani

Pejvak khaki

Nikoo Hossein Khan Nazer

Masoomeh Dibaj

Keynote Speaker

Mandana Sattari

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15th Virtual International Congress of Immunology and Allergy

Stem Cell and Immune Cell Therapy Panel

Chairman

Masoud Soleimani

Some topics presented in this panel:

- Highly Efficient and Selective CAR-gene Transfer Using CD4- and CD8-Targeted Lentiviral Vectors
- Assessment of proliferativeand anti-apoptotic and immunomodulatory activity of crocin and crocetin on adipose-derived mesenchymal stem cells from multiple sclerosis patients
- Impact of IFN-β and LIF overexpression in human adipose-derived stem cells (hADSCs) properties

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Gholamreza Khamisipour

Amir Atashi

Naser Ahmad Beigi

Naser Aghdami

Abbas Hajifathali

Mahmoud Masiha Hashemi

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15th Virtual International Congress of Immunology and Allergy

Allergy and Immunotherapy of allergic diseases Panel

Chairman

Reza Farid Hosseini

Some topics presented in this panel:

- Aangiogenesis inhibitory effect of Bevacizumab: A new strategy to cure asthmatic rats
- Chemerin Receptor 23 (ChemR23) gene polymorphisms and risk of allergic rhinitis
- Expression of plasma-derived exosomal miR-125b is associated with inflammatory markers in severe asthma patients
- Association Between Chronic Rhinosinusitis and Allergic Diseases in Adults: A GA2LEN Study

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Alireza Ranjbar

Reza Nassiri

Maryam Khoshkhui

Mohammad Fereidouni

Mohammad Gharagozlou

Mohammad Ali Assarezadegan

Sepideh Darougar

Farahzad Jabbari Azad

Keynote Speaker

Alireza Ranjbar

Reza Nassiri

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Treatment of COVID-19 Panel

Chairman

Atefeh Abedini

Some topics presented in this panel:

- Challenges in covid treatment
- cytokine storm
- The role of immunotherapy in the treatment of covid

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Alireza Nadji

Shervin Shokouhi

Keynote Speaker

Mehdi Mirsaeidi

arda kiani

Abdolreza Esmaielzadeh

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Basic Panel

Chairman

Behzad Baradaran

Some topics presented in this panel:

- The expanding word of Extracellular traps:not only neutrophiles but much more.
- Modelling and Simulation of Immune System,concepts and tools
- Infectious and Immunity: New Edition
- Does YKL-40 - a marker of inflammation- elevated in COVID 19 inflammation?
- Overview of the Inflammatory Genes and Signaling Pathways in Mustard Lung Disease

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Farshid Noorbakhsh

Gholamreza Nikbakht Brujeni

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Reproductive Immunology Panel

Chairman

Amir-Hassan Zarnani

Some topics presented in this panel:

- Thyroid autoimmunity and pregnancy loss
- Effect of autoimmune thyroiditis on women infertility
- Proteome Analogy in the first-trimester and Term Human Placentas
- Preeclampsia-exosomes: Their role in Th17/Treg axis imbalance in healthy pregnant women

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Hossein Hadi nedoushan

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Tolerance and Autoimmunity Panel
Chairman
Abdollah Jafarzadeh
Some topics presented in this panel:
Autoimmunity and COVID-19
Evaluation of TLR2,TLR4,TLR9 expression with Angiopoietin 4 proteins affection on mono nuclear cells in MS patients
Differential expression of miR-27a and miR-138a in patients with systemic sclerosis
Redox imbalance in CD4+ T cells of relapsing-remitting multiple sclerosis patients
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Mahdi Mahmoudi
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Shahnaz Rafiei Tehrani
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Immunogenetics and Bioinformatics Panel
Chairman
Ali Akbar Amirzargar
Some topics presented in this panel:
KIR variation in Iranians combines high haplotype and allotype diversity with an abundance of functional inhibitory receptors
Recent Advances in Immune Cell Therapies: Hope and Fear
Use of Ig/TCR gene rearrangements for detection of Minimal residual disease in patients with Acute Lymphoblastic Leukemia
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Hamidollah Ghaffari
Mohammad Hossein Niknam
Elham Ashouri
Shirin Farjadian
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Mahdi Mahmoudi
Ghasem Solgi
Amir Ali Hamidieh
Elham Ashouri
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Vaccine and COVID-19 vaccine

Chairman

Reza Bani Hashemi

Some topics presented in this panel:

- Research and development on the COVID-19 vaccine
- Leishmania tarentolae an efficient key for vaccine production and Immunotherapy
- Vector-based vaccines in COVID-19
- NanoInterleukin-29-adjuvanted genetic vaccine improves cell-mediated immune responses against Herpes Simplex Virus Type I

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Mojtaba Noofeli

Alireza Biglari

Ahmad Zavaran Hosseini

Farzin Roohvand

Zuhir Mohammad Hasan

Sima Rafati

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Reza Bani Hashemi

Sima Rafati

Alireza Biglari

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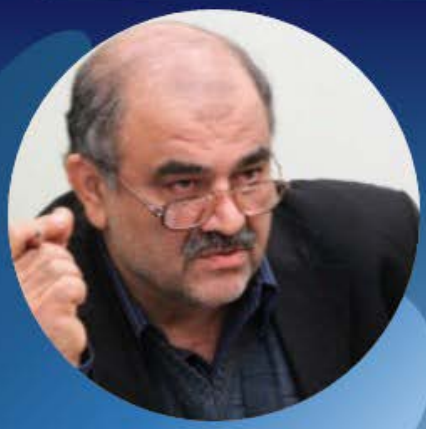
Immunology of Infectious Diseases Panel



Chairman

Seyed Mohammad Alavi

Some topics presented in this panel:

- TB/HIV:challenges and solution
- Leishmania
- Prevalence of β-lactamase producing Acinetobacter baumannii in Iran
- Influence of PRR ligands on induction of innate immunity and control of HBV infection
- Evaluation of HBx, BRCA1, and RAD51 expression in hepatitis B patients

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Sasan Mogehi

Akihiro Shimosaka

tahereh mousavi shabestari

Keynote Speaker

payam tabarsi

bhaskar Saha

Akihiro Shimosaka

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Immunology of Exercise, Aging & Nutrition Panel

Chairman

Mehri Ghafourian

Some topics presented in this panel:

- Modulatory Effects of Physical Exercise on Immune Responses in Relation to Vaccination of Older Adults
- Micronutrients and Immune Function
- Effects of an Active Lifestyle on ("Healthy") Immune Aging
- Study on the effects of vitamin D on the gene expression and DNA methylation of FOXP3 gene in the splenocytes of C57BL/6 mice
- The intrinsic and extrinsic elements regulating inflammation

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Mahdieh Molanouri Shamsi

Soosan Ardestani

Amin Isanejad

Masoud Nikbakht

Karsten Krüger

Keynote Speaker

Mahdieh Molanouri Shamsi

Ali Akbar Saboor Yaraghi

Krüger Karsten

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Cancer Immunotherapy Panel

Chairman

Jamshid Hadjati

Some topics presented in this panel:

- Highly Efficient Generation of Transgenically Augmented CAR NK Cells Overexpressing CXCR4
- CAR T cells hit the tumor microenvironment: teaching an old dog a new tricks
- Targeted knock-down of A2a Receptor Enhances the function of anti-mesothelin CAR T cells.

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Davar Amani

Hossein Asgarian Omran

Arjan Griffioen

Nowrouz Delirezh

Parviz Kookhaei

Keynote Speaker

Arezoo Jamali

Hamid Reza Mirzaei

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Immunodeficiency Panel

Chairman

Zahra Chavoshzadeh

Some topics presented in this panel:

- Introduction and Patient Presentation
- Genetic evaluation of PID patients with fungal infections
- Diagnostic methods in patients with fungal infections
- Treatment of fungal infections in patients with primary immunodeficiency
- Evaluation of effective factors on IL-10 signaling in B cells in selective IgA deficient patients

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Somayeh Sharifynia

Davood mansouri

Anne Puel

Keynote Speaker

Zahra Chavoshzadeh

Anne Paul

Somayeh Sharifynia

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Research and Development Panel

Chairman

Mahmood Jeddi Tehrani

Some topics presented in this panel:

- Current perspectives of clinical laboratory immunology in medical era
- Open innovation platform promotes university-industry alliances for R&D
- The impact of scientific authority on development and advancment of strategic technologies

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Ali Akbar Saboor Yaraghi

Mojtaba Sankian

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Ali Mostafaei

Masoumeh Baradaran

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Haleh Hamedifar

Behzad Poopak

Mohammad Javad Rasaee

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Immunomodulation and Immunoregulation Panel

Chairman

Ali Sheikhian

Some topics presented in this panel:

- Immunoregulation: The Horizon ahead in Diagnonsis and Treatment of Diseases
- Immunoregulation from a System and Computational Biology Perspective
- Crocin improves the immunomodulatory capacity of dental pulp stem cells via up-regulation of CD200 glycoprotein

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Tooba Ghazanfari

Farshid Nourbakhsh

Ali Mohamad Varzi

Arash Pourgholami

Nahid Rezaei

Nikoo Hossein Khan Nazer

Hassan Namdar

Keynote Speaker

Tooba Ghazanfari

Farshid Nourbakhsh

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Immunohematology and Transplantation Panel

Chairman

Ali Akbar Pourfathollah

Some topics presented in this panel:

- Immunological evaluations in solid organ Transplantation
- HPA and HNA allo-antibodies and Endothelial cells
- Special Anti-Hepatitis Antibody Content of IVIGs Made of Iranian Plasma
- Evidence for a rebalanced hemostatic system in pediatric liver transplantation: A prospective cohort study
- The new approach for stabilization the reactivity of coombs control cells by fixation of RBC membrane

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Mojgan Shaiegan

Behrouz Nikbin

Yadollah Shakiba

Behnaz Bayat

Keynote Speaker

Yadollah Shakiba

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Psychoneuroimmunology and Immunoendocrinology Panel

Chairman

Ahmad Ali Noorbala

Some topics presented in this panel:

- Psychoneuroimmunology of depression
- Pathophysiology of autoimmune encephalitis
- Psychoneuroimmunology of psychosis
- IL-38; as an early predictor marker for the ischemic stroke prognosis
- Assessment of plasma Osteopontin level in relapsing- remitting multiple sclerosis patients

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Roya Yaraee

Sara Hashempour

Mojdeh Ghabaee

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Sara Hashempour

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Immunopharmacology & medicinal Plants Panel

Chairman

Shahnaz Rafiei Tehrani

Some topics presented in this panel:

- Design and screening of melittin-derived peptides and evaluation of their antibacterial and toxicity activity in cell culture
- Anti-tumor effects of the aqueous seed extract of Trachyspermum ammi (L.) sprague on human cancer cell lines
- Introduction of traditional Iranian medicine and its therapeutic approach in Covid-19 disease

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Mehri Ghafourian

Mojdeh Hakemi Vala

Forouzan Karimi

Farshid Saadat

Saeed Mehrzadi

Ali Anissian

Keynote Speaker

Mojgan Tansaz

Mojdeh HakemiVala

Somayeh Ghotloo

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Congress Abstracts

Allergy and Immunotherapy of Allergic diseases

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(16913)

Angiogenesis inhibitory effect of Bevacizumab: A new strategy to cure asthmatic rats

Seyed Mohammadreza Bolandi1, Zohreh Abdolmaleki1*, Mohammad-Ali Assarehzadegan2, Mahara Hosseinabadi1

1.Department of pharmacology, Karaj Branch, Islamic Azad University, Karaj, Iran
2.Immunology Research Center, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran

Objectives: Asthma (reactive airway disease) is a chronic inflammatory disorder of lung involving allergic inflammation. Persistent inflammation in the airways can lead to structural changes, including mucosal prolapse, smooth muscle hyperplasia, sub epithelial fibrosis, proliferation of blood vessels, and infiltration of inflammatory cells. So, in this study, a new strategy was used in respiratory system disorders by angiogenesis inhibition in an ovalbumin-induced rat model of asthma.
Methods: Twenty one male Wistar rats were randomly divided into three groups (n=7 in each): 1) control, 2) ovalbumin (OVA)-sensitized and 3) OVA-sensitized with Bevacizumab (OVA+Bmab). Two and three groups were sensitized with ovalbumin (OVA) and aluminum hydroxide at day 1, 8 and challenged with OVA at day 15 by atomization for 10 days (inhalation). After OVA sensitization the OVA+Bmab treated with Bevacizumab for 2 weeks. Genes expression of IL-1β, IL-6 and TNFα were measured by Real-Time PCR System and protein expression of IL-1β, IL-6, TNFα and VEGF were assessed by immunohistochemistry in lung tissue. Moreover, the expression phenotypes of the CD4+CD8+ T cells were analyzed with flow cytometer.
Results: Ovalbumin exposure promoted the expression of VEGF and result in inflammatory factors overexertion ($p \leq 0.05$). However, rats in OVA+Bmab group showed significantly decrease in VEGFR , IL-1β, IL-6 and TNFα genes and proteins expression ($p \leq 0.05$). As well as this, results indicated that the percentages of both CD4+CD8+ T cells declined in OVA+Bmab group ($p \leq 0.05$).
Conclusion: The results show that Bevacizumab efficiently diminishes bronchial inflammation via reduced expression of VEGF and inflammatory cytokines. Regarding the effectiveness of Bevacizumab, it seems that these FDA approved drug Bevacizumab has potential therapeutic value for controlling asthma disease.

Keywords: Bevacizumab; Allergic inflammation; IL-6; IL-1β, TNF-α

(18429)

The most allergenic pollen grains in Tehran: an update study

Haleh Abdoli Sereshki [1,2], Mohammad-Ali Assarehzadegan [1,2], Reza Falak[1,2], Mohammad Nabavi[3], Mohammad-Hossein Shams[4]

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2. Immunology Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
3. Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
4. Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Over the past century, pollen allergy prevalence and incidence have developed into a pandemic health problem. Pollen grains proteins, which account for 2.5% to 61% of their dry mass, are accountable for up to 40% of respiratory allergy diseases, like asthma and rhinitis in almost half a billion people worldwide based on traditional estimates. This study aimed to report the updated prevalence of pollen allergy in IRAN, Tehran, and focused on Ligustrum vulgare (privet) as a new aeroallergen source in Tehran.

Methods: The sensitization profiles of 145 patients (ranging 7 to 60 years old) with allergic diseases referee to the Asthma and Allergy Alavi Zanjani Charity Clinic were analyzed, during March 2019 to February 2020, based on the results of skin prick tests for 20 allergen extract and the prevalence of different allergens was investigated.

Results: 145 patients had positive skin test to at least one of the aeroallergens. prevalence of most common allergens were, nine different type of trees, Privet (34.5%), Olive (28.3%), Pine (15%), Willow (22%), Birch (28%), Ash (46%), Platanus (49.7%), Elm (16.6%), Acacia (11%), and seven grasses such as Meadow grass (35.5%), Rye grass (22.8%), Mugwort (45.5%), Bermuda grass (35.9%), Timothy (35.2%), Salsola kali (57.2%), Alfalfa (30.3%) and pollen extract along with four weeds such as Lamb's Quarter (52.4%), Ragweed (34.5%), Pigweed (40%), Plantain (26.9%).

Conclusion: The most common allergenic plants were Salsola kali. In the last decade privet are widely used as either ornamental trees or hedges in parks and gardens in most parts of the Iran, especially in the north of the country and Tehran. Along with other common allergens with high prevalence (Ash, Platanus, meadow grass, mugwort), the current results showed that privet should be considered as a new allergenic pollen in areas where it is abundant and combined with other allergens.

Keywords: Privet, ligustrum, Skin prick test, Asthma

(18151)

Induction of regulatory T cell response by DC-aptamer-modified gold nanoparticles coated with ovalbumin in allergic mice model through sublingual immunotherapy

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Background: In recent years, allergic disorders being one of the most critical hygiene problems. Allergen-specific sublingual immunotherapy (SLIT) is widely considered an effective and non-invasive alternative delivery route to subcutaneous allergy immunotherapy (SCIT), whether requiring high doses of allergens. Recently, gold nanoparticles (AuNPs) for delivery of allergen have beneficial effects in sublingual immunotherapy of allergy. Also, using molecular targeting agents such as aptamers have been widely applied for targeted drug delivery. Therefore, this study aimed to assess the effect of the DCs-aptamer-modified AuNPs coating with ovalbumin (OVA) on improving sublingual allergy treatment in the murine model.

Method: Approximately 15nm diameter AuNPs were prepared by citrate reduction of $HAuCl_4$. Then, the Apt-modified AuNP complex was prepared, and OVA were loaded onto this complex. After sensitizing Balb/c mice to OVA, SLIT was performed with Apt-AuNPs containing OVA twice a week for 2 months. Then, IL-10 and TGF-β production in spleen cells were analyzed by ELISA. Also, the lungs were removed for histological analysis.

Results: SLIT treatment with synthesized formulation contain 5µg OVA in Apt-modified AuNPs complex, significantly increased TGF-β and IL-10 level compared to the PBS-treated group. Also, treatment with GNP-OVA-APT complex exhibited limited and local perivascular inflammation in lung tissue.

Conclusion: The results showed that SLIT with Apt-modified AuNPs containing 5µg OVA resulted in the induction of Treg immunomodulatory response.

Keywords: Sublingual immunotherapy, Gold nanoparticles, Aptamers

(18746)

OVA immunodominant T cell epitope encoding DNA vaccine inhibits eosinophilic infiltration in a mouse model of Allergic rhinitis

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2. Biotechnology Research Center, Islamic Azad University, Shahrekord Branch, Shahrekord, Iran

Background: Allergen-derived immunodominant T cell epitopes are administrated in peptide immunotherapy (PIT). There are no adverse effects mediated by IgE binding to the conformational epitope in the absence of B cell epitope. Despite the advantages of PIT, clinical trial outcomes have been varied. This study aimed to evaluate a new allergen immunotherapy method that benefits from the tolerogenic effects of regulatory T cell epitope (Tregitope) to suppress allergic reaction development.
Methods: A DNA vaccine containing "Signal peptide-Ovalbumin immunodominant T cell epitope-Tregitope" fusion protein under the control of a CMV-promoter was constructed. Female Balb/c mice received three intramuscular injections of vaccine prior to sensitization with ovalbumin. Following sensitization, mice were challenged intranasally. The number of sneezing and nose-scratching was counted immediately after the last challenge to evaluate nasal symptoms. Sera were collected, and OVA-specific IgE was measured by enzyme-linked immunosorbent assay (ELISA). Histological changes of nasal mucosa were evaluated by hematoxylin and eosin staining.
Results: Mice that received the DNA vaccine showed improved nasal symptoms and significantly reduced the nose-scratching events and sneezing. Eosinophilic infiltration in the nasal mucosa was significantly decreased in the vaccinated group. Moreover, the serum level of OVA-specific IgE was considerably reduced.
Conclusion: These findings suggest that allergen derived immunodominant T cell epitope fused to regulatory T cell epitope can be assumed as an effective allergen immunotherapy. Knowledge of the complete T-cell epitope map of different allergen opens the way to treatment of allergic diseases.

Keywords: Peptide immunotherapy, Allergy, DNA vaccine

(18769)

Immune responses modulation by curcumin and allergen encapsulated into PLGA nanoparticles in mice model of rhinitis allergic through sublingual immunotherapy

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Objective: The purpose of this study was combination of curcumin and ovalbumin in free form or encapsulated into PLGA NPs to enhance the efficiency of sublingual immunotherapy (SLIT) in mouse model of rhinitis allergic.
Methods: PLGA NPs containing curcumin (CUR), ovalbumin (OVA) or both were prepared by emulsion-solvent evaporation method. After sensitization of BALB/C mice with ovalbumin, SLIT with free or encapsulated formulations was carried out.
Results: The results showed that using curcumin along with allergen had enhancer effects in SLIT with more efficiency than subcutaneous immunotherapy. SLIT treatment with all synthesized PLGA formulations lead to significantly decreased total IgE. We also shown that the level of IFN-γ:IL-4 was significantly increased in groups treated by (PLGA-OVA (equal to 5µg OVA) with curcumin (10µg)) and (PLGA-CUR (equal to 5µg CUR) along with OVA (5µg)) compared to other groups. The study of nasal lavage fluid (NALF) in all treated groups showed significant decreased levels of total and eosinophil cell count in these groups. The histopathological results of NAL were also like normal with no cellular infiltration and no inflammation in the mentioned groups.
Conclusion: In this combination immunotherapy, the present of free form of curcumin or ovalbumin with encapsulated forms of the other substances lead to better allergic responses suppression compare to encapsulation of both agents into single or separated PLGA NPs.

Keywords: Allergic rhinitis, Sublingual immunotherapy, Curcumin, Ovalbumin, IgE antibody, PLGA nanoparticle

(18804)

Prevalence of Allergic Rhinitis in 6-14-Year-Old School Children in Dezful, southwest Iran

Abdolhussein Shakurnia*[1], Farhad Abolnezhadian[3], Abdolkarim Sheikhi[2]
Mohammad Nejadhosseini[1]

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2 Department of Immunology, Faculty of Medicine, Dezful University of Medical Sciences, Dezful, Iran c Caruncane co., Dezful, Iran
3 Department of Pediatric, Abuzar Children's Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Background: Allergic Rhinitis is a respiratory disorder in the upper respiratory airway, characterized by rhinorrhea, and nasal obstruction. Increasing of childhood allergic rhinitis and its heavy socio-economic burden has posed an important health problem in the world. Therefore, providing the updated relevant epidemiological information is robustly recommended. The aim of this study was to determine the prevalence of allergic rhinitis among Dezfulian schoolchildren students in Khuzestan Province, southwest Iran.

Methods: In this cross-sectional study conducted on 2908 schoolchildren aged 6 – 14 years from September to December 2019. Data were collected using the standardized international study of asthma and allergies in childhood (ISAAC) questionnaire. Cluster sampling was used for random selection of primary schools. The data were analyzed with SPSS, version 16.0

Results: A total of 2908 (1424 girls and 1484 boys) children participated in the study. The prevalence of rhinitis ever, current rhinitis symptoms and hay fever was 14.1%, 10.7%, and 5.5%, respectively; with a significantly higher rate among boys (16.6%, 12.8% and 7.4% vs. 11.4%, 8.4% and 3.6% respectively, in girls) (P=0.001). The prevalence of rhinitis ever, current rhinitis symptoms and hay fever was significantly higher rate among 13-14 years' age group (20.5%, 14.3% and 7.6% vs. 8.2%, 7.3% and 3.9% respectively, in 6-7 years' age group) (P<0.001). Allergic rhinitis was more prevalent in spring.

Conclusions: Compared with previous studies conducted in other Iranian cities using similar method, the prevalence of allergic rhinitis was lower in Dezful. This information can be used to help allergic rhinitis control.

Keywords: Allergic Rhinitis, Prevalence, schoolchildren, Dezful

(18665)

Evaluation of anticancer effects of aqueous and alcoholic extracts Artemisia and Cypress pollen from common allergenic Plants

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2. Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran
*Corresponding author

Background: Considering the increasing prevalence of different malignancies worldwide and the fairly ineffectiveness of current drugs, researchers around the world have focus to design novel and more potent medications with less side effects. In recent years, there is an increasing interest in the usage of newly identified herbal plant compounds as anticancer drugs. And numerous anticancer drugs derived from plant materials examined on various cancerous cell lines.
Methods: Pollen collected during pollination season and pure pollen achieved by sieving through micrometer meshes. Alcoholic extract was made based on Folch method and aqueous extracts was prepared in phosphate buffer saline. Both extracts were added in different dilutions to culture of two cancerous human cell lines including A549 and MCF7 and the level of cell survival was assessed by MTT method after 24,48 and 72 hours' incubation.
Results: The alcoholic extracts caused significant cell death in both cell lines at concentration of 1.2 mg/ml maximum at 24 hours' incubation. The highest rate of cell toxicity for aqueous extract was seen at concentration of 137 µg/ml after 48 hours' incubation.
Conclusion: The results of this study shown that both alcoholic and aqueous extracts of Artemisia pollen can kill cancerous cells in culture.

Keywords: Pollens, Allergies, Extraction, Cancer, Cytotoxicity

(18631)

In silico studies using active ingredients of medicinal plants to reduce allergy symptoms

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1. Farzanegan amin 2 high school, Khomeyni Shahr, Isfahan, Iran
2. Sama High School for Girls, Khomeyni Shahr, Isfahan, Iran
*Corresponding author

Background and Aim: Allergy is a very common disease in the world that occurs due to severe and abnormal reaction of the immune system to various harmless factors. Histamine released from mast cells after binding of IgE to an allergen can cause allergic reactions and inflammation. H1R antihistamines can inhibit allergic reactions by blocking this receptor. Plants contain a variety of active ingredients, many of which can bind to various receptors, including the H1R receptor. Therefore, the aim of this study was to find an antagonist of the active ingredients of medicinal plants with a higher affinity than the current histamine and antihistamines.
Methods: The active ingredients of the plants, their information, and structures were obtained through various articles and PubChem. After preparing the ligands and receptors, molecular docking was performed on them using Chimera and Auto Dock Vina software. The structure of the desired antihistamines was also obtained and docked with H1R. Thus, the binding affinity of active ingredients and antihistamines was obtained.
Results: Studies showed that the binding affinity of Cichoric acid, Violaxanthin, and BUTYL ISODECYL PHTHALATE to the H1R receptor was greater than the binding affinity of antihistamines such as Loratidine, Diphenhydramine, and Cetirizin.
Conclusion: Considering the role of histamine and H1R in inflammation and due to the binding affinity of selected ligands (Cichoric acid, Violaxanthin, and BUTYL ISODECYL PHTHALATE) compared with histamine and a number of available H1R antihistamines, it can be deduced that these three active substances can be effective. Therefore, further and laboratory studies to confirm the results of this bioinformatics study can play an effective role in the treatment and prevention of allergies.

Keywords: H1R, antihistamine, IgE, allergy

(18588)

Peripheral blood expressions of MicroRNA-146a and 218a in patient with COPD

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Background: COPD is mainly caused by cigarette smoking and is characterized by a chronic inflammation leading to obstruction of the small airways and destruction of lung parenchyma (emphysema). MicroRNAs are short single-stranded RNA molecules that negatively regulate gene expression at the post transcriptional level. This study aimed to evaluate the miR-146a and miR-218a expression levels in peripheral blood as biomarker in COPD Patients.

Methods: In this case-control study, blood samples were collected from 60 patients with COPD (Including 30 smoker and 30 Non-smoker patients) and 60 healthy controls (Including 30 smoker patients and 30 Non-smoker). Peripheral expression of miRNA-146a and miR-218a were measured using RT-PCR and the results were compared between cases and controls as well as between subgroups of the patients.

Results: We observed higher significantly expression levels of miRNA-146a in the COPD-smoking group versus COPD-Non smocking group (P=0.0004), smocking healthy controls ($P=8.03\times10^{-8}$) and Non-smocking healthy controls ($P=2.63\times10^{-8}$). Also, the mean expression levels of miRNA-146a were significantly higher in the COPD-Non smocking group versus smocking healthy controls ($P=1.85\times10^{-5}$), Non-smocking healthy controls ($P=1.15\times10^{-6}$) and all COPD patients versus all healthy controls ($P=9.32\times10^{-11}$). In addition, we found higher significantly expression levels of miRNA-218a in the COPD-smocking group versus COPD-Non smocking group (P=0.003), smocking healthy controls ($P=1\times10^{-4}$) and Non-smocking healthy controls ($P=7.15\times10^{-8}$). Similarly, the mean expression levels of miRNA-218a were significantly higher in the COPD-Non smocking group versus smocking healthy controls ($P=8\times10^{-4}$), Non-smocking healthy controls ($P=3.91\times10^{-6}$) and all COPD patients versus all healthy controls ($P=1.82\times10^{-9}$)

Conclusions: decreased expression levels of miR-146a and miR-218a in COPD patients indicate a potential for epigenetic alternations in pathogenesis of disease which could be considered as potential prognostic marker as well.

Keywords: Chronic obstructive pulmonary disease; miRNA-146a; miRNA-218a; Smoking

(18563)

Association Study of CTLA4 and FCεRIα Polymorphisms in Asthmatic Patients in Southwestern region of Iran

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Background: Asthma is a heterogeneous chronic pulmonary disease resulting from the interaction between genetic and environmental factors. The aim of this study was to investigate the polymorphisms of CTLA4 (SNP -318C >T, SNP +49 A>G) and, (SNP -344 T>C) genes in asthmatic patients in south west of Iran.

Methods: We studied 200 asthmatic patients with Arab and Bakhtiary ethnicities and 200 healthy controls. We selected the asthmatic patients and healthy controls based on spirometry test. Genomic DNA from whole blood samples was used to study the genotypes of patients and healthy controls using TaqMan assay.

Results: The results showed a significant difference between the cases and controls in SNP -318 C>T of CTLA4 gene (P=0.01). However, no significant difference was detected between the cases and controls in SNP -344 C>T of FCεR1α gene and SNP +49 A>G of CTLA4 gene. Stratification of genotypes was performed using the variables of age, sex, ethnicity and smoking and suggestive significant association was detected between SNP +49 A>G of CTLA4 gene and smoking. In addition, SNP +49 A>G was associated with sex and age.

Conclusion: The results indicated that the polymorphism of the SNP -318 C>T of CTLA4 gene could possibly play a role in developing asthma in the studied population. Meanwhile, smoking in individuals with SNP +49 A>G of CTLA4 gene can exacerbate the asthma.

Keywords: CTLA4, FCεRIα, TaqMan, polymorphism

(18555)

Evaluation The Effect of Supplements containing Vitamin D and Trace Elements in Patients with Moderate to Severe Asthma

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Background: Asthma is a common and major allergic disease in the world. We aimed to investigate the effect of supplements with vitamin D, folic acid, selenium, zinc, and copper in patients with moderate to severe asthma.

Methods: In this clinical trial study 70 patients above six years old with moderate to severe asthma, were divided into two groups, randomly; one group received daily Asmavitsyrup, 10 ml (Asmavit, Vitabiotics Ltd, London, UK), and the other group received daily vitamin D3,1200 IU for two months along with ordinary treatment for asthma. Clinical and physical examinations, immunological and biochemical tests were carried out for each patient before and after the treatment.

Results: The mean age of patients was 39.9± 14.7 years old and the mean disease duration was 8.8 ± 9.8 years. A significant increase in lung function, asthma control, and quality of life score tests was observed in both groups after the treatment ($P<0.05$). There was no significant difference in cytokines expression levels before and after the treatment ($P>0.05$). Serum levels of selenium and folic acid before treatment were associated with disease severity and serum level of vitamin D was significantly associated with an increase in forced expiratory volume in the first second (FEV1) after treatment ($P>0.05$). The level of oxidative stress in both groups significantly decreased with more reduction in the vitamin D group ($P<0.05$).

Conclusion: Supplements, especially vitamin D, in combination with standard asthma treatment, could be effective for improving the clinical symptoms and quality of life of asthmatic patients.

Keywords: Asthma, Vitamin D, Supplements, Oxidative stress

(18545)

Effects of vitamin D on the abundance of Treg cells in control group and atopic dermatitis patients

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Background: Atopic dermatitis (AD) is a chronic, relapsing, inflammatory, and severely pruritic cutaneous disease with an immunologic base. Recent studies have shown that vitamin D is a complementary treatment which can adjust the immune system. The purpose is studying the effects of vitamin D on the abundance of T reg cells in control group and patients suffering from atopic dermatitis.
Methods: We selected 20 patients suffering from atopic dermatitis and 20 healthy people, who had vitamin D level (less than 30 ng/ml) in labs. We filled the standard Atopic Dermatitis questionnaire (SCORAD) foe the experimental group. Later, both of the groups were given the vitamin D tablets and oral drops daily for 2 months with a dose of IU 1000. In blood sample of both the groups before and after the intervention to identify the percentage of CD4+CD25+Foxp3+Treg cells by Flow cytometry. At the end of the second month, the severity questionnaire was filled for the experimental group once again.
Results: Average score of SCORAD before prescribing vitamin D was 36.9±16.4 and 2 months after treating with vitamin D it decreased to 24.7±14.9 which had a meaningful abatement (P<0.001). also, the percentage of CD4+CD25+Foxp3+Treg cells before the intervention in the experimental group was (0.356±0.23) and in control group was (0.516±0.29) which was noticeably higher in the control group (P=0.067). After the intervention, percentage of Treg cells had a meaningful increase in experimental group (P=0.002, Diff=0.35) but in control group, despite the increase, it wasn't meaningful. (P=0.16, Diff=0.15)
Conclusion: It seems use of complementary vitamin D in normal bounds, can be recommend to use besides the routine treatments as a cheap and accessible treatment, in order to control the symptoms of atopic dermatitis

Keywords: Vitamin D, Atopic Dermatitis, SCORAD, Treg

(18529)

Seeking for appropriate Peanut-allergens characterization procedure in order to warrant the conformity of animal model with true Peanut allergy

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Background: Sounding the alarm, the intractable soaring-rate of Food-allergic ailments is dramatically on the rise. Although all foods can trigger an allergic response however, potent allergenic foods inducing IgE-mediated hypersensitivity-reactions, include Hen's Egg, Cow's Milk and Peanut (PN)-allergens. Concerning of coping with the above cited disorders and along with many attempts that lend themselves to enhance health care strategies, main focuses are being placed on the utilizing of meticulous identification and quantification approaches regarding to the recruiting of appropriate major allergens in food allergy model.

Methods: In our study, PN-proteins -as test allergens- were extracted from fresh/crude PNs, which is described shortly, as follows: Primarily, PN-bodies were smashed and pulverized by a mill and afterwards the procured paste was defatted by n-Hexane (1:3 v/v, 3 times). Subsequent to separation operation, remaining parts were dried out and deodorized by gentle heat-treatment. Following that, the obtained flour was mixed with Phosphate Buffered Saline (PBS), (1:10 w/v) and thereafter, exposed to extraction by shaking overnight at 4ºC. At the end, the resulted suspension was methodically, centrifuged twice for clarification purpose, as pointed below: Firstly: Centrifugation at 3500 r/min. and 4ºC for 30 min. Secondly: Centrifugation at 5000 r/min. and 4ºC for 20 min.

Results: The supernatant was filter-sterilized via 0.45-µm pore-size sterile syringe filters. Then, the gathered extract quantified by Macro-/Micro- Kjeldahl techniques and at the end stage of extraction operation, PN-allergens preparation (3 mg/ml*PBS) preserved as frozen at -20ºC until next uses.

Conclusion: Extraction/characterization of the suspected allergens from specifically, potent culprit allergenic food(s), configures a significant process in the allergen-detection systems for food-allergy modeling purposes. In this regard, urgent authentic Extraction methods for Peanut allergens characterization are necessary in-order-to guarantee the indispensable correspondence of animal model with deathful Peanut allergy and eventually, to curb accidental life-threatening risks, in PN-allergy sufferers.

Keywords: Allergen-extraction procedure, Macro-/Micro- Kjeldahl techniques, Peanut allergy model

(18481)

The importance of house dust mites in asthma and allergy

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Background: Asthma and allergies caused by arthropods are among the most common diseases and millions of people around the world suffer from it. House dust mites (HDM) are effective factors in the development of respiratory diseases such as asthma and inflammation of the respiratory tract. HDM are among the arthropods belonging to the class Arachnida, order Astigmata and family Pyroglyphidae, which grow in hot and humid areas. The aim of this study was to express the importance of house dust mites in respiratory diseases and allergies.
Methods: In this systematic review study, a search of various databases such as Science Direct, Google scholar, Scopus and SID was performed using keywords like house dust mites, mite allergy, and asthmatic mites.
Results: HMD cause runny nose, watery eyes, sneezing, respiratory problems and skin inflammation. The range of allergic reactions to mites varies from nasal allergies to asthma attacks, but mainly causes asthma, non-seasonal allergic rhinitis, and atopic dermatitis. In most people, inhaling dust containing mites, feces, and other related wastes and fungi can cause allergic reactions such as inflammation of the nasal mucosa and inflammation and itching of the skin. HMD also feed on the human body shell and other organic matter.
Conclusion: In general, the implementation of educational programs can play an important role in raising public awareness about environmental health and methods to prevent pollution of homes with HMD.

Keywords: allergy, asthma, house dust mites

(18478)

Determination of allergen fungi during normal and dust event days in Khorramabad, Iran

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Background: Allergies are a major problem in the world especially respiratory allergy. Among respiratory allergens, fungi have a special position. Despite the recent increases in fungi-induced allergic diseases such as certain form of asthma, there is no report yet in the khorramabad on concentration levels of fungi in relationship with health state. The aim of this study was to determine the air flora of Khorramabad in terms of allergenic fungi during 4 seasons in 2018 during normal and dusty days.
Methods: The samples were collected regularly every six days at three locations during April 2018–March 2019, with additional samplings during MED days. For phenotypic analyses, the Petri dishes were incubated at 25 °C for 72–120 h. Molecular identification of fungi was carried out using polymerase chain reaction (PCR).
Results: The average (±SD) of total fungal concentration was 460.9 (±493.2) CFU/m3.The fungi with the highest average concentrations included Cladosporium cladosporioides, Penicillium brevicompactum, and Cladosporium iridis, respectively. The average concentration of fungi during dust days (967.65 CFU/m3) was 3.6 times higher than those in normal days (267.10 CFU/m3). Aspergillus spp, Cladosporium spp and Alternaria spp were relatively more dominant during normal and dust days, respectively. Talaromyces albobiverticillius was detected for the first time in Iran.
Conclusion: Dust events lead to the changes in the air pollutants composition and mycobiota, identification of new fungi, and elevated allergen fungal concentrations that may extremely induce allergic diseases.

Keywords: Fungi, Dust Storm, Asthma, Khorramabad

(18431)

Immunochemical Characterization of Privet Pollen Allergens

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Background: Allergy to Privet (ligustrum vulgare) pollen is one of the most important causes of respiratory allergy in tropical countries. They are widely used as either ornamental trees or hedges in parks and gardens in most parts of the Iran, especially in the north of the country and also in the Tehran. This study was designed to evaluate IgE banding proteins of privet pollen extract.
Methods: Forty-five patients with allergic symptoms and positive skin prick tests (SPT) for privet pollen extract participated in the study. Crude pollen extract was prepared from local privet trees and used for the evaluation of allergenic profiles of privet pollen extract by Sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) and IgE immunoblotting.
Results: There were several protein bands in privet pollen extract using SDS-PAGE with the approximate range of molecular weight of 10 to 75 kDa. The most frequent IgE reactive bands among the patients' sera were approximately 10 and 66 kDa. However, there were other IgE reactive protein bands among the patients' sera with molecular weights of 10, 15, 20, 40 and 60 kDa. There are several IgE-binding proteins in privet pollen extract.
Conclusion: Results of this study indicate that several proteins such as 10,15, 20, 40, and 60 kDa could be used as diagnostic and therapeutic reagents for patients allergic to privet.

Keywords: Privet, Allergen, SDS-PAGE, Pollen

(18425)

Identification of the most common allergenic components of Acer velutinum

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Background: Tree type pollens have been identified as the greatest inducers of allergic diseases worldwide. Acer velutinum trees (Persian maple), the Sapindaceae family, are an important source of allergic pollen in Iran. This study aimed to identify the IgE-reactive components of Acer velutinum pollen among patients with respiratory allergic diseases.
Methods: Twenty-two patients with a clinical history of reaction and a positive skin-prick test (SPT) to maple pollen extract were included in this study. Identification of IgE-binding proteins in Acer velutinum extract was performed by immunoblotting using sera from maple pollen-sensitive patients. The IgE-reacted band was detected using chemiluminescence assay.
Results: Several protein bands in Acer velutinum extract were determined by SDS-PAGE with the approximate range of molecular weight of 10-250 kDa. The 72kDa band was the most frequent allergen among other IgE-binding proteins of Acer velutinum pollen extract.
Conclusion: Identification of a 72 kDa band as the most common allergen of Acer velutinum pollen extract helps diagnosis and treatment of patients who showed IgE reactivity with this allergen.

Keywords: Pollen, Allergy, Acer velutinum, IgE

(18326)

Immunochemical Characterization of Populus nigra Pollen Allergens

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Background: Pollen is one of the most common allergens that cause respiratory allergies worldwide. Pollen grains from poplars have been reported as important sources of pollinosis in many countries.
Objective: The aim of the present study was to determine the immunochemical characterization of Populus nigra (P. nigra) pollen proteins.
Methods: In this study, the pollen extract of P. nigra was analyzed by SDS-PAGE, and the allergenic profile was determined by IgE immunoblotting and specific ELISA using the sera of twenty allergic patients.
Results: There were several resolved protein fractions on SDS-PAGE which ranged from 8 to 100 kDa in P. nigra pollen extract. Several allergenic protein bands with molecular weights approximately between 14 to100 kDa were recognized by IgE-specific antibodies from P. nigra allergic patients in the immunoblot assay. Proteins with molecular weights about 14 (13, 65%), 17 (11, 55%), 27 (12, 60%) and 72 (10, 50%) kDa showed the highest reaction with specific IgE antibodies in the immunoblotting assay. Moreover, all the twenty patients had high specific IgE levels against P. nigra pollen proteins with a mean of 1.58 ± 0.13.
Conclusion:
The findings suggest that several proteins such as 14, 17, 27, and 72 kDa proteins could be used as diagnostic and therapeutic reagents for patients allergic to P. nigra pollen.

Keywords: Allergen, Pollen, Populus nigra

(14361)

Association between Chronic Rhinosinusitis and Allergic Diseases in Adults: A GA²LEN Study

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Background: Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the mucosa of the nose and paranasal sinuses. Population-based studies using the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) criteria for the assessment of CRS and allergic diseases developed by GA²LEN.

Methods: A multistage, stratified cluster, random sampling method was used to select the study participants from adult individuals living in Bushehr, Iran. The Global Allergy and Asthma European Network (GA²LEN) questionnaire, based on EPOS criteria was completed by 5,201 participants, and the prevalence of CRS and allergic diseases were assessed. Moreover, the association between CRS and allergy-related conditions was estimated by using multiple logistic regression models.

Results: The overall CRS prevalence was 28.4%, while the prevalence of asthma, allergic rhinitis (AR) and eczema were 10%, 28.8% and 29%, respectively. Additionally, the self-reported physician-diagnosed CRS and asthma were 20.0% (95%CI=19.0–21.0) and 3.9% (95%CI= 2.1- 2.5), respectively. Interestingly, CRS was associated with asthma [OR=4.1, 95% confidence interval (CI)=3.4–5.0, P<0.001], AR (OR=4.9, 95%CI=4.3–5.6, P<0.001), and eczema (OR=3.4, 95%CI=3.0–3.9, P<0.001).

Conclusions: The present study showed that the CRS and AR prevalence in Bushehr, Iran was relatively high. Moreover, these results support the idea that CRS may be a major public health problem in Iran. And, the strong association between CRS and allergic diseases play an important role in the health and economic burdens.

Keywords: Chronic rhinosinusitis, GA²LEN, Allergic Diseases

(18324)

Molecular Cloning, Expression and IgE Binding Reactivity of Pop n 2: A New Allergen of Populus nigra Pollen

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Background: Profilins from numerous species are known to be allergens, including pollen and food allergens, and profilin is thus referred to as a pan allergen. Pollen of Populus nigra (P. nigra), is an important allergenic tree pollen in Iran. This study aimed to clone, express and evaluate the IgE-binding capacity of recombinant Pop n 2 (P. nigra allergenic profilin).

Methods: Specific ELISA and Immunoblotting assays were applied to determine the immunoreactivity of sera from 20 patients who were allergic to P. nigra pollen. The P. nigra profilin-coding sequence was cloned into PTZ57R/T vector and amplified. The cDNA of P. nigra pollen profilin was then expressed in Escherichia coli using pET-21b (+) vector and purified by affinity chromatography. IgE binding capacity of the recombinant P. nigra profilin (rPop n 2) was analyzed by specific ELISA, immunoblotting, and inhibition assays.

Results: cDNA nucleotide sequencing revealed an open reading frame of 396bp encoding for 131 amino acids which belong to the profilin family. Sixteen patients (65 %, 13/20) had significant specific IgE levels for rPop n 2. Immunodetection and inhibition assays indicated that purified rPop n 2 might be similar to that in the crude extract.

Conclusion: Our data revealed that Pop n 2 is a significant allergen in the P. nigra pollen extract. Moreover, we observed that the recombinant Pop n 2 produced by the pET-21b (+) vector in the E. coli system acts as its natural counterpart.

(18322)

Chemerin Receptor 23 (ChemR23) gene polymorphisms and risk of allergic rhinitis

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Background: Allergic rhinitis (AR) is the most common upper inflammatory disorder. The omega-3 derived resolvins have been shown to have potent anti-*inflammatory* and pro-*resolution* actions through binding to Chemerin Receptor 23 (ChemR23) in several animal models of *inflammation*. In the present study we aimed to evaluate the possible correlation between single nucleotide polymorphisms (SNPs) of the ChemR23 gene and AR risk in the Kermanshah population of Iran.
Methods: We designed a case-control study including 130 AR patients and 130 healthy controls to genotype four SNPs in ChemR23 gene (rs4373981 G> C, rs73201532 C>T, rs35121177 G>A, rs4964676 G>A) by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).
Results: Our results showed no significant association regarding the distribution of allele and genotype frequencies of four SNPs in the ChemR23 gene (rs4373981 G> C, rs73201532 C>T, rs35121177 G>A, rs4964676 G>A) with AR ($p>0.05$).
Conclusion: Our research was the first study that investigated the association of between ChemR23 gene SNPs with AR. However, we did not found any correlation between of four genetic variants of ChemR23 with AR in an Iranian population.

Keyword: Allergic rhinitis, Chemerin Receptor 23, single nucleotide polymorphisms, PCR-RFLP

(18294)

Single nucleotide polymorphisms of TSLP gene are associated with asthma in Iranian population

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Background: Thymic stromal lymphopoietin (TSLP) is an epithelial cytokine encoded by a gene located in 5q22.1 chromosome. It is secreted by different cell types such as epithelial cells, mast cells, basophils, keratinocytes, and dendritic cells (DCs). several studies have shown that certain single nucleotide polymorphisms (SNPs) in TSLP gene may result in lower risk and decreased severity of asthma.

Methods: We designed a case-control study to evaluate the attribution of two commonly examined SNPs (rs2289276 & rs2289278) of the TSLP gene and risk of asthma in the Iranian population. We used TaqMan genotyping assay to Genotype the TSLP gene in 126 adult asthmatic patients and 300 healthy individuals. In addition, total serum IgE and eosinophil count were assessed.

Results: There was an inverse association between and TT genotype of rs2289276 and the risk of asthma (p value= 0.002). Similar inverse association was detected in subgroups of atopic (p value= 0.001) and non-atopic (p value= 0.005) asthma. There was a significant sex-specific association between rs2290276 and asthma in females (p= 0.004). There was no association between rs2289278 and the risk of asthma.

Conclusion: In conclusion, our findings showed that rs2290276 has a protective association with risk of asthma in the Iranian population.

Keywords: Asthma; Non-allergic asthma; Single nucleotide polymorphism; Thymic stromal lymphopoietin

(18286)

IL-33 polymorphism and its association with levels of IL-33 in patients with asthma in Tehran province, Iran

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Background: Allergic asthma is an airways inflammatory disease. Also, Interleukin (IL)-33 is a cytokine with both pro- and anti-inflammatory effects involved in the pathogenesis of auto immune diseases. The aim of the present study was to investigate the frequency of rs1342326 polymorphism of IL-33 gene and its association with levels of IL-33 in patients with Asthma and healthy subjects in Tehran Province.

Methods: In this case-control study, peripheral blood samples were collected from 90 patients with Asthma and 90 healthy subjects, who acted as a control group. SNP at rs1342326 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and serum concentrations of IL-33 were measured by the enzyme-linked immunosorbent assay (ELISA) kits (BosterBio, California, US).

Results: The results of the present study showed that the mean serum levels of IL-33 was significantly higher in Asthma patients with T/G and T/T genotypes or T allele at rs1342326 as compared with healthy subjects ($P<0.001$, $P<0.001$, $P<0.01$, respectively).

Conclusion: The results indicated that SNP rs1342326 may directly or indirectly influence the susceptibility to Asthma and the serum levels of IL-33.

Keywords: Interleukin-33, Polymorphism, Asthma, PCR-RFLP, ELISA

(18262)

Evaluation of the safety and the efficacy of newly developed domestic allergenic extracts for skin prick testing

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Background: Allergic disorders are common health problems around the world with significant socio-economic impacts. Skin prick test is the best diagnostic method which used allergenic extract. Regarding the effect of geo-climatic factors and source material of quality of allergenic extracts, the aim of study was to study the safety and efficacy of some in-house developed allergenic extract.
Methods: Fifty five different allergenic extracts including common regional pollen, foods, dog and cat hair as well as positive and negative extracts were prepared from domestic sources using optimum extraction methods. All extracts passed the stability and sterility testing and sterile final products containing 50% glycerin in two concentrations (10 w/v and 20 w/v) were used. Skin prick testing was performed on volunteer and immediate or late side effects were recorded.
Results: In total, 56 students (mean age: 21.2±2.3y, M/F ratio: 1.07) participated in this study. For inhalant allergens, all extracts except dog hair extract created positive response and Salsola kali (Russian thistle) and Fraxinius velutina (Ash tree) were the most common grass and tree pollen extracts. Among 18 different food extracts, five of them including Egg white, Tomato, Fig, Melon and Green pepper caused skin reactivity in just one person. None of the participants reported any immediate or late side effects including large local reaction or systemic response.
Conclusion: The result of the current study confirmed the safety of all in-house developed allergenic extracts. In the case of efficacy, almost all inhalant and five food allergens caused positive skin response.

Keywords: Allergenic extract, Skin prick test, in-house extract

(18236)

Immunotherapy in Allergic Rhinitis: It's Effect on the Immune System and Clinical Symptoms

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Background: Allergic rhinitis is one of the most common allergic diseases and characterized by sneezing, rhinorrhea, nasal congestion and nasopharyngeal itching. Subcutaneous immunotherapy (SCIT) for specific allergens is an effective treatment and induces the inhibitory effect of T regulatory lymphocytes and decreases clinical symptoms in allergic rhinitis. In this study effect of subcutaneous immunotherapy with specific allergens on clinical symptoms and T regulatory and T Helper cells cytokines, in patients with allergic rhinitis are evaluated. Methods: In this study, 30 patients with moderate to severe allergic rhinitis according to clinical criteria and positive skin prick test for aeroallergens were selected and treated by SCIT. Clinical symptoms and T cells cytokines IL4, IL17, IFN gamma, TGF beta, GITR, FOXP3 and IL-10 (by RT-PCR) were evaluated before and one year after initiation of treatment. Results: Thirty (30) patients with allergic rhinitis at age range 15-45 years old were treated by SCIT, and 23 (14 female, 9 male) patients continued the study, and 7 patients did not continue treatment. After immunotherapy, clinical symptoms decreased significantly. The specific cytokines TGF beta and IL10 levels increased and changes were statistically significant. (Respectively $P = 0.013$ and $P = 0.05$) The IL17 level was also increased, but not statistically significant. ($P = 0.8$) IFN gamma, IL4, GITR, FOXP3, all decreased, but the changes were not statistically significant ($P > 0.05$). Conclusion: Subcutaneous Immunotherapy for specific allergens decreases clinical symptoms in patients with allergic rhinitis and induces tolerance in T lymphocytes, especially by increasing T regulatory cells cytokines, TGF beta and IL10.

Keywords: allergic rhinitis, cytokine, subcutaneous immunotherapy

(18199)

Association of ALOX-15 Gene polymorphisms (Rs2619112 A> G and Rs7217186 C>T) with Allergic Rhinitis

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Background: Allergic rhinitis (AR) is an inflammatory disorder of the mucosal nose characterized with symptoms such as sneezing, congestion, itching and rhinorrhea. that occurs in genetically predisposed individuals due to exposure to environmental allergens. Inflammation is relieved by essential fatty-acids-derived immunoresolvents such as resolvins, protectins, lipoxins, and maresins. 15-lipoxygenase (ALOX) is a member of the lipid peroxidizing enzyme family and is involved in the biosynthetic pathway of these mediators, including protectins and neuroprotectins, and some rezolvins. The present study aimed to investigate the association of two single nucleotide polymorphisms (SNPs) in the ALOX15 gene and susceptibility to Allergic rhinitis in Kermanshah population of Iran.
Methods: A total of 130 AR patients and 130 control subjects were chosen in the case-control study, and two SNPs, rs2619112: A>G and rs7217186: C>T, were selected and genotyped by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).
Results: Our results showed that the CT genotype of rs7217186: C>T significantly associated with increased risk of AR compared with the CC genotype (p= 0.037, OR = 1.943, CI = 1.038-0.638). In contrast, there was no strong evidence for the association rs2619112: A>G with susceptibility to AR (p>0.05).
Conclusion: Our finding indicated that ALOX15 rs7217186 polymorphism may be a potential biomarker for susceptibility to AR in an Iranian population.

Keywords: Allergic rhinitis; Arachidonate 15-lipoxygenase; Single nucleotide polymorphism; PCR-RFLP

(18179)

Evaluation of size and dose effects of rChe a 3 allergen loaded PLGA nanoparticles on modulation of Th2 immune responses by sublingual immunotherapy in mouse model of rhinitis allergic

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Background: Currently, Allergen-specific sublingual immunotherapy by nanoparticles (NPs) such as poly (lactide-co-glycolide) (PLGA) is widely considered for delivery of allergen in sublingual immunotherapy of allergic rhinitis. The aim of this study was to evaluate the effect of PLGA NPs containing rChe a 3 allergen in different sizes and doses in improving sublingual allergy treatment.
Method: rChe a 3 allergen loaded-PLGA NPs were prepared in different sizes (about 200, 400, and 800 nm) by double emulsion-solvent evaporation method. Formulations with optimized size were characterized for morphology, encapsulation efficiency (EE) and release profile. After sensitized BALB/c mice to rChe a 3 as allergen, rChe a 3-loaded PLGA NPs in different sizes and doses (12.5, 25, and 50 µg/doses) were administered sublingually. Serum levels of antibodies (IgG1, IgG2a and specific-allergen IgE), as well as splenocytes proliferation and cytokines production (IL-2, IL-4, IL-10, IFN-γ, and TGF-β) in spleen cells were analyzed by ELISA. Bronchoalveolar Lavage Fluid and Nasopharyngeal lavage collected for total cell and eosinophil cell counting, also the lungs and nasal mucosa harvested for histological analysis.
Results: The results showed that EE of rChe a 3 allergen loaded into PLGA NPs were closely related to NP size. SLIT treatment of most synthesized formulations significantly increased the serum IgG2a level and TGF-β and IFN-γ in restimulated splenocytes, also reduced serum IgG1 and IgE antibodies and IL-4 levels in spleen compared to the PBS-treated group. The best results were obtained by PLGA NPs with a mean diameter of 200 nm containing 12.5 µg/dose allergen. The study of bronchial fluid and nasal lavage showed a decrease in total cell and eosinophil count. Also, the histological examination indicates the reduction of eosinophilic infiltration and the improvement of allergic rhinitis.
Conclusion: The results showed that the PLGA NPs containing rChe a 3 with a size of 200 nm could effectively enhance immunomodulatory response at low dose of allergen (12.5 and 25µg/dose).

Keywords: Allergic Rhinitis; Different size and dose of PLGA-rChe a 3; Sublingual immunotherapy; IgE

(18159)

Study effect of Ocimum basilicum seeds on mucus production and cytokine gene expression in allergic asthma mice model

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Background: Allergic asthma is a complicated disease characterized by coughing, wheezing, airway inflammation, mucus hyper-secretion and increased airway hyperresponsiveness (AHR). Basil seed, or Ocimum basilicum (OB), has an anti-inflammatory effect that is utilized in traditional medicine. The aim of this study was to investigate the effects of OB on IL-4, IL-5, IL-13 and MUC5a gene expression in an asthma model.
Materials and Methods: Eighteen female BALB/c mice were divided into three groups as follows: an untreated asthmatic group, a healthy group and an asthmatic group receiving OB. Broncho-alveolar lavage fluid (BALF) was collected and Real-Time PCR was done for IL-4, 5, 13 and mucus (MUC5a) genes, and lung histopathological sections were prepared.
Results: Asthmatic mice treated with OB had suppression of cytokines and mucus gene expression (IL-4: 2.90 ± 1.08, IL-5: 1.11 ± 0.37, IL-13 0.72 ± 0.19 and mucus: 1.83 ± 1.08) in comparison to the untreated asthmatic group (IL-4: 8.00 ± 2.54, IL-5: 2.91 ± 0.46, IL-13 2.00 ± 0.22and mucus: 12.24 ± 1.88). In the histopathological section, mucus hyper-secretion and goblet cell hyperplasia were reduced in the OB-treated group in comparison to untreated asthmatic group. Th2 cytokines and mucus gene expression were reduced in the OB-treated group in comparison to untreated asthmatic group. Mucus hyper-secretion and goblet cell hyperplasia were regulated by OB treatment in asthmatic mice.
Conclusion: OB showed immunomodulatory and anti-inflammatory effects in allergic asthma and could reverse airway obstruction.

Keywords: Allergy; Gene; Asthma; Herbal Medicine

(18158)

Investigation of the effect of probiotic yogurt and fenugreek on allergic asthma

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Background: Asthma as the variable degrees of airway obstruction is reversible and allergic asthma is a common form of asthma. Yogurt is coagulated milk and fenugreek as a plant is used in traditional medicine. Oral administration of yogurt (as food) can provide probiotic agents that have the main effects on immune responses. In this study, the effect of yogurt and fenugreek on asthma was studied.
Materials and Methods: After producing of asthma model in BALB/c mice in 4 groups, groups were treated with yogurt, yogurt-probiotics, and yogurt-fenugreek. At least, total IgE in serum, IL-4, 5, 13 in BAL (Broncho-Alveolar lavage) fluid was measured. Histopathological sections were prepared and eosinophilic infiltration and mucus-secreting were investigated.
Results: Eosinophilic infiltration and mucus hyper-secretion were decreased in treated groups. Total IgE in serum was decreased in asthma-yogurt-probiotic and asthma-yogurt-fenugreek groups in comparison with asthmatic and asthma-yogurt groups. The amount of IL-4 in BAL of the asthma-yogurt-fenugreek group was decreased. The amount of IL-5 in BAL of the asthma-yogurt-probiotic and asthma-yogurt-fenugreek groups was decreased. The amount of IL-13 was decreased significantly in three treated groups.
Conclusion: This study showed that yogurt with fenugreek and probiotic has a strong effect on suppression of progression of airway inflammation and asthma pathophysiology.

Keywords: Herbal Medicine, Probiotic, Allergy, food, Cow’s milk yogurt

(18024)

Semaphorin-3A a promising tool of therapy for allergic rhinitis

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Background: Semaphorin-3A (Sema-3A), a secreted member of the semaphorin family, is well known for having regulatory functions at all stages of the immune response. Recent evidence has demonstrated the involvement of Sema-3A in the pathogenesis of allergic rhinitis (AR), a chronic inflammatory disease of the nasal mucosa. The present review aimed to investigate the expression status of Sema-3A, as well as the therapeutic application of this molecule in AR disease.
Methods: A comprehensive literature search was done in various databases such as Google Scholar, Scopus, PubMed, and Web of Science to find studies that investigated the Sema-3A in AR disease.
Results: We found only two original articles on this subject, in which the expression of Sema-3A was reduced in both nasal mucosa epithelium layer and serum of AR murine models and patients with AR compared to their controls. Besides, intranasal (I.N.) administration of recombinant Sema-3A (rSema-3A) into AR mouse models decreased the scores of AR clinical symptoms such as sneezing and nasal itching, eosinophils infiltration, interleukin (IL)-4 and IL-17 levels, as well as T helper type 2 (Th2) cell activation. In contrast, rSema-3A treatment increased the percentage of regulatory T (Treg) cells, interferon (IFN)-γ and IL-10 levels, and the ratios of Th1/Th2 cells.
Conclusion: In summary, this survey indicates that I.N. injection of rSema-3A may compensate for the diminished expression of Sema-3A in AR, thereby contributing to alleviating disease symptoms. Altogether, these findings suggest that Sema-3A exerts a critical immunoregulatory role in AR; hence, it could be regarded as a novel therapeutic agent to treat AR.

Keywords: Allergic rhinitis, Semaphorin-3A, Nasal itching, Therapeutic

(17960)

Association between neuropsychological function and eczema in young women

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Background: Allergic disorders may have a bidirectional causal relationship with mental diseases. We aimed to judge the associations between neuropsychological function and quality of life with the presence of eczema in young women.
Methods: The diagnosis of eczema was confirmed by an expert allergist. The presence and severity of depression, anxiety, stress, and insomnia and day time sleepiness were explored using validated questionnaires. Cognitive abilities and quality of life were assessed by standard instruments.
Results: Among 181 female young participants, the prevalence of eczema was 14.9%. Additionally, the eczema group obtained a higher score on the depression and stress scale compared to those without it ($p<0.05$). Eczema cases were more likely than healthy individuals to obtain lower cognitive ability ($p<0.05$). Logistic regression analysis showed that individuals with any allergic disorder were more likely than healthy individuals to have insomnia (odds ratio [OR] =2.3; 95% CI: 1.2–4.3).
Conclusion: There was a high prevalence of psychiatric disorders such as depression and stress problems among eczema women.

Keywords: Depression, insomnia, quality of life, anxiety, Asthma

(16916)

Expression of plasma-derived exosomal miR-125b is associated with inflammatory markers in severe asthma patients

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Introduction: Recently, it has been reported that microRNAs (miRNAs) are important epigenetic regulators of gene expression. The changes in the miRNAs cargo of exosomes can exert a regulatory role in inflammatory reactions. Therefore these small molecules may play important role in the pathogenesis of severe asthma.

Objective: We aimed to investigate the possible role of selected exosomal miRNAs in inflammatory reactions. Our study showed that the change in the expression of exosomal mir125b expression is associated with the changes in serum immuno-inflammatory markers.

Method: Severe asthma patients (n=30), confirmed by clinical and laboratory criteria, and a group of age-matched healthy subjects (n=30) was enrolled as a control group. The patients referred to clinical asthma and allergy department, Masih Daneshvari Hospital, Tehran. Blood specimens were collected from each participant for the estimation of high sensitive C-reactive protein (hs-CRP) and total IgE. Plasma exosomal fractions were separated by ultra-centrifugation and processed for estimation of the expression level of miR-125b using quantitative real time-PCR (qRT-PCR).

Results: The expression of miR-125b was significantly higher in asthma patients compared to controls ($p< 0.0001$). Likewise, the hs-CRP and total IgE were significantly higher in asthma patients compared to normal individuals ($p< 0.0001$). The correlation analysis revealed that there is a significant association between the expression of serum levels of miR-125b with the serum hs-CRP (r-value 0.86 and $p< 0.0001$) and IgE (r-value 0.68 and $p< 0.0001$).

Conclusions: Differences in the plasma exosomal miRNA, in particular miR-125b and its relationship with inflammatory markers in severe asthma indicate the regulatory action of a specific miRNA in inflammatory pathways related to the pathogenesis of severe asthma.

Keywords: severe asthma, exosome, micro RNA, IgE, hs-CRP

(16844)

Relation of sleep disorders and asthma in young female

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Background: There has been a steady rise in the prevalence of atopy, in particular allergic asthma in recent decades. The study was conducted to explore the association between neuropsychological function tests and quality of life with the presence of asthma in young women.
Methods: A diagnosis of asthma was confirmed by an expert allergist. The presence and intensity of depression, anxiety, stress, insomnia and sleepiness were evaluated using validated questionnaires. Cognitive abilities and quality of life were assessed through standard instruments.
Results: Among 181 female young participants aged between 18-25 years old, the prevalence of asthma was 2.8%. Also, fifty four (29.8%) individuals had at least one type of allergic disorders. Asthmatic patients also have significantly higher insomnia severity and lower physical health-related quality of life than normal persons ($p<0.05$).
Conclusion: There was a high prevalence of psychiatric disorders such as sleep problems among asthmatic women, and a lower quality of life, that may be associated with it.

Keywords: Depression; insomnia; quality of life; anxiety; Asthma

(16819)

A Western dietary pattern is related with allergic disorders

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Background: There has been an elevating prevalence of allergic complications worldwide. Diet has been found as one probable modifier factor contributed in the pathogenesis of this disease. The aim of current was to explore the associations of dietary patterns with the presence of allergy in young women.
Method: This study was conducted on 181 female university students. The allergic diseases assessed were allergic rhinitis, asthma and eczema, and these were diagnosed by an expert allergist. Dietary information was gathered using a 65-item validated FFQ. Exploratory factor analysis was used to assess the associations among food/nutrition variables.
Results: Two main dietary patterns were identified according to principal component factor analysis, and were labeled as “Traditional” and “Western”. Odds ratio of having allergic rhinitis was 2.5 (95% CI: 1.1-5.1) for the highest versus lowest tertile of the Western dietary pattern score. Although, there were no significant relationships between the traditional dietary pattern and allergic rhinitis, asthma or eczema (P>0.05)
Conclusions: Our findings indicate a possible role of western dietary pattern, characterized by being rich in dairy products, snack, nuts and sugar in the development of allergic rhinitis.

Keywords: Allergic rhinitis; Fast food; Diary product; IgE; life style

(16728)

Some Revealed Strategy to Use for Desensitization of Cow Milk Allergy in Children

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Background: Cow milk allergy (CMA) is one of the rifest allergies in kids that affects about 2-3% of the child population. CMA can affect quality of life strongly. Severe-specific IgE response and low serum levels of cow's milk (CM)-specific IgG4 are related to persistent CMA. The objective of this review is to highlight some methods in Cow milk allergy's management and its prevention.
Methods: A comprehensive search was done in electronic databases PubMed, Scopus, Science Direct and Web of science with the keywords "Desensitization" and "Cow milk Allergy" from 2014 to 2019. 14 original articles that were related to prevention of CMA ,8 Articles were included in the study, 6 Review articles were excluded.
Results: The first therapeutic choice for food allergy is avoidance of cow milk consumption. However, an absolute avoidance diet is difficult and negatively affects the quality of life. Oral immunotherapy (OIT) is a new alternative approach in patients with food allergy. In this method, desensitization began by 1 drop of the defined dilution and continued increase in children who their CMA was confirmed by a positive skin prick test (SPT).In some articles, alternating the processed horse milk (HM) with cow's milk has suggested. Studies have shown that HM proteins and CM proteins have similar immune-reactive epitopes, but the use of technological processing for the modification of HM may lead to the development of a product with decreased immunogenic potential.
Conclusion: It is still not known whether the OIT treatment method is transient or permanent. Some reports show that children who were treated with oral immunotherapy for cows' milk allergy showed long-term desensitization, however, according to some experiences, the tolerance obtained through the desensitizing treatment is transient and so the regular allergen exposure is initial for its maintenance. Finally, it should be noted that the data about the replacement of horse milk with cow milk was insufficient and more studies are needed to prove this suggestion.

Keywords: Children, Cow Milk Allergy, Desensitization

(16719)

Allergic reactions due to Leech bite

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Background: Allergic reaction of leech bite is frequently reported due to complication of leech therapy and also unwanted leech infestation. Regularly the urticarial papules, is common and itching lasts less than 24 h. Dermal infection could induced due to leech gut flora such as Aeromonas spp and histamine as a component of leech saliva in case of leech biting process.
Methods: A 30-years-old medicinal leech breeder woman who had diabetes with complaining of inflammation, swelling, pain, and redness in the back her left hand also have a mild trouble in breathing and chest tightness, due to lasted of healing Y-shaped wound more than 5 days and intolerable pain and morbidity was referred to Ghaem Hospital in Mashhad in August 2018. In her history appeared she was bitten by a medicinal leech 5 days ago. Microbiological examination confirmed Aeromona spp. Antibiotic and corticosteroid was prescribed as ciprofloxacin 500mg and dexamethasone 4 mg/ml injection with standard protocol.
Results: One day after receiving the medicine, the pain and swelling subsided, but the redness and urticaria lasted until the third day. There was itching on the fourth day. On the fifth day, there was no itching, there were also signs of wound healing and fade of the bite site. Therapy successfully cured the patient lesion.
Conclusion: Leech breeders are more exposed with unwanted leech bites. Allergic reaction and cellulitis is common and could regard as an occupational disease. In some cases underlying diabetes and people with inadequate immune systems the risk of death due to anaphylactic shock and sepsis is high as previous reported in literature. The study pointed out hazards of leech bites and proposed preventative measures should be taken such as using gloves and boots while labors work on the farm to decrease risk of such allergic reaction.

Keywords: Leech, Cellulitis, allergic reaction

(16709)

Evaluation of anxiety and quality of life in people with allergic asthma

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Background: Asthma is a chronic inflammatory disorder of the airways that is caused or exacerbated by a number of environmental factors in people who are genetically predisposed. Asthma causes difficulty breathing and also affects physical activity. There are several types, one of which is allergic asthma. The aim of this study was to determine the relationship between anxiety and quality of life in people with allergic asthma.
Methods: This descriptive-analytical study was performed on 30 patients with allergic asthma who were selected by observation and interview. In this study, the WHO Quality of Life Questionnaire (WHOQOL_BREF) and Beck Anxiety Inventory were used. Finally, the scores obtained from the questionnaires were analyzed by SPSS .16 software.
Result: The results of this study show that the rate of anxiety in people with allergic asthma is high and this anxiety also affects the quality of life. Also, according to the data, the average anxiety scores in women are higher than men and the quality of life was better in men than women in the study.
Conclusion: Given the high level of anxiety and its impact on the quality of life of people with allergic asthma, providing training on anxiety management and coping skills and a better lifestyle to improve quality of life should be a priority.

Keywords: Quality of life, Anxiety, Allergic asthma

(16598)

Prevalence of pollen-induced allergic rhinitis to 10 common regional plants in Iran

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Background: Allergic disorders are among the most common health problem with a high impact on patients' quality of life and a significant economic burden. Pollen is the most important trigger of allergic symptoms. The type of allergenic pollen in each area is mainly determined by geo-climatic factors and knowing the allergenic potency of common pollen in each area is very important for the prevention and management of allergic symptoms. This study aimed to evaluate the rate of skin sensitivity to ten different pollens.
Methods: Ten different pollens from common regional plant were collected and after purification, the aqueous extract was prepared from each pollen. Skin prick test with ten domestic extracts as well as some commercial extracts was performed on the participants. The study was approved by the ethics committee of Birjand University of Medical Sciences and all participants received consent form.
Results: One hundred and twelve volunteer's medical students (mean age: 19.13± 4 years, M/F ratio: 1.05) enrolled in this study. The overall frequency of sensitization to any allergenic extracts was 80.59%. In the case of domestic pollen, the highest rate of skin sensitization was for Eucalyptus pollen, Rosa damascene flowers pollen, and Persian jasmine pollen (59.3%, 53.1%, and 50.0%, respectively). In the case of commercial extract, Amaranthus retroflexus and the mixture of trees' pollen were the most common (66.6% and 45.7%, respectively).
Conclusion: The results of this study showed high allergic potency of some common regional plants including Rose flower, Eucalyptus tree, and Jasmin flower.

Keywords: Allergy, Allergic rhinitis, Eczema, Pollen, Prevalence, East of Iran

(15466)

The pattern of allergic sensitization by skin prick test and immunoblotting method among patients with atopic dermatitis

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Background: Atopic dermatitis (AD) is a common allergic disorder. Exposure to different allergens has a significant role in the pathogenesis of AD. Detection of responsible allergens in patients suffering from AD by reliable methods has a fundamental role in the prevention, management and treatment of AD. The purpose of this study was to determine the most common allergens by skin prick test (SPT) and immunoblotting among AD patients referring to the allergy clinic of Birjand city, Iran.
Methods: Presence of AD was confirmed by an expert allergist. Serum levels of total and specific IgE (sIgE) against 30 food and inhalant allergens were evaluated by a commercial immunoblotting kit (AlleisaScreen). SPT was performed by a battery of 17 allergens.
Results: In total 34 patients (mean age, 28.76±17.36 years; range, 1–60 years; F/M ratio: 0.88) with AD were enrolled in this study. The sensitization rate to at least one fungus, pollen, food or indoor (house dust mite (HDM), cockroach, cat, dog and latex) allergen by the immunoblotting method were 32.35%, 61.76%, 52.94%, and 47.05%, respectively. The most prevalent allergens were ragweed (52.94), Olive tree (41.16), Eucalyptus (35.29), Date palm (35.29) and grass mix (32.28). Overall sensitivity, specificity, PPV (Positive Predictive Value), NPV (Negative Predictive Value) and kappa value of the immunoblotting method in comparison to SPT were 69.18%, 91.01%, 53.81%, 94.81% and 0.50, respectively.
Conclusion: In conclusion, 85.29% of the studied population was sensitized to at least one allergen. Pollens and Date palm were the most common allergens among AD patients but the pattern of sensitization in SPT and immunoblotting was not exactly similar. Detection of allergens in which patients are sensitized to them and avoidance can help the management of the disease and its symptoms.

Keywords: Allergen; Atopic dermatitis; IgE; Immunoblotting, Skin prick test

(14389)

Human amniotic membrane-mesenchymal stem cells-conditioned medium reduces fibrosis in ovalbumin-induced asthma in Balb/C mice

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Background: Paracrine factors secreted by mesenchymal stem cells (MSCs) have an extensive range of immunomodulatory, anti-inflammatory and anti-fibrotic properties; so the conditioned medium (CM) of these cells might have functional capabilities. The amniotic membrane is considered as the source of stem cells, thus we examined the effects of human amniotic membrane mesenchymal stem cell's conditioned medium (hAM-MSCs-CM) on ovalbumin (OVA)-induced asthma.

Methods: Forty male Balb/C mice were randomly divided into four groups including: 1- Control, 2- Asthma (sensitized and challenged with OVA), and 3- OVA+ hAM-MSC-CM, 4- OVA+ DMEM (sensitized and challenged with OVA and then treated with intravenous injection of 50µl of hAM-MSCs-CM and DMEM, respectively, on two consecutive days). 48 hours after the last challenge, mice were anesthetized and their lungs removed. Lung tissue sections stained with Masson's trichrome to evaluate fibrosis and the percentage of the fibrotic area was calculated in five random regions of each lung.

Results: Two-day treatment with hAM-MSCs-CM reduced collagen deposition and fibrosis compared to OVA-induced asthma and OVA+DMEM groups. Sub-epithelial fibrosis was also increased in the asthmatic and OVA+DMEM groups compared to the control group ($P<0.0001$). Treatment with hAM-MSCs-CM markedly reduced percentage of sub-epithelial fibrosis compared to asthma and OVA+DMEM groups ($P<0.001$). Furthermore, there was a significant difference between control and OVA+hAM-MSCs-CM groups ($P<0.0001$). However, treatment with DMEM couldn't significantly reduce fibrosis compared to asthma group ($P>0.999$).

Conclusion: MSCs have potential in the regenerative medicine field. Since the amniotic membrane is also a rich source of stem cells and conditioned medium of these cells have more functional capabilities. This study showed that hAM-MSCs-CM can improve fibrosis is balance in the immune response in an OVA-induced asthma in BALB/c mice model.

Keywords: Mesenchymal stem cell, Human amniotic membrane, Conditioned medium, Asthma, Fibrosis

Congress Abstracts

Basic Immunology

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18540)

Discovery of a novel marker for human granulocytes and tissue macrophages: RTL1 revisited

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Background: Several markers have been introduced to identify granulocytes, macrophages, as well as tumor-associated macrophages and neutrophils (TAM and TAM). In this research, retrotransposon like 1 (RTL1) is being introduced as a specific marker for peripheral blood granulocytes, tissue macrophages and macrophages and neutrophils in human cancerous tissues. **Methods:** A panel of RTL1-specific peptides were designed and used for rabbit anti-RTL1 antibody production. The antibodies were purified and their purity and specificity were tested by SDS-PAGE and ELISA and Western blotting. Reactivity of the generated antibodies was tested in a panel of human normal and cancer tissues by immunohistochemistry. The potential reactivity of the anti-RTL1 antibodies with normal and cancer cells was also tested by flow cytometry.
Results: Our results showed for the first time that one of the RTL1-specific antibodies superficially identified circulating granulocytes but not lymphocytes or monocytes. This antibody also detected human tissue macrophages, including hofbauer cells in placenta, alveolar macrophages in lung, kupffer cells in liver, tonsil inflammatory cells and splenic macrophages. Moreover it showed excellent reactivity with tumor-associated macrophages and neutrophils in breast cancer and melanoma tissues.
Conclusion: This is the first report on expression of RTL1 in cells of reticuloendothelial system. Unlike many previously-identified markers such as CD11b, which are also expressed in monocytes, this marker is exclusively expressed only after differentiation of monocytes into macrophages. Of the potential applications of this antibody is to purify and isolate these cells, as well as to target macrophages and granulocytes associated with the tumor.

Key words: Granulocyte, Macrophage, RTL1, TAM, TAN

(18640)

Induced MARCH-1 over-expression in U937 cell line promotes alternative features of (M2) macrophage

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Background: Functional plasticity of macrophages have been concerned in various disease conditions. Two macrophage subsets (M1 and M2) have been identified. M1 (classical) and M2 (alternative) macrophages have got functionally antagonistic characteristic. During the initial of inflammation, M1 macrophages dominate in the site of infection with anti-microbial activity, however M2 macrophages release anti-inflammatory cytokines which negatively regulate M1 activity and secrete products concerned in wound healing.
The Membrane-Associated RING-CH (MARCH) proteins are part of a family of RING type E3 ubiquitin ligases containing 11 known members, some of which are involved as important players in the immune responses. MARCH-1 is mainly found in secondary lymphoid organs, more specifically in the endocytic pathway of dendritic cells (DCs) and B cells. MARCH-1 reduces the half-life of peptide/MHC-II complexes by causing their redistribution from recycling endosomes to lysosomes. MARCH-1 is highly expressed in conventional immature DCs, and its downregulation by LPS stabilizes cell surface peptide. In the present study, the attempt has been done to consider transduce the MARCH-1 gene in U937 cell line and the phenotype alteration would be evaluated for macrophage plasticity.
Methods: $5x10^5$ cells of U937 (human macrophage cell line as an in vitro model) cell were transduced with lentviral vector expressing MARCH-1. Two groups of cells were including 1- the cell line with MARCH-1 expression+PMA (Phorbol 12-Myristate 13-Acetate) and 2- the cell line with no MARCH-1 expression+PMA (control) were planned. After 72 hrs of transduction, the cells were treated by 50ng/ml PMA for further 3 days. The cell morphology was considered by light microscopy. The cytokine concentration was measured by ELISA, and the expression of CD14, CD163 were considered by flowcytometry.
Results: The data showed that the concentration of proinflammatory cytokine in MARCH-1, PMA treated cells was increased in compared to control group (p. value < 0.05). The cell surface expression of CD163 was higher than control group but statistically does not reach significant. The viability of PMA treated cells was less than the control group.
Conclusion: in conclusion, our data showed that over expression of MARCH-1 on the cell line could promote anti-inflammatory features in favors of macrophage plasticity to M2 in U937 differentiated cell line.

Keywords: MARCH-1, U937, Macrophage, PMA

(16762)

Carbon nanotubes induce cytotoxicity and increase protein expression of Bax in mouse skin fibroblasts

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Background: Carbon nanotubes is one of the greatest discoveries in nanotechnology and are used in many applications in modern technology, however the related risks of long-term toxicity of those materials remain to be elucidated. Since we are widely exposed to nanoparticles and the mechanism of their toxicity is not yet known, their effect on cell viability and the possible mechanism in mouse skin fibroblasts was investigated.

Methods: Cytotoxicity of carbon nanotubes on cell viability was examined by MTT, intracellular generation of ROS by fluorometric, and lactate secretion determined by photometric method. Western blot analysis was used for detection of Bax as a key factor in apoptosis pathway.

Results: MTT results showed a significant decreased in cell viability and also increase of ROS was observed in fibroblast treated with carbon nanotubes. Western blot analysis revealed a significant increase of Bax, reflecting the effects of carbon nanotubes on cell death. Cellular lactate secretion, necessary for fibroblast proliferation and collagen synthesis, showed a significant decreased with carbon nanotubes.

Conclusion: Consequently, carbon nanotubes should be considered as the potential toxic substances for skin fibroblasts which is the body's first line of defense. Carbon nanotubes by increasing ROS and Bax may induce apoptosis in fibroblasts via Bax apoptotic-pathways. Also, suppression of lactate generation could reduce collagen production which may speed up aging process especially in the skin.

Keywords: Carbon nanotubes; skin fibroblasts; Cytotoxicity; cell viability; ROS generation: lactate secretion.

(18019)

Evaluation and determination of antibiotic resistance pattern and identification of productive genes in Cell swelling and death factor (tdc)in Escherichia coli strains isolated from wastewater

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Background: Escherichia coli is a microbial indicator of water and food. Escherichia coli a natural flora of the human gastrointestinal tract and warm-blooded animals and is an important member of the Enterobacteriaceae family. However, a number of Escherichia coli strains cause various diseases such as gastroenteritis, genitourinary tract infections, respiratory infections and neonatal meningitis in humans and animals due to the presence of genes that cause swelling and cell death (cdt). The aim of this study was to investigate the resistance pattern of Escherichia coli isolates isolated from the wastewater of Imam Khomeini Hospital in Bonab city to a number of common antibiotics and the frequency of cdt-IB, cdt-IIIB, cdt-IVB genes among them.

Methods: A total of 60 Escherichia coli isolates were collected from the wastewater of Imam Khomeini Hospital in Bonab and identified by routine differential tests. Antibiotic resistance of isolates against 9 common antibiotics was evaluated using antibiogram method. The presence of cdt-IB, cdt-IIIB, cdt-IVB genes was assessed by PCR.

Results: In the isolates, the highest resistance to cefixime and Tetracycline and the lowest resistance to Cotrimoxazole were observed. The results of this study confirm the presence of multidrug-resistant gram-negative bacilli in hospital wastewater. Most of the bacteria isolated in this study brought insecurity to the health of the community.

Conclusion: Escherichia coli bacteria isolated from the wastewater of Imam Khomeini Hospital in Bonab city have high resistance to Tetracycline and cefixime antibiotics.

Keywords: Escherichia coli, Swelling and cell death gene, Antibiotic resistance, Hospital wastewater

(18309)

Effect of inhalable Ahvaz city dust (PM10) on gene expression of TNF-α by human peripheral blood monocytes

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Introduction: Epidemiological researches have shown that exposure to inhalable airborne particles by 10 mm and less in size (PM_{10}) can lead to increase the risk of diseases such as respiratory, lung cancer and atherosclerosis. The respiratory system is the primary target of airborne particles and increase risk of lung cancer in people who exposed to them. as regard that TNF-α is a proinflammatory cytokine that exert stimulatory activity on inflammatory cells and increase transcription of inflammatory cytokines and chemokines genes, thus the aim of this study was to evaluate the capacity of inhalable Ahvaz city dust on gene expression of TNF-α by human peripheral blood monocytes.

Methods: Isolated human blood monocytes cells (250,000-300,000 cells/well) were exposed to various concentrations (62.5, 125,250 and 500µg/ml) of inhalable Ahvaz city dust (PM_{10}) in 24-well plates for different incubation periods (12, 24, and 48 h). RNA extraction and c-DNA synthesis were performed. The final goal of the study, which included measuring gene expression of TNF-α was done by real-time PCR method.

Results: The results showed that exposure to the inhalable Ahvaz city dust (PM_{10}) increased the gene expression of TNF-α by human peripheral blood monocytes. Analysis of data showed that there was a significant difference in this gene expression compare to none exposed control group ($P<0.05$). This increase in gene expression was directly related to the particle concentration at each incubation time (dose-dependent) but decreased with increasing incubation time (time-dependent).

Conclusion: Our findings showed that inhalable Ahvaz city dust contain active compounds which can stimulate immune system to expression of TNF-α, so exposure to that may possibly lead to lung damage by stimulation of inflammation in the lungs by this proinflammatory cytokine.

Keywords: Dust, monocyte, TNF-α.

(18125)

Association between air pollution and Multiple Sclerosis: A systematic review

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Abstract: Air pollution is a major public health threat. The present study is the first systematic review (SR) to determine the association of exposure to air pollution and Multiple Sclerosis (MS) Progression. A Literature search was carried out using relevant keywords within several international databases. A comprehensive literature search was carried out systematically and yielded 24 eligible studies concerning the relationship of exposure to air pollution including criteria air pollutants such as particulate matter, NOx and SOx, CO2, traffic noise, etc. and MS disease. The results of the included studies reveal that there was a significant relationship between exposure to air pollution and MS development and progression. Although the effect of air pollution in the pathogenesis of MS is not fully known, according to the results of the included studies exposure to polluted air can stimulate several mechanisms that act as risk factors for developing MS and for having disease relapses or neurological disability. The major potential mechanism is Dysimmune inflammatory responses subsequent oxidative stress (OS), which leads to neuroinflammation and breakdown of the normal balance between immunity and self-tolerance. Air pollutants induce and sustain chemical reactions that produce reactive oxygen species (ROSs) and nitrogen reactive species (RNSs) which can initiate inflammatory cascades via the redox-sensitive mitogen-activated protein kinase (MAPK) and NF-κB that recruit and activate neutrophils, monocytes, and dendritic cells that stimulate the adaptive immune responses such as Th1 and Th17 inflammatory responses. The uncontrolled inflammatory responses following these events cause cell death and the release of self-antigens capable of stimulating the production of auto-aggressive T-cells via enhancing antigen presentation and facilitate entry of these cells to the central nervous system. Thus, oxidative stress is the culprit in the systemic inflammation and immune imbalance development and progression, powerful risk factors in MS.

(18518)

Variations of airborne pollen grains and fungal spores concentrations and their possible connections with the respiratory outbreak in Ahvaz, Iran

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Abstract: In the fall season of 2013, a severe respiratory outbreak occurred in Khuzestan province, Iran particularly in Ahvaz. As a result of this incident, more than fifteen thousand referrals to hospitals and pulmonary clinics were registered in this city. This phenomenon also happened in 2014 and 2015. A wide variety of hypotheses and factors were mentioned by air quality control officials and experts as the possible causes of this phenomenon. Among which ozone, particulate matters, polycyclic aromatic hydrocarbon compounds, and acid rain were the crucial factors. These possible culprits were rejected by other investigations. However, bio-allergens were also indicated as one of the most important and potential causes of this incident. Airborne pollen grains and fungal spores are the main causes of respiratory and allergic diseases such as asthma and rhinitis. In recent decades these bio-pollutants have become increasingly widespread in all parts of the world. The present study was done to answer the question that if there is a connection between airborne pollen grains and fungal spores and the increase in the number of hospital referrals. A Hirst-type volumetric spore sampler was used in order to sample airborne pollen grains and fungal spores. Sampling was done during a six-month period including fall and winter of 2016. According to the results, *Amaranthaceae* sp. pollen grains, were the dominant contributor of total airborne pollen grain concentrations. The concentrations of airborne pollen grains were much higher in the fall season. In both sampling periods, fungal spores demonstrated a homogenous distribution. In the case of fungal spores, *Cladosporium* had the highest amount. We concluded that the severe respiratory outbreak in Ahvaz might be triggered by a mixture of airborne pollen grains and fungal spores as well as high concentrations of industrial air pollutants.

Keywords: Bio-allergens, Respiratory outbreak, Pollen grains, fungal spores, Ahvaz

(15482)

In silico design of a new anticancer immunotoxin

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Background: Human epidermal growth factor receptor 2 (HER2) which is high-regulated in breast cancer cells could be a biomarker for this cancer cells. Immunotherapy is a novel approach for targeted therapy of cancer which can eradicate cancer cells specifically. Immunotoxins are chimeric proteins that are composed of a targeting part which can be a scFv or antibody and a killer toxin which can destroy the cancer cell. In the current study we designed an immunotoxin and evaluated its structure, stability, and binding based on bioinformatics approach.
Methods: An immunotoxin were designed based on RTX-A a natural toxin and scFv. The physicochemical features were predicted via ProtParam. PROSO II and GORV were utilized for evaluation of solubility and secondary structure. I-TASSER and GalaxyRefine were employed for building and refinement of a tertiary model for designed immunotoxin. PROCHECK and RAMPAGE were used to validate the tertiary model of immunotoxin. Allergenicity and mRNA stability of our chimera were checked by AlgPred and RNAfold. Finally, ZDOCK was utilized for docking of immunotoxin and HER2 receptor.
Results: Our designed immunotoxin could be a non-allergenic protein with a stable structure. The fusion of scFv and toxin could not interrupt their secondary structure and tertiary structure of this chimeric protein would be proper. The coding mRNA of this immunotoxin could be a stable messenger RNA. In final, docking results showed the immunotoxin can bind to the receptor properly.
Conclusion: This immunotoxin which has appropriate features could be synthesize via recombinant protein technology and examined in experimental studies to find its efficiency against breast cancer.

Keywords: HER2, Breast Cancer, Immunotherapy, Bioinformatics

(18524)

Effect of long exposure of rats to extremely low frequency of magnetic field (ELF-MF) on interleukin-10 from serum and whole blood cells

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Background: Nowadays, due to large use of electrical equipment, almost all human are exposed to magnetic radiation. Therefore, the aim of this study was to investigate the effects of extremely low frequency magnetic field (ELF-MF) with an intensity of 100 µTesla (the maximum acceptable limits) for three months on the production of IL-10 in serum and whole blood cultures of rats.
Methods: Forty Wistar male adult rats (200±20 g) were randomly divided into test and control groups. Test group were exposed to magnetic field every day. The total blood of the animals was drained in two bottles, one containing anticoagulant, and the other without anticoagulant. One ml of fresh blood containing anticoagulant was suspended in 1ml complete medium containing 1µg/ml PHA and incubated for 24 h in CO2 incubator at 37ºC. Serum and as well as whole blood supernatant levels of IL-10 were determined by sandwich enzyme-linked immunosorbent assays. Student's t-test was used to compare the mean of the examined groups.
Results: Serum levels of IL-10 in the control group and the test group were 316±60 pg and 322±53 pg, respectively. Also, the whole blood supernatant levels of IL-10 were 136±39 pg in the control group and 120±19 pg in the test group.
Conclusion: Data showed that exposure to magnetic fields has no effect on the IL-10 levels in serum and in whole blood culture supernatants compared with the controls. Because IL-10 is an immunosuppressive cytokine, it seems that magnetic fields have not inhibitory effect on the immune system.

Keywords: Interleukin-10, Cytokine, Immune system

(16542)

Recommendations for diagnosis & treatment Of Acute Promyelocytic Leukemia *(APL)*

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Background: Acute Promyelocytic Leukemia (APL) is a subgroup of Acute Myeloid Leukemia (AML) with a certain clinical period, biology and treatment. APL was the deadly leukemia but today it is most curable leukemia so that it could be treated with low cytotoxicity drugs such as All-Trans-Retinoic Acid (ATRA), and the best consolidation treatment in recurrence cases is Arsenic Trioxide (ATO). The purpose of this article is introduce the APL, provides a rationale for the plan of risk-adapted protocols for further improving treatment and reduce cytotoxicity of treatment protocols.
Methods: Search was performed on PubMed, MEDLINE, Science direct and Google scholar by using of keywords such as APL, treatment, M3 variant, translocations.
Results: We found 200 articles which we selected58 articles which have relation with our subject. Articles were studied and finally extracted their information.
Conclusion: A series of tests exists for the diagnosis of APL, including Immunophenotyping, Histochemical methods such as Myeloperoxidase, Sudan black B is positive, periodic acid Schiff is negative, Nonspecific esterase <5% is weak positive and another diagnostic method is SpSp expression in AML-M3, M4. APL treatment was done with target therapy that was a new vision for leukemia treatment in order to use of drugs that have less toxicity and have the best response to treatment. It is associated with different translocation that is always involving retinoic acid receptor-α (RAR-α) gene with a variable partner gene (X-RARα or RARAα-X) that PML gene is the most partner gene. The partner gene has an impact on the response to ATRA, So that, 95% of patients were responsive to treatment with ATRA. The initial WBC and platelet count make associated with relapse, and determined the protocol cure and use or non-use of chemotherapy.

Keywords: APL, ATRA, ATO, Complete Remission

(16543)

The Effect of Honey on Candida Albicans

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Background: Fungal diseases represent a critical problem to health and they are one of the main causes of morbidity and mortality worldwide. C.albicans is a dimorphic organism that commonly inhabits in oral and vaginal mucosa and gastro-intestinal tract of human beings as one of the common organisms. Honey is a natural product that has been used for its antifungal activity.
Methods: keyword honey, in combination with antifungal activity and Candidia albicans has used in PUBMED searches from 2005 to 2015. 42 studies from clinical trials and meta-analysis with adequate quality has been used for the sources of this study.
Results: The antifungal activity of honey is thought to be attributed to the high concentration of sugars and low content of water. But some studies refuse this and some has been shown no effect of honey on C.albicans .Maybe it's because of the differences of honeys. It has been reported that honeys from different phytogeographic regions vary in their ability to inhibit the growth of yeasts. There are a great variety of components, including phenolic acid, flavonoids and other biomulcules, in different honeys.
Conclusion: Honey won't have adverse effects, it's natural and non-toxic. So it can be used for its antifungal features. Examination of different honeys shows different effects. Adding starch to honey has shown a significant decrease in the MIC (minimum inhibitory concentration), especially ginger starch has been effective.

Keywords: honey, antifungal activity, C.albicans

(16614)

Ostrich chicks Seromonitoring during Downer Syndrome 2019-2020

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Background: Iran's ostrich breeding industry is developing and well increased in Isfahan as the first ranking in the country ,It was about 20 years ago which a few African Ostrich chicks imported to Iran and at the moment we arrive to more than 5000 breeder just in Isfahan Province with about 7200 chicks for laying or meat production in future. One of the most complicated disease of the ostrich chicks is downing and constipation fallowed by respiratory problems. The clinical signs coupled with management and nutritional difficulties but the contagious signs of disease proposes an infectious habitat of the disease, meanwhile the biosecurity decreases the prevalence.

Methods: Sampling of bloods done via jugular and wing vein in the infected chicks aged 2 to 6 months from 10 farms in Isfahan and Chahar mahal provinces from March 2019 to march 2020. The samples transported to serology laboratory and the sera were prepared for HI test for ND and AI and also ELISA test kit of biochek used for chicken Aadenovirus 1 and Borna Virus investigation.

Results: Regarding to the results the Aadenovirus 1 and Borna virus infection were negative comparing to controls, but the HI test for ND and AI were positive and valid, in which the CV for ND were 237% with the Maximum of 10 ,Minimum were 2 and average of 8 ,the CV for AI (H9N2) were 236% with the Maximum titer of 9 ,Minimum titer of 3 and average of 6 , Fortunately no any infection of H5s serotypes were positive According to the clinical and paraclinical results the syndrome were related to per acute ND (enteric form) co working with AI.

Conclusion: Ostriches ND vaccination in all ages, disinfecting and biosecurity would be preventive for downer syndrome.

Keywords: Downer syndrome, AI, ND, Ostrich Chicks, Isfahan

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(16608)

KIR variation in Iranians combines high haplotype and allotype diversity with an abundance of functional inhibitory receptors

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Abstract: Natural killer (NK) cells are innate lymphocytes that eliminate infected and transformed cells. They discriminate healthy from diseased tissue through killer cell Ig-like receptor (KIR) recognition of HLA class I ligands. Directly impacting NK cell function, *KIR* polymorphism associates with infection control and multiple autoimmune and pregnancy syndromes. Here we analyse *KIR* diversity of 241 individuals from five groups of Iranians. These five populations represent Baloch, Kurd and Lur, together comprising 15% of the ethnically diverse Iranian population. We identified 159 *KIR* alleles, including 11 not previously characterized. We also identified 170 centromeric and 94 telomeric haplotypes, and 15 different *KIR* haplotypes carrying either a deletion or duplication encompassing one or more complete *KIR* genes. As expected, comparing our data with those representing major worldwide populations revealed the greatest similarity between Iranians and Europeans. Despite this similarity we observed higher frequencies of *KIR3DL1*001* in Iran than any other population, and the highest frequency of HLA-B*51, a Bw4-containing allotype that acts as a strong educator of *KIR3DL1*001*$^+$ NK cells. Compared to Europeans, the Iranians we studied also have a reduced frequency of *3DL1*004*, which encodes an allotype that is not expressed at the NK cell surface. Concurrent with the resulting high frequency of strong viable interactions between inhibitory KIR and polymorphic HLA class I, the majority of *KIR-A* haplotypes characterized do not express a functional activating receptor. By contrast, the most frequent *KIR-B* haplotype in Iran expresses only one functional inhibitory KIR and the maximum number of activating KIR. This first complete, high-resolution, characterization of the *KIR* locus of Iranians will form a valuable reference for future clinical and population studies.

Key Words: NK cells, KIR, HLA class I, Iranian populations. Immune diversity.

(16652)

RNA editing may prevent dsRNA-mediated immune response

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Background: RNA editing, the modification of specific nucleotides in RNA sequences, extensively alters the transcriptome. These editing events could have a non-synonymous effect, whenever located in a coding sequence. On the other hand, the vast majority of editing sites distributed in non-coding sequences of the genome. Therefore diversification of proteome is unlikely to be the main purpose of the abundant non-coding editing activity. It is well established that editing of endogenous dsRNA is necessary to suppress activation of the innate immune system. Herein, we investigate RNA editing sites that may function to prevent the triggering of the innate immune response.
Methods: We used GEO database to download RNA sequencing data. Adaptor sequences were trimmed from the reads and the clean sequences were aligned to the human reference genome. We used GATK for variant calling and SNP filtering. Difference between RNA sequence and reference genome annotated using SnpEff software.
Results: We found more than 12,000 editing events across the genome. Of these, only 81 editing sites have a non-synonymous effect. The remaining editing events were distributed in the 3UTR, upstream and downstream, 5UTR, and intergenic regions of the genome.
Conclusion: Vast majority of RNA editing sites occur in non-coding regions of transcriptome and innate immune response suppression may is the actual goal.

Keywords: Immune response, suppression, RNA editing, Non-coding

(16667)

Effect of kidney stem cells on TGF-β/*Smad* signaling in rats with diabetic nephropathy

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Introduction: Mesenchymal stem cells (MSCs) were proposed as a critical therapeutic candidate in diabetic nephropathy (DN). Renal stem cells as a source for repairing are controversial. The purpose of the present study was to evaluate the effect of kidney rat stem cells on DN.
Materials and methods: After separation of renal stem cells from rat kidney, the surface stem cell markers were assessed by flow cytometry analysis. To establish the diabetic nephropathy rat model STZ(60mg/kg) was used. The cells were injected to experimental groups via tail vein (2×10^6cells/rat). Phosphorylation of *Smad2/3* two weeks after induction of early diabetic nephropathy was evaluated by using standard western blotting. *TGF-β* Gene expression was evaluated by Real-time PCR
Result: *TGF-β* Gene expression upregulated in diabetic group. The phosphorylation of $smad_2$ and $smad_3$ significantly down-regulated after injection of stem cells. PAS staining showed in the presence of adult kidney stem cells histopathological changes were improved.
Conclusion: Adult kidney stem cells may be a candidate for treatment of early DN to improve the kidney function and regenerating kidney tissues in DN rats.

Keywords: stem cell therapy, *Smad*/*TGF-β* signaling, Diabetic Nephropathy, kidney stem cells

(18404)

Bioinformatic Analysis of microRNA expression in Pediatric Type 1 Diabetes

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Background: Type 1 Diabetes (T1D) is an autoimmune disease which can leads into chronic complications as a result of late prognosis and treatment. Studying small regulatory nucleotides like microRNAs could possibly shed light into the accurate pathogenesis of this disease. In the present study, our aim was to elucidate potential and prognostic Differentially Expressed microRNAs (DE-microRNAs) in Type 1 Diabetes disease through *in silico* analysis of available dataset.
Methods: The non-coding RNA expression profile microarray dataset (GSE109264) was downloaded from Gene Expression Omnibus (GEO) and was used to next bioinformatic analysis. Limma package of R software was utilized to screen out DE-microRNAs. Target genes of identified DE-microRNAs were prognosticated through miRSystem database. FunRich software was used to analyze Gene Ontology (GO) and pathways through Kyoto Encyclopedia of Genes and Genomes (KEGG). Construction of Protein-Protein Interaction network and miRNA-gene network was implemented through Cytoscape software. Additionally, hub genes of the target genes were revealed by CytoHubba package inside Cytoscape software.
Results: Totally, 25 up-regulated and 9 down-regulated DE-microRNAs were screened out. Hsa-miR-1247-3p and hsa-miR-143-3p were the most dysregulated identified microRNAs for the down-regulated and up-regulated DE-microRNAs respectively. In addition, 139 and 46 target genes were selected for up-regulated and down-regulated DE-microRNAs respectively. The PPI network was constructed with 28 nodes and 74 interactions. Moreover, 10 hub-genes of the identified genes were selected in the PPI network construction for further analysis. Ultimately, Beta 1 Integrin cell surface interaction and estrogen receptor signaling pathways were the most enriched pathway in functional analysis.
Conclusion: The results of this study recommended novel biomarkers of pediatric type 1 diabetes. Moreover, Beta 1 Integrin cell surface interaction and estrogen receptor signaling pathways may possibly be the potential pathways leading to the progression of the type 1 diabetes and the results could be utilized as novel biomarkers for prognosis and early detection.

Keywords: Bioinformatic analysis, T1D, microRNA, differentially expressed miRNA

(18573)

Identification of intrinsically disordered regions (IDRs) in SARS-CoV-2 proteome as a potential drug target

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Background: In December 2019, a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was emerged in Wuhan city, Hubei province, China, and became a global public health issue. Due to the high contagiousness and mortality rate of SARS-CoV-2 various treatment strategies are used for fighting that (https://clinicaltrials.gov/). Following phylogenic analysis, SARS-CoV-2 is now considered as a new member of the betacoronavirus genus with 29903 bp positive-sense single-stranded RNA. Despite numerous efforts, there are still blind spots in the pathogenesis of SARS-CoV-2, especially in the entrance mechanism. Intrinsically disordered proteins (IDPs) lack a three-dimensional structure. They can be fully disordered or partially contains one or more intrinsically disordered regions (IDRs). They have crucial roles in many biological processes, including signal transduction and regulation. Considering their flexible structure of IDRs, they can act as significant genes in protein-protein interaction networks (PPIs). In addition, Due to the role of IDRs in various diseases they can be considered as drug targets.

Methods: The RNA sequence of the SARS-CoV-2 virus was obtained from NCBI (Accession number: NC_045512.2). The protein sequences in FASTA format were used for intrinsically disordered analysis. In order to predict IDRs in each protein sequence, PONDR®FIT, PONDR®VSL2, PONDR®VSL3, and PONDR®VLXT were employed.

Results: Since each algorithm according to its characteristics considers a particular region as an IDR, common regions were considered as IDRs with more confidence. Disorder score above 0.5 has considered as a threshold for specifying IDRs. According to our findings, the SARS-CoV-2 proteome is significantly ordered and IDRs can be observed mostly in Orf8 and Nucleocapsid proteins.

Conclusion: Several IDRs are exits in the SARS-CoV-2 proteome despite its significant ordered structure. Due to the role of IDRs in regulating biological processes these regions can be considered as potential therapeutic targets for further studies.

Keywords: SARS-CoV-2, intrinsically disordered proteins, IDPs, Intrinsically disordered regions, IDRs

(13358)

A challenge in the knowledge of Antigen and Antibody structure

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Background: We know there are large range of antigen and antibody. Scientists believe the Y shape structure of antibody is made of proteins. And the conjunction between antigen-antibody generate with hydrogenic bands in variable part of Fab. Each antigen for example one of Staphylococcus capsule antigens just conjunct with its special antibody.
Methods: this is a review study.
Results: I believe molecule like antigen and antibody must have nucleic acid structure, because the protein anatomy (structure) of them cannot answer this question which why animals immune system can produce antibody against every antigen that enter the body? And its parallel sample is in DNA and genome. Suppose that a pice of DNA from degenerated bacteria that is presented with reticular cell, ingested with B-lymphocyte. In the ``DNA-metabolism system`` or nucleus complement chain become synthesed and maybe conjuncted with other part of antibody (Fab and Fc). Most researchers believe the cellular surface antigens have sugar structure but it look like to be funny because sugars have not complex and various structures. They look like polymeric molecule but in nucleic acid repetition (repeat) of organic bases work like codes.
But there are not valuable evidence for this hypothesis unless we have a cerfule look at cell membrane and see contrast beetween dark pink in cell membrane and pale pink in cytoplasm that refer to existence of basophylic substance such DNA.
Also about hormones I think what previous design is true. For example gonadotrophic hormone from hypophysis affect exactly follicular cell in ovary and this new two-chain DNA can force cell to make new molecule like oestrogen or progestrone or some think else. About infected cell with virus it can explains appearance of inclusion body or other changes.
Conclusion: detective molecules have nucleic acid structure.

Keywords: antigen, antibody, immune system, genome

(16614)

Ostrich chicks Seromonitoring during Downer Syndrome 2019-2020

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Background: Iran's ostrich breeding industry is developing and well increased in Isfahan as the first ranking in the country ,It was about 20 years ago which a few African Ostrich chicks imported to Iran and at the moment we arrive to more than 5000 breeder just in Isfahan Province with about 7200 chicks for laying or meat production in future. One of the most complicated disease of the ostrich chicks is downing and constipation fallowed by respiratory problems. The clinical signs coupled with management and nutritional difficulties but the contagious signs of disease proposes an infectious habitat of the disease, meanwhile the biosecurity decreases the prevalence.

Methods: Sampling of bloods done via jugular and wing vein in the infected chicks aged 2 to 6 months from 10 farms in Isfahan and Chahar mahal provinces from March 2019 to march 2020. The samples transported to serology laboratory and the sera were prepared for HI test for ND and AI and also ELISA test kit of biochek used for chicken Aadenovirus 1 and Borna Virus investigation.

Results: Regarding to the results the Aadenovirus 1 and Borna virus infection were negative comparing to controls, but the HI test for ND and AI were positive and valid, in which the CV for ND were 237% with the Maximum of 10 ,Minimum were 2 and average of 8 ,the CV for AI (H9N2) were 236% with the Maximum titer of 9 ,Minimum titer of 3 and average of 6 , Fortunately no any infection of H5s serotypes were positive According to the clinical and paraclinical results the syndrome were related to per acute ND (enteric form) co working with AI.

Conclusion: Ostriches ND vaccination in all ages, disinfecting and biosecurity would be preventive for downer syndrome.

Keywords: Downer syndrome, AI, ND, Ostrich Chicks, Isfahan

(16643)

Avian Influenza Investigation in Some Aquatic Birds

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Background: Influenza type A viruses are of most significance to public health due to their potential to cause an influenza pandemic. Influenza type A viruses are classified into subtypes according to the combinations of different virus surface proteins hemagglutinin (HA) and neuraminidase (NA). So far there are 18 different HA subtypes and 11 different NA subtypes such H9N2, H5N1 and H5N8 or H7N5 as reported in birds of Iran. Aquatic birds are the primary natural reservoir for most subtypes of influenza A viruses. There are a few of aquatic birds included Coots, Swan, Pelican, Sea gull, Ducks, Flamingo and Goose in the Isfahan bird garden and tested for AIV by serological and molecular tests.
Methods: Using sterile sirings about 2 ml of blood of wing vein collected and transferred for AIV titration, meanwhile the coanal cleft and cloacal swabs were prepared for molecular test. Monthly monitoring of 5-6% of sensitive birds were examined randomly. The technical method for serology were HI, ELISA and RT-PCR for molecular and confirmation of suspected titers.
Results: All of the birds showed positive titer for H9N2 but the highest titer were 8 for Coots,Goose and Green head duck, the lowest titer were 1 and related to pelicans, , Flamingos. The sera were negative for H5N1 and H5N8 and H7 but the swabs were checked by RT-PCR technique which confirmed the negative titers
Conclusion: This monitoring monthly well done and sanitization of gates and all areas with wide antiseptic materials carried out daily.

Key words: AI, Aquatic birds, Monitoring

(16684)

High Resolution Melting (HRM) for Ross 308 broiler chickens Genotyping

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Background: Major histocompatibility complex (MHC) has a profound influence on disease resistance or susceptibility, productivity and important economic traits in chicken. The tandem repeat LEI0258 is a genetic marker which is located within the B locus of chicken and studies have showed that it could be used for MHC typing in chickens. Furthermore High resolution melting (HRM) analysis is a novel, post-PCR method that generates DNA melt curve profiles which is specific and sensitive enough to distinguish nucleic acid variation.
Methods: In this study The MHC haplotypes/polymorphism was ascertained by genotyping the LEI0258 microsatellite locus by HRM-based and fragment analysis.
Results: Results obtained in this study showed that this technique could be used for discriminating the LEI0258 alleles. We identified more than 6 different LEI0258 alleles ranging from 194 to 443 bp.
Conclusion: In conclusion, HRM assay is a rapid and reliable method to conduct molecular genotyping that allows the correct genotyping of LEI0258 alleles in broiler chickens. It is applicable in a rapid way without post-PCR treatments such as electrophoresis. In general, the application of a precise analysis of HRM seems to be of great use in examining the diversity of chicken MHC genes.

Keywords: High Resolution Melting (HRM), MHC diversity, LEI0258 Microsatellite, Broiler chicken

(16798)

Importance of combined serological and molecular screening tests in order to detection toxoplasmic infection in sheep

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Background: *Toxoplasma gondii* is an obligate intracellular parasite which has the potential to infect all warm-blooded animals. Sheep and cattle play a main role in the economy and their infection to *T. gondii*, besides economic losses, can cause the infection of humans through the consumption of raw meat and other products. In this study, we aimed to study the importance of combined serological and molecular screening tests in order to detection toxoplasmic infection in sheep in Tehran Province.
Methods: To determine the contamination rate of *toxoplasma gondii* in sheep in Tehran province 246 samples of blood serum, fetal brain, cotyledon and whole blood in 2020 were randomly prepared and tested both with PCR and ELISA methods
Results: In order to PCR, samples' DNA were extracted. Four pairs of primers; ITS1 (Internal Transcribed Spacer-1), Rrna s18 Toxoplasma gondii Tg2, Tg1, Tg3, Tg4 (nested PCR), which amplify *Toxoplasma gondii* B gene, were used in order to DNA amplification. Serological test reveal that contamination rate of toxoplasma gondii was 18.7 %. PCR results with a pair of universal primers showed 77% of contamination and with couple primers of Nested PCR showed 61% of contamination rate which shows a higher level of contamination compared to the results obtained from the ELISA.
Conclusion: This findings suggest that it may be due to a variety of many causes, such as thyroid disease, food contamination with aflatoxins, and the use of drugs or any factor that weakens the immune system, the body is unable to produce and increase antibodies against *Toxoplasma gondii*. Therefore, serological tests alone cannot show the actual infection. Hence, in addition to serological testing, PCR testing should be performed in animal or human studies in order to obtain the actual level of infection.

Keywords: PCR, *Toxoplasma gondii*, ELISA, Sheep.

(16802)

Effects of Electrolytes imbalance on immunity against Foot and Mouth Virus Infection

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Background: Sodium (Na) and chloride (Cl) function with phosphate and bicarbonate to maintain optimum pH of the body. Taking in consideration the importance of sodium salts in calves ration, project was designed to observe the effect of excessive dietary sodium salts on weight gain, FCR, serum sodium concentration, edematous lesions and on the immune status of the calves against Foot and mouth disease (FMD).

Method: 100 female calves were divided into 4 groups. Group A, B, C and D were fed on diet with 0.36% NaCl, 0.36% sodium bicarbonate, 0.18% NaCl and 0.18% sodium bicarbonate and 0.18% sodium salts (routine) respectively. On day 8 and 28 FMD vaccine was administered to all groups. All the calves were weekly weighed to calculate FCR. Blood samples were collected on days 14, 28 and 42 day age to determine the antibody titer against FMD virus through ELISA and for the estimation of serum sodium concentration through spectrophotometry.

Results: Results showed that calves of group A had better feed conversion ratio and weight gain as compared to the calves of group B, C and D, whereas calves of group D had poor FCR as compared to the calves of group B and C. On analysis of serum sodium concentration by spectrophotometer, the calves of group A had maximum sodium concentration and calves of group D had lowest serum sodium concentration. Statistical analysis showed a significant difference in the serum sodium levels of all groups except within group B and C. The highest ELISA titer against FMD virus was observed in sera of calves of group D and the lowest in the sera of calves from group A.

Conclusion: According to the results, Electrolytes imbalance have a main effect on immunity against FMD disease.

Keywords: Sodium, chloride, FMD, sodium salts.

(16803)

Vitamin E supplementation: Effect on passive immunity of new born calves

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Background: Nutrition plays a significant role in the development and function of the immune system. Recently vitamin E also has been shown to regulate the cell-mediated immune response of farm animals. The experiment conducted to investigation the effect of Vitamin E supplementation in Holstein cows' transition period on the passive immunity of their new born calves.
Methods: A total number of 50 dairy cows three weeks prior to parturition were randomly arranged to two treatments of 25 cows each. Expiremental groups included: the control group without feeding Vitamin E and the experimental group where cows were fed 200 mg Vitamin E per kg of diet based on dry matter, individually. In order to evalute immunoglobulin's samples were taken from cows of colostrums and serum blood of calves 24 hours after birth, respectively.
Results: The result of this study revealed colostrums production was significantly higher in cows with Vitamin E diet compared to cows control group. ($p<0.05$) Concentration of immunoglobulin's in colostrums (IgG, IgM) were decreased in cows fed with Vitamin E than control group ($p>0.05$). Also, there was no significant difference among concentration of immunoglobulin's serum (IgG, IgM) in calves born from Vitamin E diet group compare to control group.
Conclusion: According to these results it could be concluded that Vitamin E supplementation of ratio in holstein cows in transition period do not induce any significant impact on absorption serum immunoglobulin's of newborn calves.

Keywords: Calf, Vitamin E, passive immunity, transition period.

(16857)

Genetic diversity of Ross 308 broiler chickens using LEI0258 microsatellite marker

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Background: Major histocompatibility complex (MHC) encodes for highly variable molecules responsible for foreign antigen recognition and subsequent activation of immune responses in hosts. MHC polymorphism should hence be related to a wide range of immune responses. MHC-related microsatellite LEI0258 which is located within the MHC locus of chicken (called B locus), is a useful biomarker for indicating MHC haplotypes.
Methods: To survey MHC haplotypes/polymorphsim in Ross broiler chickens (N=110) we used LEI0258 microsatellite marker. MHC alleles were identified through pcr and electrophoresis techniques.
Results: our results reveal that Ross broiler chickens have more than 6 different alleles ranging from 194 to 443 bp for LEI0258 microsatellite. Allele 381 bp had highest and allele 194 had the lowest frequency.
Conclusion: these findings provide more information in the direction of MHC as candidate gene marker in genetic improvment and resource conservation in broiler population, and also lay the foundation for other studies to further investigation the role of MHC as candidate gene marker for immune responses.

Keywords: MHC, polymorphism, LEI0258 Microsatellite, Broiler chicken

(18149)

Investigation of the effect of cloning in horses

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Abstract: Cloning means using genetic material (DNA) from a donor horse to produce the same genetics. Cloning involves the production of animals that are genetically identical to the donor nucleus. The most common and newest cell transfer technique is somatic cells, in which the nucleus of a body cell is transferred to an egg cell. The technique involves collecting DNA from a donor and inserting that DNA into another egg that has the DNA content removed, the donor nucleus with ovulated receptor oocytes, which then, as an embryo, cultures the embryo in the medium. Cultures and eventually transfers the embryo to the uterus of a recipient horse. Improving in vitro culture conditions, which can be suitable for egg activation, egg maturation and embryo development, is a key step in a successful laboratory test for somatic cell nucleus transfer in horses to prevent horse embryo death. In general, few studies are available on in vitro embryo production, and it has recently been reported that the complete production of pre-coagulated embryos using egg maturation has been published in vitro. This review discusses the latest developments in the technique used in horses using SCNT. The basic understanding of SCNT for in vitro culture conditions is related to increasing cloning efficiency. Here we show our recent findings that histone type H3.3 plays an important role in reprogramming and is required for the reproduction of key developmental genes in cell embryos, somatic cells (SCNT). Horse cloning is possible today, and its value to industry will be determined in the next few years. Cloning should be used as a method of production, and domestic animals can be simulated with techniques such as embryos, dividing and transferring nuclei to Genetic production is the same. There are several uses for cloning, including accelerating livestock, animal conservation, and research models. This dysfunctional process is currently due to arousal problems, placental abnormalities, and postpartum stenosis. In addition, food safety, animal welfare, public and social acceptance, and religious institutions are the most common challenges to the development of this technology. And the results have been replicated in several laboratories around the world.

Keywords: cloning, nuclear transfer, Somatic cells, SCNT, Horse

(18212)

Comparison between immunoglobulins of camel with other domestic animals

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Background: Little is known of the immunological and functional contributions of camel immunoglobulins to immune defense. We have produced and characterized IgY specific for conventional immunoglobulins of camel, cattle and sheep.
Methods: Generated IgY's specificity was shown by immunoelectrophoresis, and Western blotting.
Results: Western blotting revealed that IgY antibodies recognize the IgG heavy chain in a number of mammalian species. Anti-camel antibodies bound camel IgG sub-classes, but expect for sheep no reactivity was observed to all heavy chains in cattle and horse's antibodies. Poly-clonal IgY were specifically light chain reactive.
Conclusion: The potential was demonstrated of using egg yolk immunoglobulins as a convenient source of antibodies to camel, cattle and sheep immunoglobulins.

Keywords: Antigenic similarities, Camel, Cattle, Sheep, Immunoglobulins

(15406)

Opium increase the plasma levels of pro-inflammatory cytokines IL-23 and TNF-α in Coronary Artery Disease

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Background: In some Asian countries, the traditional belief among people is that opium may has a positive effect on coronary artery disease (CAD) health, but researches have shown that this substance may play a potential role in the development and progression of CAD. The aim of the present study was to explore the role of opium on the plasma levels of IL-23 and TNF-α (as pro-inflammatory cytokines) in the CAD opium-addicted and non-opium-addicted patients.

Methods: This case-control study was conducted on three groups: 1) CAD opium-addicted (CAD-addicted, n=30); 2), CAD non-opium-addicted (CAD, n=30); and 3) non-opium-addicted with no CAD individuals as a control group (Ctrl, n=17). Plasma levels of cytokines were evaluated by ELISA technique.

Results: The mean plasma levels of IL-23 was significantly higher in the CAD-opium-addicted group in comparison with other groups ($P<0.001$). Also, the levels of TNF-α were significantly higher in the CAD-opium-addicted group in comparison with other groups ($P<0.001$).

Conclusions: The results demonstrated that opium induces inflammation which can lead to deterioration of CAD complications.

(16670)

Investigating and Comparison the relationship between high sensitivity of serum inflammatory marker (hs-reactive protein C) and the number of coronary arteries with approximately 70% occlusion in angiographic evaluation in cardiovascular patients.

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Background: Inflammation plays a key role in the pathogenesis of atherosclerosis. There is strong evidence that cardiovascular conditions are linked with inflammation. C-reactive protein (CRP) is a protein made by the liver and increases in the blood when there is a condition causing inflammation somewhere in the body. The amount of CRP in the blood indicates inflammation due to acute conditions or to monitor the severity of disease in chronic conditions. A high-sensitivity C-reactive protein (hs-CRP) test measures low levels of CRP and may be used to evaluate an individual for risk of cardiovascular disease (CVD). hs- CRP not only is an important predictor of first myocardial infarction but also for recurrent coronary events. The aim of this study is to investigate the relationship between hs-CRP and the number of coronary arteries with approximately 70% occlusion in angiographic evaluation in cardiovascular patients.

Methods: We evaluated 375 patients with one, two, or three arteries with approximately70% clogging between the ages of 40 and 80. The sera were analyzed for the levels of hs-CRP by ELISA method. Then analyzed by SPSS by adopting a significance level for a value of $p<0.05$.

Results: The hs-CRP levels significantly increased in all three groups, including one, two, or three blocked arteries, compared to healthy individuals. The hs-CRP levels increased with the increasing number of clog vessels but the increased hs-CRP in these groups was not significant compared to each other.

Conclusion: High-sensitivity CRP (hs-CRP) test may be used to help predict a healthy person's risk of cardiovascular disease (CVD), heart attacks or strokes. According to the data of this study, abnormal amounts of hs-CRP can indicate clogged arteries from at least one vessel to more. Therefore, abnormal levels of hs-CRP can indicate damage to the minimum number of vessels and immediate action should be taken.

Keywords: Inflammation, Cardiovascular disease (CVD), High sensitive C reactive protein (hs-CRP)

(16696)

Effects of the alcoholic extract of *Dracocephalum moldavica* against the Experimental model of ulcerative colitis in rats

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Background: Given to the anti-inflammatory and potent antioxidant properties of *Dracocephalum moldavica* (Moldavian dragonhead), this investigation was done to evaluate the effects of alcoholic extract of *D. moldavica* on the experimental model of ulcerative colitis (UC) in Wistar rat.
Methods: Rectal instillation (2 ml) of 4% acetic acid was applied to induce UC in male Wistar rats. Treatment groups daily received prednisolone (2 mg/kg, orally) or alcoholic extract of *D. moldavica* (100 mg/kg, orally) for ten consecutive days. The levels of total protein, nitric oxide, myeloperoxidase, and total antioxidant capacity were determined in colonic homogenates after the rats were euthanized.
Results: The results showed that both regimens could similarly ameliorate the severity of UC symptoms. Treatment with alcoholic extract of *D. moldavica* prompted a better improvement in the levels of myeloperoxidase enzyme, and total antioxidant capacity of colonic homogenates compared to UC rats who received prednisolone. Nevertheless, the levels of nitric oxide were decreased in UC rats treated with prednisolone compared UC rats received the extract of *D. moldavica*.
Conclusion: Treatment with the alcoholic extract of *D. moldavica* may be used promising strategy to control UC.

Keyword: *Dracocephalum moldavica*, Ulcerative colitis, Acetic acid, Wistar rat.

(16712)

Is there any association between high-sensitivity C-reactive protein and Glycemic hemoglobin in the human serum?

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Background: Diabetes, characterized by chronic hyperglycemia, can lead to high risk of metabolic disorders if not controlled and treated properly. Glycemic hemoglobin (HbA1c) reflects average plasma glucose over the previous 8– 12 weeks and is a marker for diabetes monitoring.C-reactive protein (CRP) is considered to be a prime inflammatory marker of Diabetes. The CRP levels in the blood indicate inflammation due to acute conditions or to monitor the severity of disease in chronic conditions. A high-sensitivity C-reactive protein (hs-CRP) test measures low levels of CRP. Our aim is to investigate the association between hs-CRP and HbA1c in healthy, pre-diabetic, diabetic, and uncontrolled diabetic individuals.

Methods: 300 healthy with HbA1c lower than 5.7%, 300 prediabetic (HbA1c from 5.7 to 6.4%), 300 type 2 diabetic (HbA1c >6.5% and 300 uncontrolled diabetic (Lack of treatment or resistance to treatment) (HbA1c >8%), were studied. People over the age of forty were selected. The sera were analyzed for the hs-CRP levels by ELISA method. Then analyzed by SPSS by adopting a significance level for a value of $p<0.05$.

Findings: *The hs-CRP* levels did not change in the pre-diabetic group compared to healthy individuals. The *hs-CRP levels* increased in diabetic but were not significant compared to healthy individuals. The *hs-CRP* levels were significantly increased in uncontrolled diabetics compared to healthy individuals ($p<0.05$).

Conclusion: Our results indicated significant increases in *the hs-CRP levels in* uncontrolled diabetic (HbA1c >8%). Thus, in uncontrolled diabetics with high HbA1c, inflammation can increase in the body and chronic inflammation can cause a variety of diseases and conditions, including some cancers, rheumatoid arthritis, and atherosclerosis. Therefore, an abnormal increase in HbA1c levels, in addition to a sign of high blood sugar, is a warning sign of increased inflammation in the body, and blood sugar levels in diabetics should be well managed and treated.

Keywords: Diabetes, inflammation, HbA1c, hs-CRP

(16910)

Pathophysiological roles of chronic low-grade inflammation Mediators in polycystic ovary syndrome

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Background: Polycystic ovary syndrome (PCOS) is the most common hormonal imbalance disease in reproductive-aged women. Its basic characteristics are ovulatory dysfunction and ovarian overproduction of androgens that lead to severe symptoms such as insulin resistance, hirsutism, infertility, and acne. Notwithstanding the disease burden, its underlying mechanisms remain unknown, and no causal therapeutic exists. In recent years, further studies showed that inflammation processes are involved in ovulation and play a key role in ovarian follicular dynamics. Visceral adipose tissue can cause inflammatory response and maintenance of the inflammation state in adipocytes by augmented production of inflammatory cytokines, monocyte chemoattractant proteins, and recruitment of the immune cell. Therefore, the PCOS can be related to a low-grade inflammation state and inflammatory markers. Investigating the inflammatory processes and mediators that contribute to the commencement and development of PCOS can be a critical step for better understanding the pathophysiology of the disease and its treatment through inhibition or control of related pathways. In the present review, we discuss the pathophysiological roles of chronic low-grade inflammation mediators including inflammasome-related cytokines, interleukin-1β (IL-1β), and IL-18 in PCOS development.
Conclusion: Although ovulation is a semi-inflammatory state, uncontrolled inflammation can lead to the development of PCOS. However, the role of inflammatory factors including inflammasome-related cytokines (IL-1β and IL-18), along with IL-6 and TNF-α, is well-established. Nevertheless, other inflammatory factors are also quite effective in the development of PCOS. It is hoped that these inflammatory mechanisms will become more prominent, and in the future, more attention will be directed towards stopping these pathways through designing new therapies.

Keywords: chronic low-grade inflammation, IL18-, IL1-β, inflammasome, polycystic ovary syndrome

(17951)

The Effects of *Boswellina serrata* hydroalcoholic extracts on serum IL-6, IL-1 and CRP values in lysolecithin -induced demyelination in rat

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Background: Multiple sclerosis is one of the most common autoimmune complications of the central nervous system (CNS), which is diagnosed through neuroinflammation and CNS demyelination. In this study, the therapeutic and anti-inflammatory effects of administration of Boswellia Serrata hydroalcoholic extract on induced demyelination by lysolecithin through serum levels of interleukins one and six and C-reactive protein in rats were investigated.

Methods: 2 µl of lysolestine was stereotactically injected into the dentate gyrus area of the hippocampus to induce demyelination. The animals were divided into 8 groups including 6 treatment groups, positive control group and control group. The 6 treatment groups received solutions containing doses of 0.1 g, 0.2 g, 0.3 g, 0.4 g, 0.5 g, and 1 g per 10 cc of distilled water from hydroalcoholic extract of Boswellia Serrata with purity of 50 mg of active ingredient per cc from day 7 after injection of lysolecithin for 21 days. Afterwards,a behavioral study was performed using a water maze.

Results: The maximum recorded time to find the platform was observed on days 7 and 14 after lysolecithin n injection, which may be a sign of demyelination. Remyelniation on the 28th day after the lesion was significant due to the increase in level of consciousness which indicates that consumption of Boswellia Serrata extract in the treatment groups reduced demyelination. Analysis of immunological parameters showed that injection of lysolecithin increased cytokines interleukin 1, interleukin 6 and reactive protein C, especially before treatment, but at the end of the period there was significant reduction in the amount of inflammatory cytokines (interleukins 1 and 6) and reactive protein C according to the amount of Boswellia Serrata extract they received.

Conclusion: Our results showed that Boswellia Serrata extract can reduce inflammatory cytokines and C-reactive protein and repair myelin in the hippocampus and improve the learning process and spatial memory after induction of demyelination with lysolecithin and also provide neuroprotection in various neurological complications of Multiple Sclerosis.

Keywords: demyelination,remyelination ,lysolecithin , Boswellia Serrata extrac

(18032)

Association of IL-35 serum levels and FoxP3 polymorphisms in patients undergoing cardiopulmonary bypass graft surgery

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Background: Recent evidences showed that during cardiopulmonary bypass (CPB) release of pro- and anti- inflammatory cytokines may happen in response to the inflammation. One of the anti-inflammatory cytokines is IL-35 which produced by $CD4^+$ $FoxP3^+$ regulatory T cells. In this study we evaluated the relation between serum levels of IL-35 and single nucleotide polymorphisms SNPs (rs3761548, rs3761547) of the FoxP3 gene in CPB patients from south of Iran.

Methods: one hundred forty patients who underwent (CPB) were enrolled. Serum level of IL-35 was measured by enzyme linked immunosorbent assay (ELISA) before and 12 hours post operation. The genotype frequencies of FoxP3 polymorphisms rs3761548 and rs3761547 were assessed using SSP-PCR.

Results: There was no significant association between genotype frequencies of the rs3761548 or rs3761547 of Foxp3 gene and elevated IL-35 levels ($P>0.05$) before and after surgery.

Conclusion: Although FoxP3 is one of the main transcription factors in regulatory T cells and its role in transcribing IL-35 gene is proposed, but the serum levels of IL-35 are not influenced by Foxp3 promoter polymorphisms (rs3761548, rs3761547).

Key words: IL-35, FoxP3, polymorphisms, cardiopulmonary bypass

(18033)

Serum level of IL-35 in patients undergoing cardiopulmonary bypass graft surgery

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Background: Cardiopulmonary bypass (CPB) causes systemic inflammatory responses which is balanced by a significant anti-inflammatory cytokine release. Some organs might be affected by this inflammatory response. One of these organs is kidney and acute kidney injury (AKI) is a post-cardiopulmonary bypass complication (CPB-AKI), which may result in increased post-operative morbidity and mortality. IL-35 is an anti-inflammatory cytokine which is mainly produced by regulatory T cells and plays a key role in regulating severity of inflammation. In this study, IL-35 serum level was evaluated in AKI patients.

Methods: Serum level of IL-35 was assessed using enzyme linked immunosorbent assay (ELISA) in 90 patients who developed CPB-AKI. Serum was obtained before and 12 hours after operation and IL-35 was compared in AKI patients before and post operation.

Results: The serum concentrations of IL-35 after surgery were significantly higher compared to the corresponding values before surgery (19.4±7.3 versus 10.89±4.2, P=0.002). There was no significant association between IL-35 serum level and age, sex or BMI (P>0.05).

Conclusion: The elevated levels of IL-35 may contribute to the postoperative immune dysfunction and as a part of post CPB compensatory anti-inflammatory response.

Key words: Cardiopulmonary bypass, CPB, AKI, IL-35

(18111)

Lack of association between type 2 cytokines (IL-5 and IL-13) and neuregulin-4 in coronary artery disease patients

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Background: Coronary artery disease is the main cause of death in the world and many attempts have been done to clarify the mechanisms involved. Neuregulin-4 (Nrg4) is an adipokine which may protect against development of obesity and metabolic disorders and recently its protective role in atherosclerosis has been proposed. Since there is a close relation between adipocytokines and immune system, we wonder whether there is a relation between Nrg4 and athero-protective cytokines. Here we assessed the relation of Nrg4 and IL-5 in coronary artery disease (CAD) patients.
Methods: In this cross-sectional study, 90 CAD patients which their disease was confirmed by coronary angiography were enrolled. Serum level of Nrg4, IL-13 and IL-5 were evaluated using Enzyme linked immunosorbent assay (ELISA) and their correlation was analyzed.
Results: The mean age of patients was 58.4±10 and 52% were male. Serum concentrations of IL-13, IL-5 and Nrg4 were 4.1±2.4, 33.6±11 and 0.4±0.1 respectively. IL-5 and IL-13 concentrations were not correlated with Nrg4 (P=>0.05) in CAD patient.
Conclusions: Despite athero-protective effect of both Nrg4 and type 2 cytokines, our results did not support the relation between Nrg4 and IL-5 and IL-13 levels.

Keywords: Neuregulin-4, Adipokine, Atherosclerosis

(18190)

Elevated expression of IL-18 but not IL-1β gene is associated with NALP3 And AIM2 inflammasome in Polycystic Ovary Syndrome

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Background: Polycystic Ovary Syndrome (PCOS) is a common endocrinology disorder that affects women in reproductive ages. PCOS is a disorder characterized by ovulation disorders with unknown etiology. Recent studies indicated the role of inflammatory processes, including increasing the production of inflammatory cytokines in polycystic ovary syndrome. Studies on inflammatory pathway involved in the production of inflammatory cytokines, including inflammasome pathway is in the early stages. Therefore, the inflammasome pathway was targeted to investigate in patients with PCOS.
Methods: This case-control study included 30 patients with confirmed PCOS according to the Rotterdam criteria as cases and 30 women without PCOS as control group that admitted to institute of fertility and infertility of Fateme Alzahra Research Institute in Babol. Blood sample was collected and targeted to PBMC and serum isolation. RNA was extracted and, then cDNA was synthesized. Expression levels of genes involved in inflammasome pathway such as NLRP1, NLRP3, AIM2, ASC, NLRC4, IL-1β and IL-18 were determined through Real-time PCR. In addition, IL-1β was measured via ELISA.
Results: The obtained results of gene expression studies by Real-time PCR showed a remarkable increase in expression of the NLRP3, AIM2, IL-18, ASC genes in POCOS patients compared to the control group ($p < 0.05$). In contrast, the expression level of NLRP1, NAIP, NLRP12 and NLRC4 genes in the case group was not significantly different in comparison to the control group. Although, IL-1β expression level in case group was more than the control group but there was no statistically significant difference. In addition, analysis of association between inflammasome involved genes with IL-1β and IL-18 showed a significant correlation between NALP3 and IL-18 ($r = 0.72$, $p < 0.05$). Moreover, measurement of IL-1β level in serum of case and control groups showed no statistically significant difference
Conclusion: Based on the obtained results on inflammasome components along with increased expression of IL-1β especially in overweight patients, it can be concluded that IL-18 expression as well as IL-1β is probably due to activation of AIM2, NALP3 or NAIP inflammasome, which may play a critical role in immunopathology of PCOS.

Keywords: IL-1β, IL-18, Inflammasome, Polycystic Ovary Syndrome

(18195)

An overview of the innate and adaptive immune system in atherosclerosis

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Abstract: Cardiovascular disease is the leading cause of death globally. Coronary artery disease (CAD) is a chronic inflammatory disease usually caused by atherosclerosis, in which the coronary arteries become narrowed by atheromatous plaque. Plaques in atherosclerosis are formed through the accumulation of lipids and various immune cells. Both adaptive and innate immune systems are involved in the pathogenesis of atherosclerosis and facilitate plaque formation and disease progression. Almost all immune system cells, including neutrophils, B cells, T cells, monocytes, macrophages, foam cells, and dendritic cells (DCs), play a vital role in atherosclerotic plaque. Atherogenesis, the normal function of the endothelium, is initially disrupted and, then, cells of the immune system are recruited to the endothelium following increased expression of cell adhesion molecules. Accumulation of immune cells and lipids leads to the formation of a necrotic nucleus. As the disease progresses, smooth muscle cells form fibrous layers, whose rupture results in exposing the necrotic nucleus and thrombosis. Accordingly, the present review was conducted to determine the role of different cells in innate and adaptive immune systems in inhibition and progression of atherosclerosis.

Keywords: Coronary artery disease (CAD), atherosclerosis, innate immune system, adaptive immune systems.

(18210)

The serum levels of IL-32 in coronary artery disease patients

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Background: Atherosclerosis is an inflammatory disease caused by the accumulation of cholesterol-derived lipoprotein in the arteries and eventually leads to atherosclerotic plaques. Despite significant advances in atherosclerosis treatment, atherosclerotic cardiovascular disease remains one of the leading causes of death worldwide. This study aimed to investigate the serum levels of IL-32 in patients with coronary artery disease (CAD) and control group.
Methods: A total 81 subjects (42 patients with CAD and 39 controls) were included in this study. Serum concentration of IL-32 was measured by ELISA.
Results: Serum level of IL-32 was significantly increased in the CAD group compared to the control group.
Conclusion: An increase in the serum level of IL-32 may lead to progression of atherosclerosis plaque.

Keywords: coronary artery disease (CAD), Atherosclerosis, inflammatory, IL-32.

(18289)

Evaluation of serum levels of IL-1β in patients with Multiple sclerosis in Birjand city, Iran

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Background: Multiple sclerosis (MS) is an auto immune-mediated demyelinating disease of the central nervous system (CNS). Recent evidence suggested that the Interleukin-1β (IL-1β) plays a critical role in autoimmune and inflammatory disorders. The purpose of this investigation was to evaluate the concentrations of serum IL-1β in patients with multiple sclerosis (MS) and healthy subjects as a control group from Birjand in East of Iran.

Methods: In this case-control study, peripheral blood samples were collected from 90 MS patients and blood sample of 90 healthy subjects as a control group.The serum concentrations of IL-1β were measured by the enzyme-linkedimmunosorbent assay (ELISA) kits (BosterBio, California, US).

Results: The results of the present study showed that the serum IL-1β concentrations in patients with relapsing-remitting (RRMS), and secondary progressive (SPMS) forms of the disease were significantly higher than the healthy control group ($p<0.001$, $p<0.001$, respectively).

Conclusion: Our results showed increased serum levels of IL-1β in patients with MS with RRMS, SPMS, and PPMS forms. This suggests that IL-1β may be involved in the pathogenesis of MS forms.

Keywords: Interleukin-1β, Multiple Sclerosis, ELISA

(18312)

The role of exercise in the expression of different types of inflammatory microRNAs in diabetes

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Background: MiRNAs are involved in the pathogenesis of diabetes and common regulatory pathways can be identified in type 2 diabetes (T2D) and obesity by modulating inflammatory and immune processes. Exercise modulates the expression of multiple miRNAs in the short and long term, and often contributes to the pathogenesis of diabetes by setting goals that affect various cellular-molecular and immune-inflammatory processes. Further research is needed to confirm the effects of exercise on diabetes and the ability of these exercises to improve the expression of miRNAs, especially long-term effects.

Methods: This review article has been done by analyzing articles from scientific databases such as PubMed and Google scholar as an explorer. We reviewed 107 articles from 2003 to 2020 and chose 60 articles with the keywords: “Inflammatory”, “Exercise”, “microRNA” and “Diabetes”.

Results: Different miRNAs have been shown in T2D and exercise. MiR-192 decreased in T2D patients and increased after chronic adaptation to exercise. In addition, an increase in miR-192 levels was observed in humans after acute exercise. This miRNA regulates the CXCL2 gene, which is part of an inflammation-related chemokine family and may therefore be involved in the T2D-related inflammatory response. With this hypothesis, other miRNAs involved in the regulation of inflammation, including miR-146a, are expressed during exercise in T2D. Clinical studies have shown that miR-146a blood circulation can be regulated in T2D patients, aerobic exercise can increase miR-146a levels. MiR-24 levels decrease with anti-inflammatory effect in T2D patients. In an experimental study, exercise was associated with increased cardiac miR-24 expression.

Conclusion: It can be concluded that one of the mechanisms proposed to explain the regulation of exercise-mediated cellular homeostasis is by modulating the expression of inflammatory miRNAs. Identifying inflammatory miRNAs that are beneficially modulated by exercise could help develop new managements and treatments for T2D and obesity.

Keywords: Diabetes, Exercise, Inflammatory, MicroRNA

(18352)

Comparison of inflammatory cytokine production in the liver and serum of CLP induced sepsis mice

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Background: Sepsis is a systemic inflammatory disease in response to pathogens that leads to vital organ failure. Determining the severity of inflammation plays an influential role in choosing the type of anti-inflammatory drug and the administration dose. Since inflammatory responses can be examined in affected organs in addition to the serum, it is important to choose an organ that can show the severity of inflammation in proportion to the course of the disease. In the current study, the inflammatory cytokine production was compared in serum and liver of CLP[1]-induced sepsis mice.

Materials and Methods: CLP model was induced in 15 female C57bl/6 mice. IL-6, TNF-α, IL-10, and TGF-β1 cytokines levels were measured at 24, 48, and 72 hours after CLP induction in the liver tissue by the ELISA method. Serum levels of liver enzymes were analyzed by the clinical chemistry analyzer. All studies were performed in healthy mice as well. The results were reported as Mean±SD.

Results: The levels of IL-10 and TGF- β1 in the liver were significantly ($P \leq 0.05$) higher than serum. The production of IL-10 and TGF- β1 in the serum and liver reaches its maximum at peaked 24 and 72 hours after CLP induction. The level of TNF-α in the liver was significantly ($P \leq 0.05$) higher than serum with a maximum production 24 hours after CLP induction.

Conclusion: Comparative findings of the measurement of cytokines associated with inflammation in the liver and serum indicate that the level of cytokines in the liver is higher than serum, and the peak time of cytokine production is different. Therefore, serum cytokine testing does not appear to be an accurate method for assessing the status of inflammation in sepsis.

Keywords: CLP, Cytokine, Liver, Serum

(18358)

Pyrin and Hematopoietic Interferon-Inducible Nuclear Protein Domain Proteins: Innate Immune Sensors for Cytosolic and Nuclear DNA

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Abstract: The innate immune system is the first line of defense against microbial pathogens. The response of innate immunity is initiated by molecules known as pattern recognition receptors (PRRs). Such responses are often triggered by nucleic acids that are delivered to the cytoplasm or nucleus of cells. The ability to recognize foreign nucleic acids in these two locations is an important defense mechanism of the human innate immune system. Several PRRs are located in the cytosol or nucleus and detect foreign DNAs. The pyrin and hematopoietic interferon-inducible nuclear (PYHIN) domain protein is a family of PRRs that includes interferon-inducible protein 16, absent in melanoma 2, PYHIN 1 (or interferon-inducible protein X, as it is also known), myeloid cell nuclear differentiation antigen, and pyrin domain only protein 3. These nuclear and cytosolic sensors play an essential part in host defense of intracellular pathogens. In addition, members of the PYHIN family are critical regulators of immune response, apoptosis, cell growth, differentiation, and transcription. In this review, we summarize important characteristics of these innate immune sensors and their roles in several diseases. A better understanding of the role of DNA sensors in the nucleus and cytoplasm will lead to the development of novel therapeutic approaches to control infections and associated diseases.

Keywords: pattern recognition receptor, nuclear receptor, pathogen-associated molecular pattern, pyrin and HIN

(18418)

The role of macrophages in pathogenesis of celiac disease.

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Abstract: Celiac disease, is related disorder to the immune system's response to eating gluten. Although, in abounded number of studies, the role of both intrinsic and acquired immunity dimensions have investigated, little is still known about the contribution of macrophages to the onset or maintenance of the disease. Macrophage is an immune system cell that depending on its microenvironment, can have inflammatory and anti-inflammatory effects. Their inherent plasticity allows them to respond to a variety of environmental provocations by obtaining either by pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. Gliadin, the main cause of celiac disease, has been reported to trigger the production of pro-inflammatory cytokines in this cell population.
Carlsen et al. showed that the duodenal biopsy of patients with celiac disease contained a large number of CD68 + tissue macrophages that showed significant phagocytic abnormalities (1) .Also, a study by Cinova et al. showed that gliadin peptides specifically could induce high levels of the cytokines IL-8 and interferon gamma (IFN-γ) in monocytes isolated from celiac patients compared with monocytes isolated from healthy individuals (2) .Serena et al., reported that gliadin stimulated the inflammatory response in human macrophages and increased the expression of M1 phenotype cytokines, such as IL-6, IL-1β, and TNF-α, and reduces M2-specific cytokines like TGF-β (3) .Therefore according to the previous studies it is recommended that the role of macrophages should be consider in the pathogenesis of celiac disease. This review illustrates the characteristics of macrophage cells and their role in celiac disease.

Keywords: Macrophage, Gliadin peptides, Monocytes, Celiac Disease, Intestine

(18472)

Increased Amount of Pentraxin 3 and its Association with Critical Coronavirus Disease-2019 Patients

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Background: Pentraxin 3 (PTX3) and ficolin are the plasma phase of pattern recognition receptors (PRRs) and can activate complement through classical and lectin pathways, respectively, which may contribute to disease severity. This study aimed to investigate the association between PTX3 and ficolin with disease severity in patients with coronavirus disease-2019 (COVID-19.(

Materials and Methods: Seventy-three COVID-19 patients and 25 healthy controls were enrolled in this study. The participants were divided into three groups as follows: 14 patients as the intensive care unit (ICU) group, 59 patients as the non-ICU group, and 25 subjects as the healthy control group. The serum levels of PTX3 and ficolin were measured by enzyme-linked immunosorbent assay (ELISA) kits.

Results: Patients in ICU and non-ICU groups had significantly higher levels of PTX3 compared to the healthy control group ($p = 0.0002$ and $p = 0.0072$, respectively). Patients in the ICU group also had an increased amount of PTX3 (1957 ± 1769 pg/ml) compared to non-ICU patients (1220 ± 1784 pg/ml). However, this difference was not significant. On the other hand, serum levels of ficolin were not different among the three groups.

Conclusion: PTX3, as an acute phase protein, may contribute to disease severity. Its probable inflammatory role could result from the high activation of the complement system. On the other hand, it could be suggested that ficolin has no crucial role in the disease severity of COVID-19 patients.

Keywords: Pentraxin, Ficolin, COVID-19, PTX3

(18660)

The serum levels of IL-6 in coronary artery disease patients

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Background: Atherosclerosis is an inflammatory disease caused by the accumulation of cholesterol-derived lipoprotein in the arteries and eventually leads to atherosclerotic plaques. Despite significant advances in atherosclerosis treatment, atherosclerotic cardiovascular disease remains one of the leading causes of death worldwide. This study aimed to investigate the serum levels of IL-6 in patients with coronary artery disease (CAD) and control group.
Methods: A total 81 subjects (42 patients with CAD and 39 controls) were included in this study. Serum concentration of IL-6 was measured by ELISA.
Results: Serum level of IL-6 was significantly increased in the CAD group compared to the control group.
Conclusion: An increase in the serum level of IL-6 may lead to progression of atherosclerosis plaque.

Keywords: coronary artery disease (CAD), Atherosclerosis, inflammatory, IL-6.

(18787)

The impact of serum microparticles from patients with systemic lupus erythematosus on the functions of neutrophils

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Introduction: Microparticles are extracellular vesicles budded from the cell membrane of resting, activated or apoptotic cells. MPs exist in healthy serum and (other body fluids) but are raised under inflammatory conditions. MPs often carry a wide variety of biologically effective substances of the cell. They can harbor DAMPs (damage-associated molecular patterns) in a reachable form which could elicit the immune responses; the level of DAMPs in MPs isolated from patients with inflammatory disorders is higher than those isolated from healthy individuals. Indeed, MPs are one of potential biomarkers of inflammation that can influence the functions of inflammatory cells toward promoting (or suppressing) inflammation. MPs also contribute to the pathogenesis of some chronic inflammatory diseases, including systemic lupus erythematosus (SLE). In SLE, accelerated cell death together with the ineffective clearance of the subsequent debris, the augmented oxidative stress and their added effects result in a systemic inflammatory response that can affect almost all tissues and organs of the body. Previously numerous works on the role of MPs in the onset and persist of inflammation in SLE have resulted in conflicting outcomes. Likewise, there is a paucity of researches about the effect of serum MPs of SLE patients on neutrophil function. This study evaluates the effect of SLE MPs on neutrophils. The neutrophils were incubated by serum MPs (from SLE patients and healthy controls) and their activation, viability and oxidative burst ability were measured.

Methods: The blood was collected from SLE patients and healthy controls; MPs were isolated from SLE and healthy serum by high-speed centrifugation; and confirmed by flow cytometry. Neutrophils from healthy individuals were incubated by the isolated MPs and their upregulation of CD11b expression, apoptosis, and oxidative burst ability were measured.

Results: The level of the cell mortality CD11b expression were elevated in MP-treated neutrophils. Also, the elevation caused by the SLE MPs was higher than that produced by the healthy MPs. SLE MPs decreased the oxidative burst capacity of neutrophils but healthy MPs increased it.

Discussion: The decreased neutrophil viability was not due to the increase in apoptosis; rather, it was because of the augmentation of other inflammatory cell-death modes. The upregulation of CD11b implies that MPs cause neutrophils to more actively contribute to inflammation. The decreased or increased oxidative burst capacity of neutrophils can play a double role in inflammation. Overall, the effects induced by MPs on neutrophils help prolong inflammation; accordingly, the MPs from SLE patients is stronger than the MPs from healthy individuals.

(16640)

Seromonitoring of parrots for AI and ND on 2019-2020

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Background: Now a days pet birds are going to be most popular due changing the life cycle and more incoming of the humans. Parrots are one of the birds with most popularity in new civil social and locations, in current study some different strains of parrots which were referred to the Isfahan birds clinic will be studied by serology for ND and AI, There was no any suspected clinical sign and no any vaccination done, Due to a close relationship between parrots and the owners also regarding to owner request, public health and epidemiological reports the study have been done.

Methods: In current study during 2019 March to March 2020 about 200 parrots including large parrots (Grass Parakeets, King Parrots, Mula Parrots, Ring-neck Parakeets, Princess Parrots, Rosella, Aras and African gray parrots) and small parrots (Budgies , Parrotlets , Love birds, Small Conures, Cockatiels) were studied at the birds garden, the sampling method were Blood which prepared using wing vein ,the sera were tested for AI and ND by HI.

Results: Regarding to the results the ND titer were ranged from 0 to 7, with the average of 6 and CV of 147%, The titer of the sera for H5N1 were 0 but for H9N2 were ranged from 1 to 6 and the mean titer were 5.5 with C.V. of 156..

Conclusion: The seromonitoring of parrots and pet birds must be carried out for AI and ND control and surveillance.

Keywords: Parrot, AI, ND, Seromonitoring

(18131)

What is the antibody titer for AI and ND in the Immigrant Birds of Gavkhouni Area?

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Background: The Zayandeh Rood River originates in the Zagros mountains and continued about 300 km, toward *Batlaq-e- Gavkhuni*, which located in central Iran, east of city of Esfahan provienc, Gavkhouni is a salt marsh with a salinity of 315‰ and an average depth of about 1 m, every winter and spring this beautiful swamp is the migratory bird sanctuary of more than 2500 of about 35 species for Passing the winter, housing and even reproduction. Because of its location in the central part of Iran and environmental habitat some of the aquatic birds such as Anseranser, Tadornaferruginea ,Tadornatadorna, Anasplatyrhynchos, Anascrecca, Anasacuta, Aythya farina, Duck sp., Fulicaatro, Ardeacinoea, Egretta alba, Phoenicopterusruber and swans rest for a period of time and selected for current work..

Methods: Here in last spring and summer about 44 birds were trapped and some blood samples were prepared via wing vein, also some cloacal samples were prepared and transported near the ice to lab. Sera were isolated and screened for ND and AI (H5 N1, H7N8 and H9N2) by HI test. The results showed no any positive signs in the sera for H5 and H7, but all of them were positive for H9 (Mean titer =4.9, C.V.=168%) ,In ND most of the sera(#78%) were positive (Mean titer=5.2,C.V.=127%).

Results: Regarding to the results its oriented that AI virus were circulating in the examined birds and should be alert for HP serotypes, meanwhile a mixed ND and AI infection would be important for poultry industry.

Conclusion: The seromonitoring of immigrant birds must be carried out every year for AI control and surveillance.

Keywords: Seromonitoring, Immigrant, Bird, Gavkhouni, ND, AI

Congress Abstracts

Cancer Immunology

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

18463

Suppression of granzyme B production in B cells by tumor cells in a co-culture system

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Background: B cells play different and sometimes opposing roles in immunity against cancer. Granzyme B-producing B cells can directly kills tumor cells or effector T cells leading to the suppression or enhancement of the tumor growth, respectively. The aim of this study was to investigate the effect of breast cancer cell lines on granzyme B production by B cells derived from breast tumor draining lymph nodes (TDLNs).

Methods: Mononuclear cells were isolated from seven fresh axillary lymph node samples using Ficoll-Hypaque gradient centrifugation. Lymphocytes were co-cultured with breast tumor cell lines (MCF-7 and MDA-231) in the presence of recombinant IL-21 and Anti-BCR for 24 hours with Berefeldin A added in the last 6 hours of the culture. Then, cells were stained for CD19, fixed and permiablized and stained for granzyme B and subjected to flow cytometry.

Results: Our analysis showed that stimulation of B cells in the absence of the tumor cells in the control group lead to the production of granzyme B in 17.1±7.3% of $CD19^+$ B cells. However, direct co-culture of lymphocytes with either MDA-231 or MCF-7 cancer cells resulted in significant reduction of the granzyme B production in B cells (5.5±6.1%, P=0.048 and 3.7±3.8%, P=0.0032, respectively). In a set of experiments, we added Berefeldin A from the beginning of the co-culture to inhibit protein secretion. Similar reduction was observed in the expression of granzyme B in B cells in the presence of tumor cells ruling out the possibility of the secretion of granzyme B from B cells in the presence of tumor cells.

Conclusion: B cells can express granzyme B upon proper stimulation, however tumor cells are able to inhibit this process. Further investigations are required to elucidate the mechanism of this observation.

Keywords: Granzyme B, B cells, Tumor draining lymph node, Breast cancer

18266

Title: HNSCC progression from non-invasive early stages to invasive advanced stages is associated with a shift from Th1/Tc2 patterns to Th2/Tc2 response

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Background: Little is known about the immune profile of tumor draining lymph nodes (TDLNs) in head and neck cancers, therefore, this study was designed to investigate changes in the cytokine profile of CD8+ and CD4+ T cells in TDLNs of head and neck squamous cell carcinoma (HNSCC) during disease progression.

Methods: Mononuclear cells were isolated from 39 fresh homogenized lymph nodes. The frequencies of $CD4^+CD25^+Foxp3^+CD127^{low/-}$ Treg cells and IFN-ɣ-, TNF-α-, IL-4-, IL-17-, IL-10- and TGF-β-producing T cells were assessed by flow cytometry.

Results: A significant decrease in $CD4^+TNF\text{-}\alpha^+$ and $CD4^+$ $TNF\text{-}\alpha^{hi}$ cells was found in metastatic lymph nodes (P=0.015 and P=0.019 respectively), advanced stage of the disease (P=0.032 and P=0.010, respectively) and patients with larger tumor size (P=0.026 and P=0.032, respectively). Frequencies of $CD8^+IFN\text{-}\gamma^+$ and $CD8^+IFN\text{-}\gamma^+$ $TNF\text{-}\alpha^+$ T cells showed negative relationship with tumor grade (P=0.035 and P=0.043, respectively). While, $CD4^+IL\text{-}4^+$, $CD8^+IL\text{-}10^+$ and $CD8^+IL\text{-}4^+$ T cells were higher in higher stages of the disease (P=0.005, P=0.041 and P=0.030, respectively). Moreover, negative associations were found between frequencies of $CD4^+CD25^+Foxp3^+$ and $CD4^+CD25^+Foxp3^+CD127^{low/-}$ Treg cells and stage of the disease (P=0.015 and P=0.059, respectively).

Conclusion: Our data collectively suggest the induction of a predominant Th1 and Tc1 response in non-metastatic LNs and early stages of HNSCC, with a shift toward a Th2 and Tc2 response in metastatic LNs and advanced stages. Moreover, Foxp3+Treg cells were found to be associated with good prognostic indicators of the disease.

Keywords: Head and neck squamous cell carcinoma, Tumor draining lymph nodes, T lymphocytes, Regulatory T cells

18268

Ibrutinib and everolimus modulate the expression of immune checkpoint molecules through STAT3-mediated suppression of breast cancer cells

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Background: Tumor targeted therapy using small molecule inhibitors has been introduced as a powerful therapeutic strategy for a variety of malignancies. But, little is known about their possible associations with immune evasion mechanisms of tumor cells. In the present study, the association of AKT/mTOR and BTK signaling pathway inhibitors was evaluated with the expression of immune checkpoint ligands PD-L1, CD155 and Gal-9 in a breast cancer cell line.

Methods: MCF-7 breast cancer cells were treated with small molecule inhibitors everolimus (mTOR inhibitor), MK-2206 (AKT inhibitor) and ibrutinib (BTK inhibitor) either alone or in combination for 48h. The optimum dose for all drugs was determined by MTT assay. Following incubation, the mRNA expression of PD-L1, CD155 and galectin-9 (Gal-9) was measured by Real-Time PCR assay using β-actin as a housekeeping gene. Protein expression of phosphorylated STAT3 was also evaluated by immunoblot technique.

Results: Based on IC50 results obtained from MTT assay, the optimum treatment dose was found 200, 320 and 2000 nM for everolimus, MK-2206 and ibrutinib, respectively. The mRNA expression of PD-L1 and CD155 was significantly downregulated following treatment with everolimus and ibrutinib, but not MK-2206. Regarding Gal-9 expression, there were no differences between single-treated groups and control, but combined treatment with everolimus and ibrutinib has increased its mRNA expression. Treatment with everolimus and ibrutinib hindered the constitutive phosphorylation of STAT3 which was more remarkable in combined treatment.

Conclusion: Our findings regarding downregulation of PD-L1 and CD155 as well as upregulation of Gal-9 following treatment by small molecule inhibitors highlight the crosstalk between modulation of PD-L1, CD155 and Gal-9 immune checkpoints molecules with the AKT/mTOR and BTK signaling pathways which was mediated through STAT3 as a key transcription factor.

Keywords: Breast cancer, small molecule inhibitors, PD-L1, CD155, galectin-9, STAT3

18247

Prognostic power of PD-1 and PD-L1 in tongue and larynx squamous cell carcinoma: introducing a new scoring system

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Background: Checkpoint inhibitor immunotherapies, especially PD1/PD-L1 blockade are promising therapeutic approaches in head and neck squamous cell carcinoma. In this regard, we retrospectively evaluated the prognostic effect of PD-1 and PD-L1 expression in tongue and larynx squamous cell carcinomas (SCCs).

Method: Formalin-fixed and paraffin embedded tissue blocks of 103 tongue and larynx SCCs stained for PD-1 and PD-L1 by immunohistochemistry and were evaluated by an expert pathologist who was blinded to patients' data. Association of PD-1/PD-L1 expression with clinicopathologic parameters were evaluated by Chi-square, and their prognostic effect on disease-free survival (DFS) and overall survival (OS) were analyzed by univariate and multivariable Cox regression analysis.

Results: PD-L1 expression in tumor cells (TC-PD-L1) (P=0.001) and its expression intensity (P=0.002) were significantly correlated with high percentage of PD1 positive Tumor infiltrating lymphocytes. In univariate survival analysis, negative TC-PD-L1 and its low expression intensity had positive effect on both DFS (HR: 0.203; P=0.003 and HR: 0.320; P=0.005) and OS (HR: 0.147; P=0.002 and HR: 0.322; P=0.005). Conversely, low PD-L1 expression on immune cells (IC-PD-L1) and its low expression intensity had significant negative effect on DFS. Based on the multivariate analysis, PD-1 (DFS: HR: 3.202; P=0.011, OS: HR: 2.671; P=0.027) and TC-PD-L1 (DFS: HR: 0.174; P=0.006, OS: HR: 0.189; P=0.009) were independent prognostic markers. Considering this different prognostic behavior, a number of scoring systems were defined based on the expression status of PD-1 and PD-L1. In multivariate analyses, PD-1/TC-PD-L1 (DFS: P=0.001, OS: P=0.003) scoring systems showed superior prognostic effect. Interestingly, in highest levels of these scores, none of the patients experienced recurrence and cancer-caused death.

Conclusion: This study suggests different prognostic behavior for PD-L1 based on its origin. The proposed scoring system is a strong prognostic marker and may provide an insight about immunogenicity and immune-inhibitory potential of tumors. Additionally, these scores may predict proper candidates for PD-1/PD-L1 checkpoint inhibitor therapy.

Keywords: Checkpoint inhibitors, PD-1, PD-L1, Head and Neck Squamous Cell Carcinoma, Prognostic marker.

18141

A murine monoclonal antibody against myosin heavy chain-9 expressed in pancreatic cancer

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Background: The myosin 9 which also known as myosin heavy chain 9 (MYH9), is an actin-binding protein that plays an essential role in cell adhesion, migration, proliferation, and division. Recently, MYH9 is thought to contribute in cancer progression, and metastasis.
Methods: In this study, a monoclonal antibody against MYH9 was generated and characterized by hybridoma technology and using Faraz-ICR, an acinar pancreatic cancer cell line as source of antigen. MYH9 expression was investigated in cancer cell lines and pancreatic cancer resections using flow cytometry and immunohistochemistry, respectively. For investigation of the inhibitory effect of produced anti-MYH9 mAb on proliferation of Faraz-ICR cells, MTT assay was performed.
Results: Extra- and intra-cellular staining of pancreatic cancer cell lines including Faraz-ICR, MIA-PaCa 2 and PaTu 8902 showed that both Faraz-ICR and MIA-PaCa2 cells had about 100% reactivity with produced anti-MYH9 mAb. While, PaTu 8902 cells only showed intracellular target antigen expression (about 83%). Immunohistochemical staining of the acinar cell tumor section which was the source of Faraz-ICR showed strong MYH9 expression and from 21 pancreatic ductal adenocarcinoma, 9 (42.8%) cases expressed MYH9 with low intensity, while 10 (47.8%) and 2 (9.5%) cases expressed MYH9 with moderate and strong intensities, respectively. 4H12 mAb inhibited Faraz- ICR cells proliferation significantly with IC50 values 12.09±4.19 µg/ml and 7.74±4.28 µg/ml after 24 and 48 hours treatment with produced anti-MYH9 mAb, respectively.
Conclusion: These data suggested that 4H12 mAb has the potential for laboratory research and can serve as a tool for investigation of MYH9 roles in pancreatic cancer biology and prediction of its outcome.

Keywords: Monoclonal antibody, Myosin 9, acinar cell carcinoma, Ductal adenocarcinoma, Pancreas

18161

The heterogeneity of human lymphocytes expressing intracellular and membranous forms of TNF-α in breast tumor draining lymph nodes

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Background: Being known as a pleiotropic cytokine, tumor necrosis factor alpha (TNF-α) can be produced by a wide variety of immune cells, and serve different physiological or pathological functions. After its intracellular production, TNF-α integrates to the cell membrane as a transmembrane protein, followed by its cleavage from the membrane and the release of soluble TNF-α. Herein, we assessed the expression of intracellular and membranous TNF-α (ic/mTNF-α) in B and T lymphocytes derived from breast tumor draining lymph nodes.

Methods: Lymphocytes were isolated from 41 axillary lymph nodes of patients with breast cancer, and stimulated for 5 hours with PMA/Ionomycin in the presence/absence of Brefeldin A. Cells were then stained for CD4, CD8, CD19, TNF-α and mTNF-α, and acquired on flow cytometer.

Results: 31.1 ± 0.5, 9 ± 5.6 and 13 ± 9.3 percent of $CD4^+$, $CD8^+$ and $CD19^+$ lymphocytes expressed mTNF-α, respectively. However, significantly higher percentages of these cells expressed icTNF-α with higher intensities compared to mTNF-α. Moreover, the frequency of icTNF-α-producing $CD8^+$ T cells was significantly lower than the frequency of icTNF-α-producing $CD4^+$ T or $CD19^+$ B cells. In contrast, the geometric mean fluorescence intensity (gMFI) of icTNF-α was significantly higher in $CD8^+$ T cells than in $CD4^+$ T or $CD19^+$ B cells. The frequency of mTNF-α-expressing cells and the gMFI of this cytokine were significantly higher in $CD4^+$ T cells than in $CD8^+$ T or $CD19^+$ B lymphocytes.

Conclusion: icTNF-α has a different expression pattern from mTNF-α in various lymphocyte subsets. Therefore, the evaluation of the expression and function of different forms of TNF-α can help us deeply understand the role of this cytokine in immunity against breast cancer.

Key Words: TNF-α, Membranous TNF-α, Lymphocytes, Tumor draining lymph nodes, Breast cancer

16856

The frequency of natural killer (NK) cell subsets in peripheral blood of the patients with breast cancer: a reflection of the disease

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Background: Natural killer (NK) cells are $CD3^{negative}$ innate lymphocytes and critical players to eradicate the tumor and viral-infected cells in the first line of body defense, under a process called immune surveillance. Human peripheral NK cells constitute around 10-15 % of all lymphocytes and classify into tumor-promoting/suppressing subpopulations. The purpose of this study was to assess the NK cells and their subsets in peripheral blood of the patients with breast cancer (BC) in comparison with healthy individuals.

Methods: Twenty-nine untreated female patients with BC and 20 age-matched healthy women were enrolled in the current study. Fifty microliters of fresh peripheral blood samples were collected and directly incubated with the desired concentration of fluorescent-conjugated antibodies against CD3, CD56, and CD16 markers. Red blood cells (RBCs) were then lysed using RBC lysis buffer and removed by washing. At last, the stained cells were acquired by the flow cytometer.

Results: Our results demonstrated that 12.92% 1.17 and 15.65 1.57 of peripheral blood lymphocytes of BC patients and controls showed NK phenotype ($CD3^{-}$ $CD56/CD16^{+/-}$), respectively. The frequency of $CD56^{dim}$ $CD16^{+}$ cytotoxic NK cell subset was significantly decreased (76.08 1.69 vs. 81.72 1.45, P=0.018), whereas $CD56^{-}$ $CD16^{+}$ dysfunctional subset was observed to be increased (9.00 1.11 vs. 5.45 0.74, P = 0.025) in BC patients compared to healthy controls. There was no difference between groups in the frequency of $CD56^{dim}$ $CD16^{-}$ immature and $CD56^{bright}$ $CD16^{-}$ regulatory NK cell subsets.

Conclusion: The decrease in the frequency of cytotoxic NK cell subset among BC patients along with an increase in the frequency of dysfunctional NK cell subset may imply the presence of an immunosuppressive environment in these patients that affects the phenotype distribution of NK cells and their response. However, our suggestion needs more investigations to be fully clarified.

Keywords: Breast cancer, NK cell, NK cell subsets, innate immunity

16748

Increase in Helios-expressing regulatory T cells in lymph nodes of breast cancer mice treated with Everolimus

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Back ground: Everolimus is a mammalian target of rapamycin (mTOR) inhibitor which used as an anti-tumor drug in cancer. However, it can induce Tregs in cancer. Higher expression of Helios molecule in Treg cells increases inhibitory activity of these cells compared to $Foxp3^{+}Helios^{-}$ cells. Helios targeting converts Tregs into effector T cells. The aim of this study was to evaluate the frequency of $CD4^{+}$ $Foxp3^{+}$ $Helios^{+}$, $CD4^{+}$ $Helios^{+}$ and $CD8^{+}$ $Helios^{+}$ cells, as well as Helios mean fluorescent intensity (MFI) in a mice model of breast cancer treated with Everolimus.

Method: MC4-L2 cell line was used to induce breast cancer in mice**.** Breast tumor-bearing mice were randomly divided into 3 groups of 5 that first and second groups treated with 10mg/kg and 5mg/kg doses of the Everolimus. The third group only received vehicle (Na-CMC). After killing mice, lymphocytes were isolated from lymph nodes. The cells were stained with anti CD4, CD8, Foxp3, and Helios fluorochrome-conjugated antibodies, and then acquired by flow cytometry.

Results: Our results indicated that both dosage of everolimus (10 mg/kg and 5 mg/kg) potentially reduced tumor size, and inhibited the growth of tumor cells. The frequency of $CD4^{+}Helios^{+}$ and $CD4^{+}$ $Foxp3^{+}$ $Helios^{+}$ cells as well as MFI of Helios was found to be significantly higher in group that received 10mg/kg of Everolimus in compared to those treated with 5mg / kg or vehicle.

Conclusion: Our result shows that Everolimus reduces tumor growth in a mice model of breast cancer. However, it can inhibit the immune system responses, at least in part, by an increase in Helios-expressing cells more especially at 10 mg/kg dose. It is suggested to use a Helios inhibitor to improve the efficacy of this mTOR inhibitor drug in breast cancer.

Keywords: Everolimus, Helios, $CD4^{+}$ $Foxp3^{+}$ $Helios^{+}$cells, Breast Cancer ،Lymph nodes.

16585

The effects of PI3K/Akt/mTOR signaling pathway inhibitors on immune evasion mechanisms of Acute Myeloid Leukemia

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Background: Acute myeloid leukemia (AML) is a hematopoietic malignancy defined by abnormal proliferation, differentiation and accumulation of myeloid lineage cells in bone marrow and peripheral blood. Over-activation of PI3K/Akt/mTOR signaling pathway has been frequently observed in AML and attributed to the leukemogenesis mechanisms. The small molecule inhibitors of these pathways have been introduced as a promising therapeutic strategy. In addition, one of the most important immune escape mechanisms of AML is the up-regulation of immune checkpoint ligands such as PD-L1, galectin-9 (Gal-9) and CD155. Herein, we investigated the relationship between the inhibitions of the PI3K/Akt/mTOR signaling pathways with the expression of the immune checkpoint ligands of AML cells.

Methods: HL-60 cell line was treated with different signaling pathway inhibitors including Idelalisib as PI3K inhibitor, MK-2206 as Akt inhibitor, and Everolimus as mTOR inhibitor for 48 hours either in single or combination therapy. Cell viability and apoptosis were evaluated using MTT and flow cytometry assays, respectively. After that, total RNA was extracted from all samples, converted to cDNA and the relative expression of PD-L1, Gal-9, and CD155 mRNA was determined by Real-Time PCR using β-actin as a housekeeping gene.

Results: Our finding demonstrated significant decreasing in proliferation and increasing in apoptosis of HL60 cells after treatment with Idelalisib, MK-2206, and Everolimus. As expected, combined treatment showed more growth inhibition when compared to single treatment. Interestingly, our results demonstrated that the expression of PD-L1 and Galectin-9, as immune checkpoint ligands, was significantly decreased after treatment with Idelalisib and Everolimus but not MK-2206. Regarding CD155, the mRNA expression of this molecule was down-regulated after treatment with Everolimus, but not Idelalisib and MK-2206. However, combined treatment of HL-60 cells with two or three inhibitors significantly decreased the expression level of PD-L1, Galectin-9 and CD155 checkpoint ligands.

Conclusion: We showed that PI3K/Akt/mTOR pathway inhibitors not only serve as cytotoxic drugs, but also regulate the expression of immune checkpoint ligands and interfere with the immune evasion mechanisms of AML leukemic cells. Combinational therapy approaches to block these pathways might be a promising and novel therapeutic strategy for AML patients via interfering in immune escape mechanisms.

Keywords: PI3K/Akt/mTOR, immune escape, AML, Idelalisib, MK-2206, Everolimus

(18750)

MIR129-2 Methylation and Gastric Cancer

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Background: Development of gastric cancer affected by genetics and epigenetics. The mutation of the MIR129-2 gene is a significant cause of many cancers, particularly gastric cancers. The goal of this research was to examine differences in the methylation of the MIR129-2 gene in tumors and normal tissues in patients with gastric cancer.
Method: This study involved 50 gastric cancer patients of Iranian Azari ethnic origin. Genomic DNA was derived from normal and tumor tissues. The promoter regions of the MIR129-2 gene were then examined by methylation-specific PCR (MSP) to determine the presence or absence of methylated CpG sites.
Results: There was a statistically important difference in the methylation frequency of the MIR129-2 gene between tumor and normal tissues. It has been found that 84% of CpG cites have been methylated in tumor tissues by compression versus 13% of CpG cite in normal tissues.
Conclusion: In this study, we concluded that MIR129-2 gene was hypermethylated in tumor tissues, these results indicating that methylation is important in the growth of gastric cancer.

Keywords: MIR129-2, CpG sites, gastric cancers, Hypermethylation

18795

Effects of adipose derived mesenchymal stem cells secretome onanaplastic thyroid carcinoma C-643 cells

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Introduction: Previous studies have proven that substances secreted by mesenchymal stem cells have remedial properties. The main purpose of this study was to investigate the effect of material secreted by adipose-derived mesenchymal stem cells on the growth rate and apoptosis of anaplastic thyroid carcinoma cells (C-643).

Materials and methods: Initially, thyroid carcinoma cells were exposed to the 25 and 50 µg/mL ADSCs secretome for 24 and 48 hours, to evaluate of the proliferation and cytotoxicity of the C-643 cells, MTT test and colony assay was performed. Ethidium bromide/Acridine orange staining was done to evaluate apoptosis. The expression of apoptosis-related genes was determined by real-time PCR technique.

Results: Cell viability and colony numbers in secretome treated groups was significantly lower than control group. The amount of apoptosis-related genes (Bax/Bcl2, P53, Caspase3 and Caspase 8) expression in secretome treated groups was more than control group.

Conclusion: The results showed that ADSCs secretome caused the significant reduction of cell growth and increase of apoptosis in C-643 cells.

Keywords: thyroid carcinoma, secretome, apoptosis, viability, mesenchymal stem cells

18512

High expression of immune checkpoint molecules in different types of thyroid cancer

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Background: PD-1 and PD-L1 are two essential members of immune checkpoints. Their expression in various types of cancers attenuates the host immune response to cancer cells, and results in to tumor immune escape. However, the expression of PD-1 and PD-L1 molecules in thyroid cancer has not been well explored. The study aimed to investigate the expression of PD-1 and PD-L1 in four tumor types of thyroid cancer, and determine their association with the clinicopathological characterization of patients.

Methods: The specimen from 65 patients with primary thyroid cancers including PTC (papillary thyroid carcinoma), FTC (follicular thyroid carcinoma), MTC (medullary thyroid carcinoma), and ATC (anaplastic thyroid carcinoma) tumor types were enrolled in this study. The expression of PD-1 and PD-L1 molecules was evaluated by immunohistochemistry in formalin-fixed paraffin-embedded (FFPE) tissues.

Results: Our results showed that expression of PD-1 and PD-L1 in tumor cells as well as tumor infiltrating lymphocytes (TILs) is different among four major tumor types of thyroid cancer. However, their expression in both tumor cells and TILs were found to be significantly higher in ATC than the other tumor types ($P<0.001$). Additionally, the expression of PD-1 and PD-L1 molecules was significantly associated with advanced stages, higher tumor size, tumor necrosis and mitosis in patients with thyroid cancer ($P<0.05$).

Conclusion: Our results show that higher expression of PD-1 and PD-L1 molecules may contribute to tumor progression in the patients with thyroid cancer. The findings suggest that immune check inhibitor therapy might be a promising strategy for treatment and/or outcomes improvement in patients with thyroid cancer especially those with ATC tumor type.

Keywords: Immune checkpoint, PD-1, PD-L1, Thyroid cancer, Immunohistochemistry

18783

MiRNA-29a reverses P-glycoprotein-mediated drug resistance and inhibits proliferation via up-regulation of PTEN in colon cancer cells

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Background: Colon cancer is a serious malignant type of cancer in the world. Acquisition of multi-drug resistance (MDR) during chemotherapy is still a controversial challenge during cancer treatment. Accordingly, detection of safe and impressive MDR-reversing targets such as microRNAs (miRNAs/miRs) can play critical role in cancer treatment. **Methods:** Here, the functional effects of miR29a in chemo-resistant colon cancer cells is scrutinized. The effect of doxorubicin (DOX) on cell proliferation after miR29a transfection has been evaluated using MTT assay in HT29 and HT29/DOX cells. Rhodamine123 (Rh123) assay is used to identify the activity of common drug efflux through membrane transporters P-glycoprotein (P-gp). P-gp and PTEN mRNA/protein expression levels were measured by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blot analyses. Flow cytometry was employed to the investigation of apoptosis. ANOVA followed by Bonferroni's and Sidak's tests were used to compare the data from different groups. **Results:** Thus, it was shown that miRNA29a overexpression considerably inhibited the HT29/DOX viability. miR29a significantly down-regulated P-gp expression and activity in HT29/DOX cells and declined drug resistance through elevation of intracellular DOX. Furthermore, upon miRNA29a transfection, PTEN expression could be restored in resistant cells. These results have indicated that miR-29a target PTEN ultimately P-gp, which is downstream of PTEN, inhibit drug resistance, proliferation, and apoptosis through PI3K/Akt pathway. **Conclusion:** As a result, miR29a overexpression is led to enhance the sensitivity of HT29/DOX cells to DOX-treatment by targeting P-gp. MiR-29a might proffer a novel promising candidate for colon cancer therapeutics during chemotherapy.

Keywords: Colon cancer, microRNA-29a, multi-drug resistance, PTEN, PI3K/Akt, P-gp

18684

GM-CSF Producing Lymphocytes in Tumor-Draining Lymph Nodes of Patients with Bladder Cancer

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Background: Bladder cancer (BC), which arises from the tissue of the urinary bladder, is the tenth common cancer worldwide. Despite the presence of recent treatments and chemotherapy drugs, the survival rate of BC patients is still low. Manipulation of the immune system is recently introduced as an interesting alternative option for this immunogenic cancer to remove tumor cells with fewer side effects. In this way, considering the importance of the immune system, in the present study we explored the frequency of GM-CSF producing lymphocytes in tumor-draining lymph nodes of BC patients and evaluated their relationships with clinical-pathological prognostic factors.
Methods: Lymph nodes were recruited from 54BC patients who received no treatment. The peripheral blood from 5 healthy people was also obtained as controls. Mononuclear cells were obtained from fresh homogenized lymph nodes or peripheral blood using Ficoll-Hypaque gradient centrifugation. The cells were then washed, activated and subjected to surface and intracellular staining by appropriate fluorochrome-conjugated antibodies specific for CD4, CD8 and GM-CSF markers.
Results: Analyses by flow cytometry revealed that GM-CSF producing lymphocytes in both $CD4^+$ and $CD8^+$ populations were significantly lower in draining lymph nodes of BC patients than those in the peripheral blood of healthy controls. In addition, the higher frequency of GM-CSF producing lymphocytes and also higher expression of GM-CSF in $CD4^+$ lymphocytes was seen in patients with free lymph nodes comparing to those having at least one tumor-infiltrated lymph node. No other significant relationships were observed among clinical-pathological prognostic factors and the frequency of GM-CSF producing subsets. However, there was a positive correlation between the different subsets of GM-CSF producing lymphocytes and the expression of GM-CSF by them.
Conclusion: Collectively, based on the lower frequency of GM-CSF producing subsets in patients than healthy individuals and the higher production of GM-CSF in patients with less progressed tumor, we conclude the protective role for this cytokine in the context of BC.

Keywords: Bladder cancer, GM-CSF, $CD4^+$, $CD8^+$, ThGM, TcGM

18690

Association of IL-1β (C+3954T) Gene Polymorphism with Acute lymphoblastic leukemia (ALL) in Iranian child

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Background: ALL is a progressive and malignant disease with the origin of B or T lymphocyte precursors. This disease is caused by the incomplete proliferation and development of lymphoblasts in the bone marrow. ALL is one of the leading malignancies leading to death, especially in infants. Cytokines have different functions in causing and developing cancers in the body. One of the factors influencing the type of cancer is genetic aptitude. IL-1β is a pro-inflammatory cytokine that exerts its biological function by binding to IL-1RI. IL-1β contains different SNPs that IL-1β C+ 3954T is located in the fifth exon of the IL-1β gene and is said to affect its expression, and individuals with T allele have higher expression. This study aimed to investigate whether the IL-1β C+3954T polymorphism gene is associated with an increased risk of ALL.

Methods: The single-nucleotide polymorphism of the IL-1β gene (C+3954T) was analyzed in 80 patients with ALL and 80 age- and sex-matched control groups in Iranian children finite fragment polymorphism (RFLP) strategy.

Results: After a statistical analysis of different IL-1β C+3954T genotypes, there was no significant relationship between the case and control groups (P= 0.23). Also, the frequency of different IL-1β alleles (C+3954T) was not significant in healthy and control groups (P= 0.317).

Conclusion: This is the first study to examine the association between IL-1β C+3954T polymorphism and the risk of ALL. Our data did not show a significant relationship between the incidence of ALL and IL-1β C+3954T polymorphism.

Keywords: Genetic susceptibility, polymorphism, IL-1β, acute lymphoblastic leukemia (ALL)

18483

Immunomodulatory effect of omega-3 fatty acids in patients with differentiated thyroid cancer scheduled for radioiodine ablation

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Background: Inflammation is considered one of the hallmarks of cancer development and progression. Massive thyrocyte destruction following radioiodine treatment may cause further inflammation. Omega-3 is introduced as a component with potent anti-inflammatory and immunomodulatory effects. This study was designed to identify the effect of omega-3 on cytokine levels in patients with differentiated thyroid cancer along with radioiodine treatment.

Methods: A total of 49 patients with differentiated thyroid cancer were divided into two corresponding groups, one with (test group, n=19) and another without (control group, n=30) omega-3 consumption. Each group was also subdivided based on radioiodine dose to intermediate-dose with 100 mCi and high-dose with 150 mCi. Every patient in the test group took omega-3 one month before till one month after radioactive iodine (RAI) ablation. Serum levels of IL-6, IL-2, IL-4, IL-5, IL-13, IL-17A, IL17F, TNF, and IFN-ɣ were measured by multiplex bead-based assay in different time points.

Results: Serum levels of IL-17F decreased 1 week after ablation with intermediate-dose RAI in control group (P=0.039). Serum levels of IL-6 in intermediate-dose group (P=0.008) and IL-17A in high-dose group (P=0.034) significantly decreased after treatment with omega-3. There was a significant decrease in IL-17F levels after high-dose RAI ablation in test group (P=0.028). Following the use of omega-3, TNF levels dropped sharply (P=0.018). However, its levels increased after RAI and did not reach to its initial level (P=0.028). Cytokine changes 1 week and 1 month after RAI ablation when adjusted to their values in the time point immediately before RAI ablation, showed significantly higher changes of TNF in test group than control group one month after high-dose RIA. A remarkable increase in IL-17F changes was seen in test group compared to control group a week after intermediate-dose RAI.

Conclusion: Omega-3 can significantly reduce some potent pro-inflammatory cytokines in differentiated thyroid cancer. Due to the specific accumulation of radioactive iodine in thyrocytes, extensive systemic inflammation may not be induced after RAI ablation.

Keywords: differentiated thyroid cancer, radioiodine ablation, omega-3, cytokine

18679

Association between Prognosis factors and Response to Therapy in Patients by Lymphoma Cancer

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Introduction: Lymphoma is a group of blood and immuno cancer that develop from lymphocytes. Signs and symptoms may include enlarged lymph nodes, fever, drenching sweats, unintended weight loss, itching,and constantly feeling tired. The two main categories of lymphomas are Hodgkin lymphomas and the non-Hodgkin lymphomas.TheWorld Health Organnization (WHO)includes two other categories as types of lymphoma: multiple myeloma and immunoproliferative diseases. About 90% of lymphomas are non-Hodgkin lymphomas.Lymphomas and leukemias are a part of the broader group of tumors of the hematopoietic and lymphoid tissues. The aim of the present study was to observation the response to treatment and prognosis of patients lymphoma.

Methods: 40 patients with aggressive lymphoma treated with chemotherapy consisting of the CHOP regimen followed by radiotherapy controls were enrolled in this study. 14 patients had Stage I, 16 had Stage II, 7 had Stage III and 3 had Stage IV disease. According to the International Prognostic Index (IPI), 15 had low, 18 had low-intermediate, 3 had high-intermediate and 4 had high IPI. After three to six cycles of chemotherapy, involved-field radiotherapy was performed. We evaluated the response to treatment by computed tomography (CT), magnetic resonance imaging (MRI) and gallium scintigraphy (Ga-67) at the time of completion of chemotherapy and at the time of completion of radiation therapy. The median follow-up period was 48 months. P-values less than 0.05 were considered statistically significant.

Results: The 2-year progression-free survival rates of the patients with Ga-67 positive uptake and Ga-67 negative uptake after completion of chemotherapy were 78% and 26% (P = 0.008), respectively. There was a significant associations between progression free survival and the response after completion of chemotherapy determined by CT (P = 0.045) or MRI (P = 0.019). The response to treatment at the time of completion of overall treatment was useful for prediction of prognosis.

Conclusions: The result of this study showed a significant association of Prognosis factors and Response to Therapy and risk of lymphoma cancer development.

Key words: aggressive lymphoma, chemotherapy, gallium scintigraphy

18691

Interleukin-1 receptor antagonist gene polymorphism and ALL in Iranian child

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Background: Acute lymphoblastic leukemia is the most common cancer in children under 15 years of age. Its prevalence is increasing in Iran and the world. Malignancies of B and T lymphocyte precursors cause ALL. Various environmental factors such as nuclear radiation exposure and genetic factors such as genetic syndromes and gene translocation can play a role in ALL's development. Although the association between interleukin1 and cancer has been studied, the role of this interleukin1 in the tumor microenvironment and cancer induction is still debated. IL-1Ra is a member of the IL-1 family that binds to interleukin-1 receptors and competitively inhibits IL-1a and IL-1β binding, and exerts its antagonistic function by inhibiting intracellular signaling. IL-1Ra has a VNTR in the second intron that contains an 86bp sequence with different replications. This study aimed to investigate whether the VNTR polymorphism of IL-1Ra is associated with an increased risk of ALL.
Methods: VNTR polymorphism of the IL-1Ra gene was analyzed in 80 patients with ALL and 80 age- and sex-matched control groups in Iranian children using PCR strategy.
Results: The frequency of different IL-1Ra genotypes in the case and control groups did not show a significant relationship. The count of different IL-1Ra alleles in the case group and its comparison with the control group had no meaningful relationship.
Conclusion: Our study is the first study investigating the association between IL-1Ra polymorphism and the risk of ALL. Statistical analysis did not show a significant relationship between the incidence of ALL and IL-1Ra polymorphisms. Further studies are needed to obtain more definitive results.

Keywords: Genetic susceptibility, polymorphism, IL-1Ra, acute lymphoblastic leukemia (ALL)

18776

Subcutaneous Panniculitis-Like T-Cell Lymphoma in a young girl with a periorbital edema and fever

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Background: subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare, highly malignant, extra-nodal lymphoma that preferentially infiltrates into subcutaneous adipose tissue. No case of SPTCL with the periorbital swelling has been reported. **Methods:** we report a very rare case of SPTCL complicated by sever periorbital swelling in a young girl. **Results:** our patient was a ten-year-old girl who had a right periorbital swelling for about one week before referral, who was initially treated with an antibiotic for the diagnosis of pre-septal cellulitis, but gradually fever and left periorbital swelling were added to symptoms. And finally, painless swelling in the cheeks area also spreads and become weakness and high grade fever and also the lesions become ulcerative. **Conclusion:** we described a young girl patient who presented with fever and facial swelling and painless ulcerative lesion with a hemophagocytic syndrome accompanying histopathological features of SPTCL with clinical and morphological involvement of subcutaneous tissue with a good response to chemotherapy.

Keyword: Systemic lupus erythematosus- Subcutaneous panniculitis-like T-cell lymphoma

18745

Upregulation of PD-1 immune checkpoint molecule and its ligands, PD-L1 and PD-L2, on infiltrating lymphocytes in patients with bladder cancer

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Background: It is now well-established that despite the immune system effort to fight the tumors, they escape from immune responses using different mechanisms. One of them is inhibition of tumor-infiltrating lymphocytes through the expression of immune checkpoint molecules. Accordingly, we investigated the expression of PD-1 and its ligands, PD-L1 and PD-L2, on the tumor /stromal cells as well as infiltrated immune cells in bladder cancer. The expression of these markers was also studied on the main T cell subsets: helper $CD4^+$ T cells and $CD8^+$ cytotoxic T cells.

Methods: Totally, 24 tumor tissues from patients with bladder cancer were obtained and mechanically minced and filtered to obtain a single-cell suspension. The cells were then counted and divided into two groups. The first were directly stained for CD45, PD-1, PD-L1, and PD-L2 using specific fluorochrome-conjugated antibodies. The second were subjected to enrichment for immune cells using Ficoll and then stained for CD3, CD4, CD8, PD-L1, and PD-L2. The cells were acquired on a 10-color FACSAria flow cytometer and analyzed with FlowJo software. The frequency of cells expressing PD-1, PD-L1, and PD-L2 were then determined in each group.

Results: We observed that approximately 2% of tumor/stromal cells with $CD45^{neg}$ phenotype, expressed PD-1, PD-L1, and PD-L2 molecules. Whilst, 65% of tumor-infiltrated immune cells ($CD45^+$) were positive for PD-1 and more than 21% and 27% of them expressed PD-L1 and PD-L2, respectively. Furthermore, PD-L1 and PD-L2 ligands were observed to be highly expressed on both $CD4^+$ and $CD8^+$ subsets since more than 80% of the $CD4^+$ helper and 77% and 41% of $CD8^+$ cytotoxic T cells were positive, respectively.

Conclusion: The highly expressed of PD-1 immune checkpoint and its ligands, PD-L1 and PD-L2, on immune infiltrated cells showed that the immune system in patients with bladder cancer is exhausted and probably dysfunctional, leading to tumor progression.

Keywords: Bladder cancer, tumor-infiltrated immune cells, PD-1, PD-L1, PD-L2.

18678

Association of IL-27 rs12144160 and rs693655 Polymorphisms with Risk and Response to Therapy in Acute myeloid Leukemia

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Introduction: Interleukin-27 is a cytokine with important anti-cancer activity. This study has evaluated the effects of IL-27 rs12144160 and rs693655 single nucleotide polymorphisms (SNPs) on risk of acute myeloid leukemia (AML) development, as well as their impact on prognosis and patient survival.

Materials and Methods: A total of 160 patients and 200 healthy subjects were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). There were 40 new cases that had received no chemotherapy at enrollment. We used the samples from these patients for IL-27 serum measurements by enzyme-linked immunosorbent assay (ELISA). The laboratory and clinical characteristics recorded at presentation were sex, age, white blood cell counts, platelet counts, immunophenotype, and hemoglobin (Hb) level, percentage of blast in the bone marrow and peripheral blood, and extra-medullary involvement (EMI). During the period of follow-up, response to therapy was evaluated by measuring complete remission (CR) rate, CR duration (CRD) and overall survival. Statistical analyses were accomplished using SPSS version 23 for Windows. P-values less than 0.05 were considered statistically significant.

Results: We observed a higher frequency of rs12144160 AG and rs693955 AC genotypes and allele G, C in patients compared to controls ($p<0.001$). Combined G, C variant genotypes (AG+GG and AC+CC) also conferred significantly greater risk of AML. There was a significant correlation between the genotypes of both SNPs with event-free survival (EFS). Patients with GG, CC genotypes of both SNPs and those of rs12144160 AG and rs693955 AC had a shorter EFS than patients with rs12144160 AA and rs693955 AA genotypes ($p\leq0.025$). Combined G, C variant genotypes for both SNPs showed poorer response to therapy in all patients ($p<0.035$) as well as B-AML (rs12144160, $p<0.001$) and T-AML (rs12144160, $p=0.036$) patients. In multivariate analysis, rs12144160 combined G variant genotype was associated with shorter EFS (relative risk=8.6, $p=0.035$). Among those who relapsed, 86.2% had the rs12144160 AG genotype and 74.5% had the rs693955 AC genotype ($p<0.01$). Patients had higher IL-27 serum levels compared to controls.

Conclusions: The aassociation of IL-27 rs12144160 and rs693955 polymorphisms with risk of AML development and their impact on EFS suggested an important role for this cytokine in biology and response to AML therapy.

Key words; Interleukin-27, Acute myeloid leukemia, polymorphism

18685

Evaluation of the prognostic value of CD56 (140 kDa isoform) expression in breast cancer tissues: an eight-year retrospective study

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Background: Breast cancer is one of the most prevalent malignancies among females. Recognizing specific antigens is highly beneficial for early detection, diagnosis, staging, and prognostic predictions. This study aimed to evaluate the expression and prognostic value of CD56 (140 kDa isoform) in invasive ductal carcinoma (IDC).

Methods: In this retrospective study, we included 65 patients with IDC who underwent radical surgery or mastectomy as the primary treatment. Proper formalin-fixed and paraffin embedded tissue blockes of the patients were prepared and stained by immunohistochemistry for CD56 molecule. Chi-squar and fisher exact tests were used to compare the results against the clinicopathologic data of patients. Kaplan-Meier and log-rank test were employed to study the prognostic value of the target antigen.

Results: The pattern of expression of CD56 was granular and cytoplasmic. There was significant associations between the intensity of CD56 expression in invasive cells and carcinoma in situ (P=0.005) and normal ducts (P=0.010). Among all clinicipathologic parameters, there was only a significant association between the expression of estrogen receptor (ER) and CD56 (P=0.023). Neither overall survival (P=0.356) nor disease-free survival (P=0.976) shared significant associations with CD56 expression.

Conclusion: Our data indicate that the CD56 marker offers no prognostic value in terms of predicting the overall survival or disease-free survival for up to 8 years after primary surgery. Furthermore, its expression intensity is similar between normal, non-invasive, and invasive cells. Considering the generally better outcome of ER+ breast cancer patients than their ER- counterparts, the CD56 marker may be indirectly associated with a more favorable prognosis among IDC patients.

Keywords: CD56; breast cancer; prognosis; survival

18683

Investigation link between the miR-155 expression with cytokines levels in Non-small cell lung cancer patients

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Background: Nonsmall cell lung cancer (NSCLC) is the major type of lung cancer. MicroRNAs (miRNAs) are currently considered as novel markers and targets in cancer therapy as tumor suppressors and oncogenes. Previously we have shown that miRNA 155 playing a role in susceptibility to NSCLC. Thus, in this study we aimed to test link between expression of miRNA-155 and the serum cytokines levels in NSCLC patients.

Methods: Thirty three NSCLC patients and 30 healthy subjects were recruited in this study at Masih Daneshvari Hospital. Quantitative real-time PCR (qRT-PCR) was used for the measurement of the expression level of miR-155 in peripheral blood mononuclear cells (PBMCs). Serum cytokines (IL-1, IL-6, TNFα, TGF-β, IL4, and IFN-ɣ) levels were determined by ELISA methods.

Results: No difference was found in expression of miR-155 between patients and healthy subjects. IL-6 and TGF-β levels were elevated in NSCLC patients than healthy subjects group (P=0.001, P=0.018 respectively). A positive correlation between miR-155 and IL-1 level (r= 0.567, p≤0.001) was observed in NSCLC patients.

Conclusion: There was not different in expression of miR-155 between patients and controls but miR-155 expression associated positively with IL-1 level.

Keywords: MicroRNA-155, Cytokine, Diagnosis, Non-small cell lung cancer

18645

Impact of Cytarabine (Ara-C) on human lymphoblastic leukemia cell lines via targeting experssion of DNMT3B

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Background: Cytarabine (cytosine arabinoside, Ara-C), a pyrimidine nucleoside analog, has antimetabolite, antineoplastic, antiviral, and immunosuppressant properties. Moreover Cytarabine is an S-phase-specific drug and an effective chemotherapeutic agent for the treatment of acute myelogenous leukemia and lymphocytic leukemia. In this study, we investigated the role of Cytarabine (Ara-C) in the treatment of lymphoblastic leukemia by targeting DNMT3B and its effects on Nalm6 cells proliferation and apoptosis.

Methods: In this research, Nalm6 cells and normal peripheral blood mononuclear cells (PBMCs) were cultured in RPMI 1640 medium with 10% fetal bovine serum and treated with Cytarabine (Ara-C) at their exponential growth phase at 37 °C in a 95% humidified atmosphere with 5% CO2. Annexin-V/PI staining and FACS analysis performed to estimate the cell apoptosis levels. The cytotoxicity of Ara-C treatment in the Nalm6 cells was evaluated using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay. The mRNA expression of DNMT3B was analyzed by reverse transcription-polymerase chain reaction (RT-PCR). And the end one-way ANOVA and t-Test were used for statistical analysis.

Results: Based on the results, exposure to Ara-C stimulates apoptosis and inhibits cell proliferation in the Nalm6 cells line. After Ara-C treatment, expression of DNMT3B gene in Nalm6 cells line decreased significantly compared with the control group ($P<0.05$).

Conclusion: In sum, we showed that Ara-C could display notable cytotoxicity against leukemia Nam6 cells and can suppress their proliferation and attenuate survival by down regulation of DNMT3B expression that suggests the epigenetic changes such as DNA hypermethylation may be appropriate goals in the development of new therapies.

Keywords: DNA methyltransferase (DNMTs), Leukemia, Cytarabine (Ara-C)

18302

The effect of hydro alcoholic extract of Citrullus colocynthis on induction of apoptosis in oral squamous cell carcinoma cell line

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Background: Induction of apoptosis is one of the important mechanisms for removing of cancer cells. Plants have a long history in the treatment of cancer. The plant Citrullus colocynthis, belonging to Cucurbitaceae family, is known as "Hendevaneh Abujahl in Persian. A few studies have investigated the antioxidant and anti-inflammatory effect of this plant. In this study, the effect of hydroalcoholic extract from Citrullus colocynthis plant on induction of apoptosis in OCC-2 cell line was investigated.
Materials and Methods: The growth inhibitory effects of hydroalcoholic extract from Citrullus colocynthis plant on OCC-2 cell line was determined by MTT assay. The most effective concentration was analyzed by flow cytometry for apoptosis induction.
Results: Hydroalcoholic extract showed growth inhibitory effects on OCC-2 cell line. IC50 of 353 µg/ml and 232.9 µg/ml were obtained for hydroalcoholic extract after 24 and 48 h, respectively. Moreover, hydroalcoholic extract able to significantly induce apoptosis at concentration of 500 (15.22±0.08, $P<0.01$) and 1000 µg/ml (46.02±4.18, $P<0.0001$) for 24 h and 500 (34.69±3.49, $P<0.001$) and 1000 µg/ml (57.5±4.29, $P<0.0001$) for 48 h on OCC-2.
Conclusion: our results showed that hydroalcoholic extract from Citrullus colocynthis plant had inhibitory effect on OCC-2 cell line (dose and time-dependently manner). It might be good candidates for more studies in regard to its possible therapeutic usefulness in oral squamous cell carcinoma.

Key words: Apoptosis, Oral squamous cell carcinoma cell line, Citrullus colocynthis

18451

Evaluating the expression levels of Glycogen Synthase Kinase α (GSKα), GSKβ and Wilms' Tumor gene product 1 (WT1) in patients with Acute Myeloid Leukemia (AML)

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Background: The genes overexpression play an essential role in the prognosis of most forms of Acute Myeloid Leukemia (AML). Although several research studies have tried to quantitatively analyze different genes such as Wilms' tumor (WT1), GSK-, and GSK- in AML prognosis, there is no group evaluation for all such genes yet. The goal of this study was to evaluate the expression levels of GSK-, GSK-, and WT1 genes in AML patients before receiving chemotherapy and then investigate their relations together in AML prognostication.

Method: 2 ml of blood was obtained from 30 AML patients (average age:) before receiving chemotherapy as well as 20 control individuals (average age: 51.2112.7). Based on the Traizol method, total RNA was extracted and subsequent to cDNA synthesis, real-time PCR analysis was performed. Collected data was analyzed using Livak (ΔΔCT). After that, the fold change in gene expression was calculated using Fold-change = $2^{(-\Delta\Delta Ct)}$. Normal individuals without any interventions were used as calibrators. The normalization was performed against TFRC (housekeeping gene).

Results: Our results demonstrated a significant increase in GSKα (Mean ± SD: 1.5 ± 0.35 vs 0.84 ± 0.39; P<0.0001) GSK-β (190.2±127.8 vs 1.03±0.64; P<0.0001) and WT1 (26.89 ± 18.3 vs 1.11 ± 0.59; P< 0.0001) expression compared to normal individuals. In AML patients, GSK-β (8.1 to 561.5 fold vs 0.23 to 2.3 fold) and WT1 (5.9 to 67.4 fold vs 0.24 to 2.1 fold) expression level was varied within wide range.

Conclusion: Our results showed that higher expression of WT1, GSKα and GSKβ genes may contribute to AML progression in patients. These findings suggest that WT1, GSK- and GSK-, might be promising to be used as a biomarker in AML prognosis and evaluating the performance of treatments in AML patients.

Keywords: AML, Wilms' tumor, Glycogen synthase kinase

18454

CD45RO expression in tumor tissue of breast cancer patients with different molecular subtypes as a prognostic and predictive factor

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Background: It has been well-documented that memory T cells are a crucial participants of tumor cells elimination. We previously observed that CD45RO$^+$ lymphocytes, consisted one of the most infiltrates in breast tumor tissues, seems to be a reliable marker for predicting patient's prognosis and outcome. In present study, we confirmed the importance of CD45RO expression in larger population of patients with special focus on molecular subtypes.

Methods: Formalin fixed and paraffin embedded tissue blocks of 300 untreated breast cancer patients with known molecular subtypes (luminal, triple negative and Her2-enriched) were selected and stained immunohistochemically for CD45RO marker. The number of CD45RO+ cells were then counted using ImageJ software and adjusted per area unit (mm^2).

Results: Mean frequencies of CD45RO$^+$ lymphocytes were 2643.12 cells/mm^2 in the invasive margin and 1818.04 cells/mm^2 in the center of tumor. Infiltration of CD45RO$^+$ cells showed significant variation among tumors with different molecular subtypes ($P<0.05$). Accordingly, Her2-enriched tumors had the highest frequency of CD45RO$^+$ cells in both center and invasive margin of the tumor while the luminal tumors represented the lowest infiltration ($P<0.0001$). The frequency of these cells also showed a notable association with paraclinical and pathological features i.e. histological grade, tumor type, and age of the patients ($P<0.05$).

Conclusion: Our data indicated a remarkable difference in memory responses among different subtypes of breast cancer, critically effecting disease progression and patient's outcome.

Keywords: Breast cancer, Memory T cells, CD45RO

18419

The effect of serum-derived exosomes of breast cancer patients on the Hexokinas2 gene expression in peripheral blood mononuclear cells

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Background: Cancer cells affect immune cells in a variety of ways. One of the mechanisms that tumors inhibit and alter the cell program of immune cells is the secretion of nanoscale vesicles, or in other words, the secretion of exosomes. Various studies have been performed on the effect of tumor exosomes on immune cells, and various pathways have been investigated. However, some pathways are not yet fully elucidated, such as metabolic pathways. The study aimed to investigate the effect of tumor exosomes on the expression of the Hexokinase 2 gene, which is an important protein in the glycolysis pathway in immune cells.

Methods: For this study, serum samples of breast cancer patients in grades 3 and 4 were collected and the exosome was isolated. After confirmatory tests, peripheral blood mononuclear cells were treated with the exosome for 72 hours, then the expression of the Hexokinas2 gene was measured by real-time PCR method.

Results: Relative expression of the Hexokinase 2 gene in the adjacent group with serum-derived tumor exosomes was significantly increased ($P < 0.05$) compared to the control group.

Conclusion: Our results showed that tumor-derived exosomes can cause metabolic changes in peripheral blood mononuclear cells and possibly increase the metabolic pathway of glycolysis in them.

Keywords: tumor-derived exosomes, Hexokinase 2, glycolysis

18446

Prognostic value of tumor infiltrating lymphocytes in tongue and larynx squamous cell carcinoma

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Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent neoplasm worldwide with the 5-year survival rate of 60%. Tumor-infiltrating lymphocytes (TILs) as important components of tumor microenvironment appear to be valuable prognostic biomarkers that predict cancer patients' outcome. However, their role in the HNSCC requires further studies.
Methods: in this retrospective study FFPE tissue samples of 102 patients with primary larynx (N=63) and tongue (N=39) SCCs were immuno-stained for CD3 (clone EP41), CD4 (clone EP204), CD8 (clone SP16), and CD45RO (clone UCHL1). An expert pathologist acquired digital micrographs from center of the tumor (CT) and the invasive margin of each stained marker. The number of positive-stained cells was counted by Fiji software.
Results: Non-parametric Mann-Whitney U test showed that the mean frequency of CD8+ TILs in IM of patients older than 60 was significantly higher than younger patients (P=0.046). The infiltration of CD3+ (P=0.028) and CD4 + TILs (P=0.028) were significantly higher in IM of poorly differentiated tumors. The mean frequency of CD3+ (P=0.041), CD4+ (P=0.023), and CD8+ TILs (P=0.025) in CT, and CD4+ TILs (P=0.002) in IM of patients with TNM-I, II were significantly higher. In survival studies, univariate Cox regression analysis in both disease-free survival (DFS) and overall survival (OS) showed a statistically significant negative prognostic effect of lymph node invasion (HR=2.354, P=,0.041and HR=2.192, P=0.05, respectively) and a positive effect of higher CD45RO-IM (HR=2.628, P=0.017, and HR=2.407, P=0.025, respectively). From the multiple Cox proportional hazard model, the frequency of CD45RO+ cells in IM had significant prognostic effect on both OS (P=0.019, 95% CI=1.1.175-6.029, HR=2.662) and DFS (p=0.020,95% CI=1.177-6.558, HR=2.778).
Conclusion: CD45RO+ tumor-infiltrating immune cells in the IM of tumors are strong prognostic markers that are associated with favorable OS and DFS in patients with tongue and larynx SCC.

Keywords: Head and Neck Squamous Cell Carcinoma, Tumor Infiltrating Lymphocytes, Prognostic Marker, Tumor Microenvironment.

18439

WT1-mRNA over expression in the Glioblastoma Multiform (GBM) patients

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Background: Glioblastoma multiform (GBM), a WHO Grade IV glioma is the most common primary brain tumor. Recently, WT1 protein has been considered as a new molecular target of cancer immunotherapy for several solid tumors. The goal of the current study was to determine whether WT1 mRNA was expressed in tissue specimen's glioblastomas.
Method: Relative expression of WT1 gene was examined by reverse transcription polymerase chain reaction (RT-PCR) in all tissue samples from 27 glioblastomas, 3 medulloblastoma (high grade (IV) childhood brain tumor; as negative control) and compared with in human leukemia cell line K562 which expresses a high level of WT1 (as positive control). WT1 mRNA level in K562 leukemia cells was defined as 1.0. The normalization was performed against TFRC (housekeeping gene).
Results: Our results showed that WT1 mRNA was expressed at levels ranging from 0.8 to 6.57 fold in the glioblastomas. However, in the medulloblastoma tissues, WT1 mRNA was detected at low levels ranging from 0.01 to 0.19 fold. Eventually, these results demonstrated that the expression levels of WT1 mRNA in the glioblastoma tissues were significantly higher than those in the medulloblastoma tissues (Mean ± SD: 1.99 ± 1.45 fold and 0.075 ± 0.099 fold, respectively; $P< 0.001$).
Conclusion: These observations suggest that the WT1 gene might be closely associated with tumorigenesis of glioblastoma compared to medulloblastoma. Accordingly, WT1 peptide might be applicable as a potential treatment option for patients with glioblastoma.

Keywords: Wilms' tumor gene 1 (WT1); Glioblastoma Multiform (GBM); Medullablastoma; K562

18433

HVEM/BTLA immune checkpoint expression in development of gastric cancer

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Aim: Regarding the role of BTLA/HVEM in tumorigenesis, we determined the HVEM/BTLA expression in gastric cancer.
Methods: 114 patients were enrolled in the study. They were divided into groups of NUD (n=32), IM (n=19), and GC (n=63). BTLA and HVEM in gastric biopsies were evaluated using SYBR Green based Real-Time PCR and Immunohistochemistry. The sHVEM concentration and Anti- *H.pylori* IgG antibody were assessed in sera of all study subjects.
Results: Our result showed that HVEM protein expression was significantly higher in GC compared to the NUD and IM groups (p <0.0001 and p = 0.0002, respectively), in contrast to mRNA. BTLA mRNA expression was significantly higher in GC compared to the IM and NUD groups (p = 0.004 and p = 0.0003, respectively), also significantly higher in the advanced stages of GC (p=0.039). Concurrently, IHC results showed higher expression of BTLA in GC and IM compared to NUD group (p = 0.0002 and p = 0.008, respectively), also higher in advanced stages (p = 0.005). The sHVEM concentration was also higher in GC compared to NUD groups (p = 0.001).
Conclusions: High expression of BTLA/HVEM suggests that it involved in immune regulation and progression of IM and GC; so these molecules can be used for diagnosis and prognosis of GC.
Keywords: Herpesvirus entry mediator (HVEM), B and T lymphocyte attenuator (BTLA), Gastric cancer, soluble HVEM (sHVEM), Immune checkpoint

18328

Cold atmospheric plasma induces NLRP-3 and GSDME dependent pyroptotic inflammatory pathway through ROS generation in mice melanoma

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Background: Pyroptosis is a new form of programmed necrosis that occurs through activation of the NLRP-3 inflammatory pathway that resulting in caspase-1-dependent inflammation as well as GSEME activation through degradation of N-terminal domain by caspase-3-actived. In this pathway, the continuous proliferation of cells destroys the cell membrane and activates pro-inflammatory factors such as IL-6, IL-1β and TNF-α. Numerous studies have shown that CAP exposure increases intracellular ROS levels, which, in addition to apoptosis and necrosis, induces other types of cell death, such as pyroptosis, in chemotherapy-resistant tumors. Our aim in this study was to assess the effect of CAP on induction of pyroptosis inflammatory pathway in Balb/c B-16 melanoma mice.

Materials and Methods: We first after induction of three times of CAP treatment in B-16 melanoma mice, measured the serum levels of IL-6, IL-1β and TNF-α by ELISA and evaluated the genes expression of caspase-1, caspase-3 and caspase-9 by real-time PCR. Finally, to evaluate the activation of pyroptosis by CAP in tumor tissue, we examined the expression of NLRP-3 and GSDME-N by immunohistochemistry.

Results: Interestingly, increased levels of IL-1β and TNF-α but not IL-6, induced by activation of the inflammatory pathway were observed in the serum of CAP-treated mice. Also, CAP-induced ROS production was detected to initiate pyroptotic signaling, then activation of caspase-9 / caspase-3 and the presence of NLRP-3 and GSDME-N in our study showed that CAP-induced pyroptosis depends on activation of mitochondrial pathways (JNK / cytochrome c / caspase-9 / caspase-3) and the cleavage of GSDME but not Gasdermin D (GSDMD).

Conclusion: Overall, baseline levels of the GSDME protein were positively correlated with CAP sensitivity in mice melanoma, suggesting that GSDME may be a potential prognostic biomarker in the treatment of cancer by CAP. These results complement our knowledge of CAP-induced cell death and provide a strategy for optimizing the therapeutic effect of CAP in cancer.

Keywords: Cold Atmospheric plasma (CAP), mice melanoma, pyroptosis, NLRP-3, GSDME, inflammation

18298

Indoleamine 2, 3-dioxygenase (IDO) silencing in adipose derived mesenchymal stem cells (ASCs) and its possible effects on cancer

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Background: Mesenchymal stem cells (MSCs) indicate immunomodulatory function by secreting soluble factors including indoleamine 2, 3-dioxygenase (IDO) which induces immunosuppressive effects through catabolizing tryptophan (Trp) and generating Kyn pathway metabolites. Herein, we purposed to evaluate the effects of IDO silencing on immunosuppressive properties of adipose derived mesenchymal stem cells (ASCs), the phenotype of T cells co-cultured with IDO-silenced ASCs and the progression of MDA-MB-231 cancer cell line cultured with IDO-silenced ASC's condition media. **Methods:** Normal adipose tissues obtained during mammoplasty surgery were exploited for ASCs' isolation and IDO siRNA was transfected into ASCs by lipofectamine. Gal-3, TGF-β1, HGF and IL-10 expression were evaluated in ASCs using qRT-PCR. Flow cytometry and qRT-PCR were applied for T cell phenotyping and assessing IFN-γ and IL-17 expression in co-cultured PBLs. The migration of tumor cells was examined using scratch assay. **Results:** Induced expression of Gal-3 and HGF downregulation were significant in IDO-silenced ASCs relative to control groups ($P< 0.05$). Regulatory T cells (Tregs) including $CD4^+CD25^+FOXP3^+$, $CD4^+CD25^{High}FOXP3^+$, and $CD4^+CD25^-FOXP3^+$ T cells indicated lowered frequency in PBLs co-cultured with IDO-silenced ASCs. The number of $CD4^+IL4^+$- T cells (Th2) was partially lower in PBLs co-cultured with IDO-silenced ASCs than scramble group. IFN-γ upregulation and IL-17 suppression were observed in PBLs co-cultured with IDO-silenced ASCs. The migration of MDA-MB-231 cancer cells was suppressed in condition media of IDO-silenced ASCs relative to untransfected ($P< 0.01$) and scramble transfected ASCs ($P< 0.05$). **Conclusion:** IDO silencing can alleviate immunosuppressive and tumor-promoting properties of ASCs. This project may create clearer perspective to elucidate the role of IDO pathway in immunosuppressive mechanisms and innovate novel clinical scenarios for cancer treatment. Nevertheless, enhancing the efficiency of therapeutic approaches may be achieved by simultaneous inhibition of several immunomodulators and combination therapeutic strategies.

Keywords: Adipose derived mesenchymal stem cell; indoleamine 2, 3-dioxygenase; Immunomodulatory function; Tumor microenvironment; Regulatory T cell; Tumor invasion

18380

Association of Foxp3 polymorphism with IL-35 concentration in gastric adenocarcinoma patients

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Background: T regulatory cells (Tregs) and related-cytokines are effectively engaged in the process of tumor immune escape and functionally inhibit immune response against the tumor. This study aimed to investigate the association of Foxp3 gene single nucleotide polymorphism (SNP) (rs3761548) with serum IL-35 level in gastric adenocarcinoma (GA) patients.

Methods: The blood samples were obtained from 150 GA patients and 166 control subjects. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was done to genotyping of Foxp3 gene polymorphism (rs3761548). The serum IL-35 level was measured using the ELISA method. The Kaplan-Meier method was used to plot the overall survival curves and comparisons were estimated by the log-rank test.

Results: According to genotyping, the AA, and AC genotypes and A allele demonstrated significantly greater risk of GA. Considering the Lauren classification, our results revealed a greater risk of GA progression in patients with AC + AA genotype compared to CC genotype. Moreover, significantly increased level of IL-35 was observed in GA patients compared to controls and also in diffuse-type compared to the intestinal type of GA patients. The IL-35 concentration in GA patients displayed significant differences between the participants with CC, AC and AA genotypes. Further analysis indicated the prognostic role of serum IL-35 level in GA patients. Additionally, univariate analysis expressed that serum concentration of IL-35 has predictive value for overall survival in GA.

Conclusion: Our results confirmed that the Foxp3 polymorphism (rs3761548) could influence the predisposition to GA and the serum IL-35 level. Thus, this polymorphism might be involved in the GA progression through influencing Tregs function and the secretion of immunomodulatory cytokines.

Keywords: Gastric adenocarcinoma, Foxp3 gene polymorphism, Tregs, IL-35

18407

Tumoral Exosomes Enriched by MiR-34a Efficiently Represent Tumor Suppressive Effects and Restrict Viability and Migration of Colorectal Cancer Cells

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Background: MicroRNA-34a (miR-34a) as a master tumor suppressor in colorectal cancer (CRC) is capable of modulating several genes involved in tumor proliferation, invasion, immune evasion and inflammation-induced progression. Exosomes are novel nanocarriers with the ability of delivering crucial mediators to various cells. Here, we investigated the anti-proliferative and progressive effects of tumor-derived exosomes (TEXs) isolated from starved tumor cells as a vehicle to transfer miR-34a mimic into CRC cell line CT-26.

Methods: TEXs were isolated from starved CT-26 cells and enriched by miR-34a through calcium chloride (CaCl2) modified solution. MiR-34a expressions were determined in the enriched TEXs using real-time PCR, the viability of CT-26 cells treated with multiplicity concentrations of TEX-miR-34a was evaluated. Then the expressions of miR-34a target genes related to tumor progression were examined in the treated CT-26 cells and migration of tumor cells subjected to TEX-miR-34a was determined in vitro.

Results: The results showed that TEX-miR-34a was able to decrease the viability of CT-26 cells dose-dependently and restrict the migration levels of tumor cells as well as the expressions of tumor promoting genes significantly. Interestingly, TEXs also prevent the viability and migration of the cells.

Conclusion: Exosomes derived from starved tumor cells were promising carrier to shuttle miR-34a properly into CT-26 cells and maintain miR-34a functionality in the term of down regulating tumor progressive genes and TEXs alone not only showed no positive effects in favor of cancer cells, but also act probably as a hopeful adjuvant in CRC therapy.

Key words: MicroRNA, Colorectal cancer, Nanocarrier, Migration, Viability

18396

Evaluation the possible effects of AZD1152-HQPA on cellular and molecular aspects of cell migration in glioblastoma

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Background: Glioblastoma (GB) is one of the most invasive central nervous system (CNS) tumors. Aurora kinase B as an oncogene is upregulated in proliferative cells and involved in the segregation of chromatids and cytokinesis through diverse stages of mitosis. Concerning the fact that overexpression of AURKB is associated with tumor invasion and metastasis, its inhibition by using AZD1152-HQPA and the subsequent effect on GB cell's migration have remained obscure. We tried to assess the AZD1152-HQPA inhibitory effect on U87MG metastasis character and we focused on the connotation of different dosages of AZD1152-HQPA and GB associated miRNAs as there is a complex network of miRNAs involved in cell migration in glioblastoma.
Methods: U87MG cells were treated with different concentrations of AZD1152-HQPA to obtain MTT and colony formation assay. The rate of apoptosis was discovered by Flow cytometry. Scratch assay was used for assessing the effect of AZD1152-HQPA on cell migration. Real-time PCR was performed to analyze the expression levels of miRNAs and genes.
Results: Our data showed a moderated decrease in metabolic activity and an effective decrease in colony formation of U87 cells. Flow-Cytometry analysis of treated cells indicated increases in the rate of apoptotic cells. AZD1152-HQPA effectively inhibited tumor cell migration in scratch assay. Expression levels of 22 miRNAs and 9 genes related to cell migration has been increased or decreased by AZD1152-HQPA treatment.
Conclusion: We found that survival, progression, and migration of U87 cells have decreased considerably as the cells treated with AZD1152-HQPA. Also, consider the importance of the miRNAs in GB and their role in pathogenesis and disease progression, AZD1152-HQPA by altering expression levels of miRNAs can be efficient. Hence, we proposed that AZD1152-HQPA can be a novel therapeutic agent in GB treatment. However, there is a need for further in-vivo studies to confirm such a conclusion.

Keywords: Glioblastoma, CNS, Aurora kinase B, AZD1152-HQPA, U87MG, miRNA, cell migration.

18399

Evaluating the expression levels of Vascular Epithelial Growth Factor (VEGF) and Wilms' Tumor gene product 1 (WT1) in Newly Acute Leukemia Patients Undergoing Chemotherapy

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Background: Today, leukemia is one of the most common worldwide. The expression of Wilms' tumor gene (WT1) and the vascular endothelial growth factor (VEGF) gene increased in patients with various cancers. This study focuses on the relationship between expression of WT1 and VEGF in patients with acute leukemia.

Materials and Methods: We investigated expression of WT1 mRNA and VEGF mRNA using real-time quantitative RT-PCR in the peripheral blood of 8 newly diagnosed AML and 4 newly diagnosed ALL patients, serially monitored for 8 weeks. A further 12 normal PB samples served as controls.

Results: In the patient group, in comparison with the normal ranges, WT1 and VEGF gene expression was elevated, whilst the average rate of the expression of these two genes being 0.2852±0.11 and 0.2029±0.018, respectively. While was no significant association between the two genes pre-treatment, a positive link between the two genes in 75% of patients with AML was noted during the procedure of chemotherapy, whereas in 75% of patients with ALL a negative correlation was observed.

Conclusions: Leukemia is associated with the expression rate of WT1, which may affect the expression of VEGF.

Keywords: WT1, VEGF, acute leukemia, chemotherapy

18441

Evaluation of PDL-1 expression after radiotherapy in a BALB/c mouse tumor model

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Background: Effects of radiation therapy (RT) are systemic and partially mediated by the immune system. Likely that radiation alone can hardly transform the immune-suppressing environment into an immunostimulatory one. Therefore, due to the immune-modulatory potential of RT and because the effects of RT are recognized by the immune system, we are looking for an effective combination of radiation therapy with immunotherapy; a treatment that may provide a new opportunity with high efficacy for the cancer patient to recover. So, we intend to investigate the PD-L1 expression changes that occur in the microenvironment of the tumor due to different RT regimens with the same biologically effective dose (BED).

Methods: In this study, female BALB/c mice that were inoculated with CT26 tumor cells irradiated with different RT regimens that included Ablative RT (1*15 gray (Gy)), Hypofraction RT (2*10 Gy), and Conventional RT (10*3 Gy). Then, PD-L1 expression was analyzed with immunohistochemistry (IHC) staining on days 2, 20, and when the size of tumors reaches 2cm^2 after RT. IHC results analyzed by panoramic scanner.

Results: All treated groups expressed PD-L1, but the group receiving single ablative high dose RT showed higher expression of PD-L1 than the other groups. In addition, no significant differences in PD-L1 expression were observed at different times.

Conclusion: These findings showed that different doses of RT have various effects on the tumor microenvironment (TME), so combining therapy with RT and immune checkpoint blockers can be offered for optimal treatment of cancer patients. Finally, these findings help to select a suitable immunotherapy type such as anti-PD-L1 therapy in combination with single high dose RT.

Keywords: Radiation therapy, Tumor microenvironment, PD-L1, IHC

18265

Higher frequency of TNF-α producing B cells in HNSCC draining lymph nodes correlates with good prognostic factors

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Background: B cells play different roles in immunity against tumors. In different types of cancer they contribute to either suppression or progression of the tumor growth. In this study, we investigated the relationship between cancer progression and B cell cytokine production in patients with head and neck squamous cell carcinoma (HNSCC).

Methods: Thirty-six lymph nodes with or without tumor involvement were collected from untreated HNSCC patients undergoing surgical operation. After isolation of mononuclear cells, they were stimulated with CpG (10µg/ml) and recombinant CD40L (200ng/ml) for 10 hours with PMA/Ionomycine and Berefeldin A added to the culture for the last 6 hours. Then, cells were stained with antibodies for CD19, IL-10 and TNF-α and subjected to flow cytometry

Results: The percentage of TNF-α+$CD19^+$ B cells was found to be higher in non-metastatic lymph nodes (P=0.006) and low stage of the disease (P=0.041). Whereas, the frequency of IL-10^+CD19^+ B cells showed an increasing trend in tumor draining lymph nodes (TDLNs) of patients with grade II+III compared to grade I (P=0.054).

Conclusion: Our data showed that in TDLNs of HNSCC, the frequency of TNF-α-producing B cells show significant associations with good prognosticators and their functions should be further investigated.

Keywords: HNSCC, B cells, Tumor draining lymph nodes, TNF-α

18280

A Child with Solitary Cutaneous Mastocytoma on the Scalp: A Case Report and Literature Review

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Background : Mastocytomas, as solitary mast cell tumors, are generally seen on the trunk and the extremities. Childhood-onset mastocytomas on the scalp are also extremely rare. **Case Presentation:** in this study, a child with solitary cutaneous mastocytoma on the scalp was evaluated and a review of previous literature was conducted. The case recruited in this report was a one-and-a-half-year-old toddler boy, presenting with a yellow-brown plaque on the scalp. **Results :**biopsy specimens taken for this purpose revealed mast cell accumulation in the upper dermis. Such cells were uniform with a fried-egg appearance, whose cytoplasmic granules were visible during the Wright-Giemsa staining. The previous literature demonstrated the difficulty of diagnosing solitary mastocytomas as a very rare disease with non-specific clinical findings. The c-KIT mutation has been further reported in more than 95% and 40% of affected adults and children; respectively. In most studies, Darier's sign has been also observed. Accordingly, histamine H1-receptor antagonists are the first-line therapy. **Conclusion:** childhood-onset mastocytoma on the scalp is extremely rare. Given the limited number of reports in this field, it seems that plaque-type lesions on the scalp can be respected among differential diagnoses, particularly if blistering develops during physical stimulations and no alopecia appears on the lesion site.

Keywords: Mastocytoma, Solitary mastocytoma, c-KIT, Darier's sign

18164

The status of B cells with regulatory phenotype in the draining lymph nodes of head and neck squamous cell carcinoma

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Background: B cell can be of special importance in immunity against head and neck squamous cell carcinoma (HNSCC) as they can stimulate or regulate the immune responses. In this study, we investigated the changes in the immune regulatory capacity of B cells in the HNSCC draining lymph nodes during disease progression.

Methods: Lymph node samples were obtained from 26 patients with HNSCC. Mononuclear cells were isolated, and lymphocytes were stained with antibodies against CD19, CD39 and CD73. Lymphocytes were also stimulated with PMA/Ionomycin for 6 hours, and then stained for CD19, PD-1 and PD-L1. Cells were finally subjected to flow cytometry.

Results: $CD19^+$ B cells comprised 40.2 ± 10.7% of lymphocytes in the tumor draining lymph nodes of HNSCC. The frequency of $CD19^+$ B cells was higher in patients with stage III + IV in comparison with stage I + II ($P = 0.035$), and also showed a direct correlation with the tumor size ($r = 0.4$, $P = 0.021$). A small fraction of unstimulated B cells expressed PD-1 or PD-L1, but the frequency of PD-$L1^+$ B cells increased rapidly upon a brief stimulation ($P < 0.0001$). The percentage of PD-$L1^+$ B cells showed an inverse correlation with the tumor size in both unstimulated and stimulated conditions ($R = 0.4$, $P = 0.021$ and $R = 0.4$, $P = 0.070$, respectively). Besides, the frequency of another subset of B cells with regulatory phenotype ($CD73^+$ B cells) showed a decreasing trend in patients with grade II + III compared with grade I ($P = 0.051$).

Conclusion: The percentage of $CD19^+$ B cells showed association with poor prognostic indicators of HNSCC such as tumor size and stage, whereas the frequency of B cells with regulatory phenotypes showed associations with good prognosticators.

Key words: Co-stimulatory molecules, Regulatory B cells, Tumor draining lymph nodes, HNSCC

18275

Evalution of Pyrazolo[1,5-a]pyrimidine-3-carboxamide on K562 tumor cell line and peripheral blood mononuclear cells (PBMCs)

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Background: Previous studies indicated that pyrimidine derivatives possess anticancer properties. This study was set out to evaluate the Pyrazolo[1,5-a]pyrimidine-3-carboxamide as a pyrimidine compound, on K562 human erythroleukemia cell line and peripheral blood mononuclear cells (PBMCs) as normal control cells

Methods: The K562 cells or PBMCs (1×106 cells/100 µl/well) were incubated for different time (24, 48 and 72 h) with serial logarithmic dilution of analogue (1.5625-200µg/ml) .At end time of incubation, the survivability present of cells was determined by MTT methods .after IC50 value determining ,apoptosis and necrosis of cells measured by propidium iodide and acridine orang (PI/AO)staining.

Results: Our data indicated that this compound had a profound cytotoxic effect on the k562 cell line in a dose dependent manner, so the apoptosis increased and the survival test (MTT) decreased. Interestingly, the half maximal inhibitory concentration (IC50) value of this compound against K562 was lower than IC50 value of this compound against PBMCs.

Conclusion: As a result, this compound provide more favorable cytotoxicity against K562 cell line without any additive cytotoxicity against PBMCs.

Key words:K562,PBMC,Pyrazolo[1,5-a]pyrimidine-3-carboxamide,apoptosis,PI/AO,IC50,MTT

18293

Evaluation of 3-Amino-2-methylbenzyl alcohol on K562 tumor cell line and peripheral blood mononuclear cells (PBMCs)

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Background: Previous studies indicated that amino-alcohol derivatives possess anticancer properties. This study was set out to evaluate the 3-Amino-2-methylbenzyl alcohol as an amino-alcohol derivatives, on K562 human erythroleukemia cell line and peripheral blood mononuclear cells (PBMCs) as normal control cells.

Methods: The K562 cells or PBMCs (1×10^6 cells/100 µl/well) were incubated for different time (24, 48 and 72 h) with serial logarithmic dilution of analogue (1.5625-200µg/ml) .At end time of incubation, the survivability present of cells was determined by MTT methods .After IC50 value determining, apoptosis and necrosis of cells measured by propidium iodide and acridine orang (PI/AO) staining.

Results: Our data indicated that this compound had a profound cytotoxic effect on the k562 cell line in a dose dependent manner, so the apoptosis increased and the survival test (MTT) decreased. Interestingly, the half maximal inhibitory concentration (IC50) value of this compound against K562 was lower than IC50 value of this compound against PBMCs.

Conclusion: As a result, this compound provide more favorable cytotoxicity against K562 cell line without devastating impacts upon PBMCs

Key words: K562, PBMC, 3-Amino-2-methylbenzyl alcohol, apoptosis, amino-alcohol, PI/AO, IC50, MTT.

18165

Evaluation of lactate dehydrogenase and fatty acid synthase serum levels in Bladder cancer patients

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Background: bladder cancer is one of the most prevalent cancers in the world with a substantial economic burden on the health system. The role of various molecules and enzymes in this cancer has been extensively studied in recent years. Among these, the role of LDH and FASN has been studied less than others. In this study, we examined the role of these two factors in patients with bladder cancer.

Methods: Sixty patients who were diagnosed with bladder cancer and 36 age-sex match healthy people as a control group were analyzed. LDH and FASN serum levels in both case and control groups were measured with a commercially reliable sandwich enzyme-linked immunosorbent assay (ELISA) kit.

Results: In general, serum levels of LDH and FASN increased in bladder cancer patients compared to healthy individuals (P=0.001, P<0.001 respectively). Furthermore, patients with stages T1 and pT3b of tumor had significantly higher LDH serum levels (P=0.040 and P=0.022 respectively). Regarding FASN, patients who presented with stage pT2a of bladder cancer, showed elevated FASN serum levels (P=0.019). There was a statistically significant relationship between the history of smoking and the serum level of FASN (P=0.044). Age, sex, tumor size, and grading of tumor were not affecting serum levels of LDH and FASN in the present study.

Conclusion: The data indicate that serum LDH and FASN may have the potential to be useful as a biomarker for the detection of bladder cancer although further studies are needed

Keywords: Bladder cancer, LDH, FASN, ELISA

18193

Human starved fibroblasts produced some factors with anti-cancer stem cell activity

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Background: Breast cancer counts as a principal cause of cancer origination mortality in the world. The tumor microenvironment is a competition Bundle that includes the interactions of cancer cells, immune cells, fibroblast, Etc. In a previous study, we showed that 16_SFS (16h- serum-starved fibroblasts culture supernatant) has a Downregulation of stemness gene effect on LA7 breast cancer stem cell-induced tumor. Here in the in vitro model, we investigated the effects of 6_SFS on the LA7 cell line.

Methods: Human foreskin fibroblasts were isolated and cultured to collect 6_SFS. The cell culture of LA7 was performed in 4 groups (n=3) in the presence of 6-SFS, 6-SFS+ 5%FBS (Phosphate-buffered saline), DMEM (Dulbecco's Modified Eagle Medium), and DMEM +5%FBS as control during 24h incubation. After that, the cell count and viability test an MTT assay were obtained. To understand the effect of this solution on the differentiation of LA7, Real-time PCR was performed for evaluation of oct4 as a stemness gene (one time).

Results: The count of cells in the 6-SFS group was significantly reduced compared to the control group ($P<0.046$). Outputs of MTT assay showed significantly reduced metabolic activity in all groups ratio to control group ($P<0.001$), Also was observed significant reduction metabolic activity in the 6-SFS group compared to 6-SFS+5%FBS and DMEM group, respectively ($P=0.09$, $P<0.001$). The fold change of OCT4 in all groups was reduced by at least 70% compared to the control group.

Conclusion: Our findings show that Serum starvation stress results in an anti-cancer function. The significant reduction of LA7 proliferation, in adjacency the 6-SFS, showed that this result can be more effective about 6-SFS. Which, means the factors in 6-SFS was able to reduce the cell number even in the presence of serum. This study opens a new window in the understanding of the cancer stem cell-fibroblast relationship.

18273

Evaluation of 4-(3-pentylamino)-2, 7-dimethyl-8-(2-methyl-4methoxy-phenyl)-pyrazolo-[1, 5-a]-pyrimidine on K562 tumor cell line and peripheral blood mononuclear cells (PBMCs).

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Background: Previous studies indicated that pyrimidine derivatives possess anticancer properties. This study was set out to evaluate the 4-(3-pentylamino)-2, 7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1, 5-a]-pyrimidine as a pyrimidine derivatives, on K562 human erythroleukemia cell line and peripheral blood mononuclear cells (PBMCs) as normal control cells.
Methods: The K562 cells or PBMCs (1×10^6 cells/100 µl/well) were incubated for different time (24, 48 and 72 h) with serial logarithmic dilution of analogue (1.5625-200µg/ml) .At end time of incubation, the survivability present of cells was determined by MTT methods .after IC50 value determining, apoptosis and necrosis of cells measured by propidium iodide and acridine orang (PI/AO) staining.
Results: Our data indicated that this compound had a profound cytotoxic effect on the k562 cell line in a dose dependent manner, so the apoptosis increased and the survival test (MTT) decreased. Interestingly, the half maximal inhibitory concentration (IC50) value of this compound against K562 was lower than IC50 value of this compound against PBMCs.
Conclusion: As a result, this compound provide more favorable cytotoxicity against K562 cell line without any additive cytotoxicity against PBMCs

Key words: K562, PBMC, 4-(3-pentylamino)-2, 7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1, 5-a]-pyrimidine, apoptosis, PI/AO,IC50, MTT.

18166

Endocan serum levels in patients with low and high grade meningiomas: does this biomarker have an indicative role?

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Background: Meningiomas are one of the most common tumors of the brain and central nervous system. The key role of endocan in predicting tumor growth and prognosis has been shown forseveral types of cancers, however, this role in meningiomas have not been evaluated. In the current study, we investigated the relationship between endocan serum levels with low and high grades meningiomas.
Methods: The study group consisted of 60 consecutive patients suffering from meningiomas as the case group as well as 30 age-sex matched healthy individuals without any evidence of malignancy or abnormal clinical conditions as the control group. Endocan serum levels were measured by a commercially reliable enzyme-linked immunosorbent assay (ELISA) kit in both case and control groups.
Results: The serum level of endocan in the group with meningiomas was 283.34(242.09-358.70) pg/ml and in the control group was 250.29(207.56-329.71) pg/ml respectively (P = 0.172). Afterwards, patients were divided into three different groups (grade I, II, and III) and compared to the control. The level of endocan in the group with grade I of meningioma showed no significant difference compared to control individuals (P =0.86). When patients with grade II and grade III compared with the control group, endocan serum levels were statistically significant (P=0.002, P<0.001 respectively). Moreover, our findings showed that the different grades of meningiomas were statistically significant compared to each other (P<0.001) regarding endocan serum levels, meaning that the higher the grade, the higher the endocan serum levels.
Conclusion: Our findings revealed that higher grades of meningioma had higher endocan serum levels, however, the role of endocan in pathogenesis or progression of this type of tumor requiring further exclusively assessment.

Keywords: Cancer biomarker, Endocan, Meningiomas,

18172

Investigation of IL-17A serum levels in patients with Non Melanoma Skin Cancer

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Background: Role of Interleukin 17A (IL-17A) in carcinogenesis and cancer growth is controversial. Although some researches support its anti-tumor activity, some other suggests that it promotes the growth and development of different types of cancer including skin cancer by activation of STAT3. Although the function of the cytokines like IL-17A has been extensively studied in various types of cancer, Non Melanoma Skin Cancer (NMSC) has not received much attention. *Therefore, the present study* was aimed to investigate the serum levels of IL-17A in NMSC patients.
Methods: This cross-sectional study was performed on 60 patients with Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) as well as 57 age-sex matched healthy individuals as control group. Measurement of IL-17A serum levels in both case and control groups were performed by a commercially reliable sandwich enzyme-linked immunosorbent assay (ELISA) kit.
Results: In this study, we observed that IL-17A serum levels in NMSC patients were significantly higher than control group ($P<0.001$). Also, both BCC and SCC patients had higher levels of IL-17A in their sera in comparison to controls ($P=0.001$ and $P<0.001$; respectively). However, there was no significant difference between SCC and BCC patients regarding serum levels of IL-17A.
Conclusion: According to our results, it can be concluded that IL-17A may play a role in inducing the growth and progression of NMSC and it can be used as a therapeutic target in these patients in future.

Keywords: Interleukin 17A, NMSC, BCC, SCC

18202

Evaluation of BRAF mutation in patients with colorectal cancer in east of Iran

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Background: Colorectal cancer characterized by a sequence of genetic alterations in cell growth regulatory genes, such as BRAF. Diagnostic tests, based on nucleic acid extracts from formalin-fixed and paraffin-embedded tissues, are now becoming increasingly common due to the introduction of biological agents for cancer therapy. This study aimed to analyze the incidence of BRAF mutation in patients with colorectal cancer.

Patients and method: Fifty paraffin-embedded blocks of colorectal cancer were obtained from Imam Reza Hospital of Birjand, Iran. DNA extracted from paraffin-embedded tissue with an improved method, and exon 15 of the BRAF gene was PCR amplified and subjected to sequencing.

Results: BEAF V600E mutation was detected in 2/43 (4%) of patients with colorectal cancer. All the mutations were observed in patients >50 years old.

Conclusion: In order to low incidence of BRAF mutation in east of Iran further work is necessary to study the prevalence of HNPCC cases in this region and also try to understand the interaction between genetics and environmental factors that contribute to this low incidence of BRAF mutations in this region.

Keywords: Colorectal cancer, BRAF mutation, PCR, Sequencing

18205

Can we consider soluble Herpes Virus Entry Mediator (sHVEM) as a tumor marker?

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Background: Immune checkpoint molecules have critical roles in directing immune responses into co-inhibitory and co-stimulatory signals. Herpesvirus entry mediator (HVEM) is a receptor of tumor necrosis factor receptor superfamily with unique features due to its interaction with both inhibitory and stimulatory ligands. The aim of this study was to measure the serum level of the soluble form of HVEM in patients with gastric, colorectal, and breast cancers and evaluating its diagnostic and prognostic value.

Methods: The concentration of the soluble HVEM (sHVEM) was determined in the serum of 36 patients with breast cancer, 50 patients with colorectal cancer and, 59 patients with gastric cancer using ELISA method. Moreover, 50 healthy donors (HD), as well as 31 patients with non-ulcer dyspepsia (NUD) were used as control groups. The patient's samples were obtained from the Biobank of Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

Results: The level of sHVEM was significantly higher in patients with gastric ($p=0.006$) and breast cancer ($p=0.01$) than in control groups (HD). The higher level of sHVEM observed in colorectal cancer patients in comparison with HD group; although, it was not significant. Moreover, the elevated level of sHVEM was shown to be higher in stage III and IV compared to stage I and II in all three types of cancers.

Conclusion: the results of the present study suggest that the serum level of sHVEM may be considered as a promising indicator for diagnosis as well as evaluating the progression of cancers such as gastric, breast, and colorectal cancers.

Keywords: Herpesvirus entry mediator, Gastric cancer, Breast cancer, colorectal cancer

18097

MiRNAs are associated with prostate cancer metastasis

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Background: Metastasis is an important lethal step in cancer progression [1,2]. posttranscriptional regulation of mRNAs is conducted by miRNAs (miRs) which are short RNA molecules. Recent studies showed that miRs are important regulators of apoptosis, proliferation, invasion and metastasis in cancer cells [1,3]. In this review, we provide an update on metastasis associated miRNAs in prostate cancer.
Methods: Electronic databases (PubMed, Scopus, Google Scholar) and Persian language databases (Magiran, Scientific Information Database [SID]) were searched.
Results: Several studies indicate that variation in specific miR levels are related to cancer cell metastasis [1,3–6]. Following miRs are up/down regulated in prostate cancer: miR-143[7], miR-205 [8], miR-34a [9] are upregulated. In contrast, miR-106b-25 cluster[4] , miR-29b [5] are downregulated in prostate cancer.Accordingly,up/down regulation of specific miRs may have a prognostic/diagnostic value. Furthermore, a study showed that, miR-29b functions as an anti-metastatic miR by regulating the Epithelial- mesenchymal transition (EMT) in prostate cancer [5]. Additionally, Chou et al reported that "GATA3 promotes miR-29b expression and suppresses lung metastases in breast cancer [10]." These data suggest that regulation of miR levels may have a therapeutic value.
Conclusion: Metastasis is a fatal step in the progression of cancers [11]. As mentioned in this review, miRNAs may have a prognostic/diagnostic value in different types of cancers. Additionally, regulation of miR levels may have a therapeutic value. Further studies are required to standardize miRNA utilization as a therapeutic target and/or as a biomarker for prostate cancer metastasis.

Keywords: Cancer, Metastasis, miRNA, miR, Prognosis, Diagnosis, biomarker

18066

Inhibition of semaphorin 4D enhances chemosensitivity by increasing 5-fluorouracile-induced apoptosis in colorectal cancer cells

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Background: Overexpression of semaphorin 4D (SEMA4D), an immune semaphorin, is found in various human malignancies, including colorectal cancer (CRC). In this study, we explored the relationship between silencing SEMA4D expression and 5-fluorouracil (5-FU) response in the colorectal cancer cell line.

Methods: SW48 cells were transfected with a short interfering RNA (siRNA) in order to silence SEMA4D gene expression and then exposed to 5-FU for 48 h. The down-regulation of SEMA4D expression was confirmed by qRT-PCR and the particular concentration of 5-FU was acquired using MTT assay. Flow cytometry and western blot were used to evaluate apoptosis rate and pro- and anti-apoptotic expression levels of proteins involved in apoptosis including Bax, Bcl-2, P53, and caspase-3. Other oncogenic activities including epithelial-mesenchymal transition (EMT) process, cancer stem cell (CSC) markers, and β-catenin pathway were investigated using qRT-PCR, and western blot. The proliferation was analyzed via colony formation test.

Results: Our data demonstrate that SEMA4D silencing results in strikingly elevated apoptosis in response to 5-FU treatment and leads to down-regulation of Bcl-2 and overexpression of Bax, P53, and caspase-3 in protein levels. Furthermore, the mRNA and protein expression levels of β-catenin, as well as transcript expressions of CSCs and EMT markers, were remarkably diminished. However, mRNA expression of E-cadherin as an epithelial marker was significantly increased in 5-FU treatment combined with siRNA SEMA4D.

Conclusion: This study implicates that the silencing of SEMA4D by siRNA promotes the chemosensitivity of SW48 cells to 5-FU and it may be a potential therapeutic agent for colon cancer therapy.

Keywords: SEMA4D, Colorectal cancer, 5-FU, Apoptosis, EMT

18099

Cold Atmospheric Plasma Is a Potent Tool to Improve Chemotherapy in Melanoma In Vitro and In Vivo

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Background: Abstract: Malignant melanoma is a devastating disease. Because of its aggressiveness, it also serves as a model tumor for investigating novel therapeutic avenues. In recent years, scientific evidence has shown that cold atmospheric plasma (CAP) might be a promising modality in cancer therapy. In this study, we aimed to evaluate the effect of CAP generated by an argon plasma jet alone or in combination with dacarbazine (DAC) on melanoma cells in vitro and in vivo.
Methods and Results: The effects of the CAP on inducing lipid peroxidation and nitric oxide production were higher in B16 melanoma cells in comparison to non-malignant L929 cells. Assays on cell growth, apoptosis, and expression of genes related to, e.g., autophagy processes, showed CAP to have a substantial impact in melanoma cells while there were only minor effects in L929 cells. In vivo, both CAP monotherapy and combination with DAC significantly decreased tumor growth.
Conclusion: These results suggest that CAP not only selectively induces cell death in melanoma but also holds promises in combination with chemotherapy that might lead to improved tumor control.

Keywords: apoptosis, B16F10, combination therapy, dacarbazine, plasma medicine

16876

Evaluation of Berberine effect on miR-155 expression in chronic lymphocytic leukemia

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Background: Chronic lymphocytic leukemia (CLL) is a common blood malignancy and characterized by abnormal accumulation of $CD5^+/CD19^+$ B lymphocytes in the peripheral blood, bone marrow, and lymph nodes. BCR signaling plays an important role in the pathogenesis and/or progression of CLL. CLL biology can be affected by some microRNAs. MiR-155 is an oncomiR that is associated with a higher risk of death in CLL patients. The levels of miR-155 can influence the relative expression of SHIP1 in CLL and subsequently affects activation of BCR signaling pathway. Berberine is a natural isoquinoline alkaloid that has been shown to inhibit the proliferation and induce apoptosis in tumor cells. In this study, we investigated the effects of Berberine on miR-155 expression in CLL Patient-Peripheral blood mononuclear cells (PBMCs).
Methods: PBMCs were isolated from 10 CLL patients using Ficoll-paque. Isolated cells cultured in RPMI-1640 medium supplemented with 10% FBS and 1% Penicillin/Streptomycin in the presence and absence of Berberine (25 µM) for 24 hours in 37°C, 5% CO_2 humidified incubator. The levels of miR-155 expression were subsequently evaluated by real-time PCR.
Results: We found that Berberine (25 µM) reduces the expression of miR-155 in comparison to the control group (P value < 0.05).
Conclusion: Berberine treatment has led to decrease of miR-155 expression in PBMCs of CLL patients. Since miR-155 plays an important role in BCR signaling pathway, this result provides proof of principals for further investigation of Berberine in clinical setting for CLL treatment.

Key words: Chronic lymphocytic leukemia; Berberine; miR-155

17996

Rapid isolation of parental sphere-forming cells as a potential immunotherapeutic target in gastric adenocarcinoma

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Background: Gastric cancer (GC) as a malignancy cause associated with high death rate in the world. Cancer stem cells (CSCs) are a rare immortal subpopulation of cells within tumors with characteristics of ability to self-renew, initiate tumor, and differentiate into defined progenies as well as and high resistance to conventional therapies. Therefore, rapid isolation of parental CSCs in order to therapeutic targets, especially immunotherapy is very important.
Methods: Parental cancerous cell suspension isolated from patients with GC was cultured in the serum-free medium containing EGF, bFGF, LIF, and heparin under non-adherent culture conditions to generate spheres. Tumorgenicity using subcutaneous injection of parental sphere-forming cells to nude mice, expression of stemness transcription factors OCT4, SOX2, SALL4, and Cripto-1 as well as CD44 variable isoforms (CD44v6, CD44v3) using real time PCR and molecules of CD44, CD44V8-10, CD54, DLL4 and EpCAM as gastric CSC markers as well as Oct4 using flow cytometry were investigated.
Results: A few parental cancerous cells were able to generate three-dimensional spheroid colonies and also form xenograft tumors in mice. Moreover, these cells upregulated stemness factors that associated with pluripotency and self-renewal. Finally, molecules of CD44, CD44V8-10, CD54, DLL4 and EpCAM as gastric CSC markers, as well as CD44 variable isoforms were overexpressed in parental sphere-forming cells.
Conclusion: We suggested that the sphere formation and tumorigenicity assays are two procedures, leading to the rapid isolation of cancer cells with certain stem-like properties in order to potential immunotherapeutic targets in patients with advanced disease.

Keywords: CSC Markers, Gastric cancer, Sphere, Tumorgenicity

17959

Circulating levels of monocytic myeloid-derived suppressor cells (M-MDSC) are raised in NSCLC

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Background: Myeloid-derived suppressor cells (MDSC) exist as granulocytic (G-MDSCs) and monocytic (M-MDSCs) subtypes and their expansion plays a role in cancer progression. Recruitment to the cancer site depends upon the presence of chemoattractants. We aimed to investigate the presence of MDSC subtypes and of interleukin-8 (CXCL8) in the peripheral blood in lung cancer subtypes including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients.
Materials and Methods: Peripheral blood from 26 NSCLC patients, 18 SCLC patients and 8 healthy control donors (HDs) was harvested and the surface expression of CD14, CD15, CD11b and HLA-DR on MDSCs measured by flow cytometry. The level of serum CXCL8 was measured in these patients by ELISA methods.
Results: The frequency of circulating M-MDSCs was significantly higher in patients with NSCLC than in SCLC and HDs. In contrast, there was no statistical difference in the frequency of circulating G-MDSCs across the 3 groups. The concentration of CXCL8 was significantly higher in the NSCLC and SCLC patients than in HD controls.
Conclusion: Our data show that the presence of circulating M-MDSCs higher in NSCLC lung tumors than healthy controls and correlated with levels of CXCL8 in serum and may suggest for predication and differential diagnosis of NSCLC.

Key words: Myeloid-derived suppressor cells, Lung cancer, CXCL8, NSCLC, SCLC, MDSC

17989

Association of A / T single nucleotide polymorphism of CYP14A gene with lung cancer

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Background: Lung cancer is the most common cancer in patients with lung problems in the world. CYP12A is an extrahepatic enzyme in humans and its expression in lung, placenta and lymphocytes induced mutations in the A / T nucleotide sequence after degradation. In region 3, the non-coding part of this gene disrupts the cell cycle control process. The aim of this study was to investigate the association of A / T single nucleotide polymorphism of CYP14 A gene with the incidence of lung cancer in men.

Materials and Methods: Our statistical population in this study includes 65 men with lung cancer referred to the hospital from 1996 to the end of 1997 and 60 blood samples of a healthy person as a control group. DNA extraction was performed by salt deposition method to determine the sequence. Genotypes The samples were analyzed by PCR-RFLP method and finally the data were analyzed by T-test and SPSS V24 software.

Results: The frequency of T allele in the patient group was 71.24% and in the control group was 87.91%, which indicates a significant relationship with the incidence of the disease (P = 0.01). Also, the frequency of dominant homozygous (TT) genotype in patients was 49.72 (P = 0.02), which indicates a significant relationship with disease incidence, while heterozygous (TC) and recessive homozygous (CC) genotypes. Frequency was 28.12% and 22.16%, which indicates a significant lack of correlation (P> 0.05). Also, the incidence of the disease was 28% in male smokers compared to non-smokers (P = 0.05) (CL = 1.19-3.71-OR = 95%

Conclusion: Based on the results, dominant homozygote (TT) is more susceptible to lung cancer due to mutation in the A / T nucleotide sequence of CYP14 A gene. Also, smokers were more likely to develop the disease than other individuals. This parameter was used as a pre-exposure factor.

Keywords: Polymorphism - Cancer - Single nucleotide - CYP14A gene

17966

Peripheral PD-1/PD-L1 Expression and Plasma IL-6 as Predictors of Tumor Response in Metastatic Colorectal Cancer Patients Treated with FOLFOX

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Background: Although several therapeutic approaches were used, colorectal cancer (CRC) is still the second lethal cancer worldwide. Therefore, finding biomarkers predicting the response to the treatment will be useful to choose the best treatment. This study was conducted to evaluate the predictive impact of peripheral programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) expression and plasma levels of interleukin 6 (IL-6) in patients with metastatic CRC who received FOLFOX regimen.

Methods: 25 patients with metastatic CRC who received the mFOLFOX6 regimen for six cycles were enrolled in this study. Flow cytometry and Enzyme-linked immunosorbent assay (ELISA) were used to assess the PD-1+ or PD-L1+ peripheral blood cells and plasma levels of IL-6, respectively, before and after the chemotherapy. The tumor response was measured according to the response evaluation criteria in solid tumors (RECIST) guideline version 1.1. The association between markers and tumor response and changes in markers during the treatment were assessed.

Results: All the biomarkers expect PD-L1+ lymphocytes were significantly decreased after chemotherapy. High plasma levels of IL-6 were associated with worse tumor response (RR = 0.11; 95% CI: 0.02 - 0.72; $P < 0.001$). Moreover, High PD-L1 expression on granulocytes was non-significantly related to the good clinical response (RR = 2.33; 95% CI: 0.83, 6.54; P = 0.07).

Conclusion: The FOLFOX regimen can significantly reduce the PD-1/PD-L1 expression on peripheral blood and plasma levels of IL-6. Furthermore, the strong relationship between plasma levels of IL-6 and tumor response suggests that it can be an independent predictor of unfavoured clinical response in patients with metastatic CRC. Although the results showed that PD-L1 expression on granulocytes is a small predictor of good response, more studies need to achieve a significant and conclusive result.

Keywords: PD-1, PD-L1, IL-6, colorectal cancer, tumor response

16873

Effect of mTOR inhibitor everolimus on Helios expression in CD4, CD8 and Treg cells isolated from spleen in a mouse model with breast cancer

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Background: mTOR inhibitor everolimus blocks tumor proliferation and cancer growth. Everolimus increases sensitivity to endocrine therapies in breast cancer, and could improve patient outcomes. Despite benefit effect on cancer cells, it has been shown that treatment with Everolimus promotes cells with suppressive phenotype in metastatic renal cell carcinoma. However, its effect on immune cell subsets has not been well investigated in breast cancer. The study aimed to investigate the effect of everolimus on frequency of $CD4^{+}Foxp3^{+}Helios^{+}$, $CD4^{+}Helios^{+}$ and $CD8^{+}Helios^{+}$ cells isolated from spleen as well as Helios expression in a mouse model with breast cancer. Methods: After breast cancer induction, mice were randomly assigned into three groups: groups 1 and 2 received 10mg/kg and 5mg/kg everolimus per day and group 3 (or control group, only received vehicle (Na-CMC)). After mouse killing, tumor tissue and spleen were removed. The cells were isolated from spleen mechanically. The isolated cells were stained by fluorochrome conjugated antibodies, and then acquired by flowcytometry. Results: Our result indicated that both 5 and 10 mg/kg dose of drug potentially reduced tumor volume and tumor weight. After Bonferroni correction, a significant increase in mean percentage of $CD4^{+}Helios^{+}$ lymphocytes as well as no significant increase in mean percentage of $CD4^{+}foxp3^{+}Helios^{+}$ cells was found in both groups treated with Everolimus compared to the vehicle-treated group. Additionally, treatment with everolimus increased Helios expression (mean florescent intensity) more especially in $CD4^{+}Helios^{+}$ lymphocytes. Conclusion: Our study shows although the mTOR inhibitor everolimus suppress the tumor growth in mouse model with breast cancer, it may promote the expansion of $CD4^{+}Helios^{+}$ lymphocytes as well as $CD4^{+}foxp3^{+}Helios^{+}$ cells among spleen cells. Our study suggests that Helios targeting in combination with everolimus may improve anti-tumor responses.

Key words: mTOR inhibitor, Everolimus, $CD4^{+}Foxp3^{+}Helios^{+}$, Spleen, Breast cancer mice model.

17990

Association of A / T 529 gene polymorphism of cyclooxygenase 2 gene with lung cancer in men

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Background: Cyclooxygenase (COX) is one of the most important structural enzymes in the production of inflammatory mediators in the body. The enzyme cyclooxygenase then converts arachidonic acid to prostaglandin H2, which is a precursor to other prostaglandins. The aim of this study was to investigate the association of C / T 724 gene polymorphism of cyclooxygenase 2 gene with lung cancer.
Materials and Methods: Our statistical population in this study included 95 men with lung cancer from Urmia city as a control group and 110 healthy blood samples as a patient group. DNA extraction was performed by salt deposition method to amplify the sequence of PCR and to Sequencing was performed using the RFLP technique. Finally, the obtained data were analyzed using SPSS V.24 software.
Results: The mean age of the patient group was 52 7 7 years. The frequency of C allele in the patient group was 69% and the frequency of T allele was 31%. Also, genotypes of heterozygous group (TC) were equal to 51% (P = 0.03) while dominant homozygotes (CC) and recessive homozygotes (TT) were equal to 19% and 30%, respectively, indicating no association with disease (P> 0.05) Also, in women who had consanguineous marriage, 18% and women who had a family history of developing this cancer reported 42% more than other individuals and groups of the disease (P = 0.04) (CL = 1.19-3.71- OR = 95%).
Conclusion: Based on the results of mutation in A / T polymorphism 529, cyclooxygenase 2 gene can be used as one of the pre-infection identification factors.

Keywords: Polymorphism, Cyclooxygenase, A / T 529, Lung cancer

16887

Assessment of release of Hyaluronic Acid-coated exosomes in supernatant of fibroblast cells after radiation

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Background: Hyaluronan (HA) is present in extracellular spaces and interstitia of many tissue types. HA provides ideal conditions for cell migration and proliferation. In addition, aberrant synthesis of Hyaluronan accelerates tumor growth, angiogenesis, and metastasis. The fibroblasts are probably responsible for most of the hyaluronic acid (HA) accumulation in the tumor microenvironment after radiotherapy. Hyaluronan contributes to the pathogenesis of many human diseases and in numerous experimental conditions. Our goal is to investigate and compare radiation and lactate effects on HA levels in supernatant and exosome isolated from the supernatant of primary mouse fibroblast cell culture.

Methods: Fibroblast cells were isolated from the skin of C57BL6 mice and cultured in DMEM F12 medium. These cells were divided into two groups (no treatment and irradiated cells). Then the supernatant was harvested from FBS-free culture media after 48 h. Exosomes were purified by differential centrifugation (300 × g for 10 min, 2000 × g for 30 min, 16500 g for 30 min) and were pelleted by ultracentrifugation (150,000 × g for 180 min). The size of exosomes was determined using a Zetasizer. HA concentration measured using a HA ELISA Kit. Data were analyzed using a t-test.

Results: We observed a significant increase in HA-coated exosomes isolated from supernatants of irradiated cells compared to untreated cell ($P < 0.001$), figure 1.

Conclusion: The routine radiation therapy leads to massive shedding of HA-coated exosomes by normal fibroblast cells and thus exosomes-HA may contribute to tumor promotion and induction of the premetastatic niche. Besides, HA could contribute to the generation of a pro-tumorigenic inflammatory environment and recruitment and activation of inflammatory cells, such as macrophages.

Keywords: Exosomes, hyaluronic acid, radiation

17998

Combined Extract of Heated TC1 and a Heat-Killed Preparation of *Lactobacillus Casei* and alpha-galactosyl ceramide on cervical cancer induced by Papilloma virus in a mouse model

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Background: As a leading death factor, cervical cancer is highly prevalent among women in developing countries. Almost all cervical cancer cases can be assigned to human papillomavirus (HPV) infection. HPV infection types are classified as high-risk and low-risk strains according to their oncogenic capacity. HPV low-risk strains could be asymptomatic or could result in anogenital warts, while high-risk strains of HPV are oncogenic. The cause of above 99 percent of cervical carcinomas and precancerous lesions (cervical dysplasia) is high-risk HPV infection. The present work was performed aiming at determining the anti-tumor potential Combined Extract of Heated TC1 and a Heat-Killed Preparation of Lactobacillus Casei and alpha-galactosyl ceramide on cervical cancer caused by Papilloma virus in a rat model.

Methods: We challenged female C57BL/6 (n = 50, 6–8 weeks old) subcutaneously in the flanks having TC1 cells. After the development of a palpable tumor in all the mice, they were equally placed in five groups and treatment was applied. The experimental groups' tumor-bearing mice were treated with the heated TC1 extract or heated *Lactobacillus casei* extract or alpha-galactosyl ceramide or a combination of them, twice per week. The control group's animals were treated with phosphate-buffered saline. After one week following the last treatment, we euthanized half of the animals for determining the immune response profile.

Results: nitric oxide production was significantly amplified in the mice treated with the combined agents. Moreover, the IFN-γ secretion was increased, and conversely, the IL-4 and TGF-β secretion was diminished in the splenocytes cases in comparison to the splenocytes of the other groups.

Conclusion: Beneficial outcomes were conferred in our animal model of cervical cancer using combined treatment with Heat-Killed Preparation of Lactobacillus Casei and Heated TC1 and alpha-galactosyl ceramide.

Key Terms: cervical cancer, TC1 cell line, alpha-galactosyl ceramide, Lactobacillus casei

18030

Innate lymphoid cells, the frontliners of immune defense against colorectal cancer

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Background: Innate lymphoid cells (ILCs) have been shown to play important roles in tumor immunity. We studied the frequency of three subsets of ILCs in a mouse model of colorectal cancer (CRC).
Methods: Two mouse models of CRC were developed, including a chemically-induced model, via injection of azoxymethane/dextran sulfate sodium (AOM/DSS), and an orthotopic mouse model, using the CT-26 cell line. Based on histopathological examinations, mice with reparative or dysplastic changes were enrolled in the study. A sham group was also considered in which mice were screened for stresses that originated from interventions and injections. Flow cytometry analysis was performed to evaluate the frequencies of ILC1, ILC2, and ILC3 in the peripheral blood of all studied mice.
Results: The frequency of ILC1 was significantly higher in the chemically-induced reparative change group compared to dysplasia and sham groups. ILC2s showed higher frequencies in the dysplasia group than reparative change and sham groups. In addition, altered composition of ILCs was observed in peripheral blood of dysplastic mice skewing toward ILC3s in the dysplasia groups compared to sham and chemically-induced reparative change groups. There was no significant difference in the total number of ILCs among studied groups.
Conclusions: A higher frequency of ILC1 in the reparative change group suggests their potential tumor suppressive role. Also, higher ILC2s might be in favor of differentiation from the reparative change stage to the dysplasia. In addition, it seems likely that ILC3s play a role in the primary stages of CRC development.

Keywords: Innate lymphoid cell; colorectal cancer; Reparative change; Dysplasia.

18029

Codelivery of HIF-1α siRNA and Dinaciclib by carboxylated graphene oxide-trimethyl chitosan-hyaluronate nanoparticles significantly suppresses cancer cell progression

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Background: Hypoxia-inducible factor (HIF) is one of the critical components of the tumor microenvironment that is involved in tumor development. HIF-1α functionally and physically interacts with CDK1, 2, and 5 and stimulates the cell cycle progression and Cyclin-Dependent Kinase (CDK) expression. Therefore, hypoxic tumor microenvironment and CDK overexpression lead to increased cell cycle progression and tumor expansion. Therefore, we decided to suppress cancer cell expansion by blocking HIF-1α and CDK molecules.
Methods: In the present study, we used the carboxylated graphene oxide (CGO) conjugated with trimethyl chitosan (TMC) and hyaluronate (HA) nanoparticles (NPs) loaded with HIF-1α-siRNA and Dinaciclib, the CDK inhibitor, for silencing HIF-1α and blockade of CDKs in CD44-expressing cancer cells and evaluated the impact of combination therapy on proliferation, metastasis, apoptosis, and tumor growth.
Results: The results indicated that the manufactured NPs had conceivable physicochemical properties, high cellular uptake, and low toxicity. Moreover, combination therapy of cancer cells using CGO-TMC-HA NPs loaded with HIF-1α siRNA and Dinaciclib (SCH 727965) significantly suppressed the CDKs/HIF-1α and consequently, decreased the proliferation, migration, angiogenesis, and colony formation in tumor cells.
Conclusions: These results indicate the ability of CGO-TMC-HA NPs for dual drug/gene delivery in cancer treatment. Furthermore, the simultaneous inhibition of CDKs/HIF-1α can be considered as a novel anti-cancer treatment strategy; however, further research is needed to confirm this treatment in vivo.
Keywords: Carboxylated Graphene Oxide; Trimethyl Chitosan; nanoparticle; Hypoxia inducible factor-1α; Dinaciclib; Cyclin dependent kinases; hyaluronate

18001

Combined thermoradiotherapy with Gold nanoparticles and NDV oncolytic virus induces apoptosis in A549 cell line (lung cancer)

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Background: Lung cancer has recently turned into the most prevalent cancer and it is a leading death factor assigned to cancer. In the present work, it is aimed to specify the anti-proliferative capacity of combined thermoradiotherapy with gold nanoparticles (NPs) and NDV (Newcastle disease virus) oncolytic virus on A549 cell line (lung cancer).
Methods: The A549 cells as the cultured were randomly placed into T25 flasks and then were treated with gold NPs (100 µg/ml) and NDV oncolytic virus (MOIs of 40 for 1 h) combined with hyperthermia (41 ^{0}C for 1 h) and irradiation (200 cGy). Apoptosis was determined, hyperthermic chemo sensitization tests and MTT assays were conducted, Caspase-8 and 9 activities were measured, and the cell viability was determined by propidium iodide and acridine orange staining.
Results: Highest hyperthermia and irradiation were observed in the group under treatment with 100 µg/ml gold NPs combined with NDV oncolytic virus, and the lowest apoptosis and cytotoxicity percent were found in the hyperthermia treated group in comparison with the other groups ($P<0.05$). No significant change was noticed in the caspase-8 activity after treatment. Nevertheless, in treated. However, a significant increase was observed in the caspase -9 activity in the gold NPs, NDV oncolytic virus and groups treated with combined method.
Conclusion: As a conclusion, it can be stated that gold NPs combined with NDV oncolytic virus, hyperthermia, and irradiation caused mitochondrial-dependent apoptosis through caspase-9 expression up-regulation.

Key words: Hyperthermia, irradiation, Gold nanoparticles, Newcastle oncolytic virus, A549 cells

18040

Restoration of miR-193a expression suppresses Osteosarcoma cancer cell proliferation, viability, and migration

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Background: Osteosarcoma have highest mortality among in children in the worldwide. MicroRNAs, are major key of function and regulate the expression of target gene. In this study miR-193a that reported with abnormal expression in osteosarcoma was used by miRNA replacement therapy method and Taxol, used by combination therapy, which were selected to treat this disease. In addition we evaluated effect of miR-193a and combination therapy on P53, MMP-9, c-MYC, Bcl-2, Caspase-3 genes expression in MG63 cell line and evaluated proliferation, metastasis and apoptosis.
Methods: The MG63 cell line was cultured. Then, miR-193a was transfected into the cells by the jetPEI reagent and for other group miR-193a plus Taxol. Then using the qRT-PCR technique to evaluated expression of miR-193a, as well as the expression of P53, MMP-9, c-MYC, Bcl-2, Caspase-3 genes after transfection and combination. Furthermore we used methods such as MTT, wound healing, annexin-V staining, DAPI staining, colony formation and cell cycle assay.
Results: Our data demonstrated that miR-193a was upregulated in MG63 cell line after replacement therapy. Furthermore, the qRT-PCR analysis showed that the cells which transfected by miR-193a mimic or combination groups significant increase mRNA expression level with decrease of MMP-9, c-Myc, and increase Bcl-2, P53, Caspase-3 mRNA expression levels in MG63 cell line. Our treatment significantly suppressed cell migration, cell viability and proliferation, cell cycle and effect on induction of apoptosis.
Conclusion: We showed that reduced miR-193a expression predicts poor Osteosarcoma survival and that stable restoration of miR-193a expression in Osteosarcoma cells has a broad range of tumor-suppressive effects. This indicates that miR-193a is a promising candidate for miRNA replacement therapy for Osteosarcoma.

Keyword: miR193a, osteosarcoma, miRNA replacement therapy, proliferation

18037

In silico identification of HLA-G and CLU as critical genes assisting human hepatocellular cancer cells to escape from immune system

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Background: Hepatocellular carcinoma (HCC) is the second reason of cancer-related deaths in all over the world. Several studies have documented chronic hepatitis B (HBV) and C (HCV) viral infection cause immune modulation and subsequently HCC development. Therefore, detecting genes that regulate these pathways is demanding.

Methods: To explore essential genes for HCC, seven expression profiles (GSE76427, GSE112791, GSE36376,GSE62232, GSE45436,GSE116174,GSE25097) were downloaded from the Gene Expression Omnibus (GEO) database. The Limma and sva packages of R software were applied to normalize, merge and screen out differentially expressed genes (DEGs) between HCC and normal liver samples. Db2db and EnrichR Databases were used to perform Gene Ontology (GO) and pathway enrichment analysis respectively.

Results: A total of **94** upregulated genes and 57 downregulated genes were identified. The majority of the downregulated have roles in cholesterol metabolism, chylomicron-mediated lipid transport pathways. However, genes that had high expression in HCC mainly present in ribosome and viral mRNA translation pathways. Gene ontology analysis of them also showed FTH1, HLA-G, SERINC5, CD164, CLU and IPO7 genes mostly involve in immune response process. Among these genes, Clusterin (CLU) is a molecular chaperone which is responsible for clearance of cellular debris and apoptosis. It can protect tumor cells from cytokine- or drug-induced apoptosis also. What is more, HLA-G (HLA-G) which is a non-classical major histocompatibility complex (MHC) class I molecule cause tolerance through interaction with its receptors.

Conclusion: Our study suggests that HLA-G and CLU over -expression in HCC cancer cells can associated with the ability of cancer cells to evade from immune system. Therefore, these genes can be considered as potential therapeutic targets.

Keywords: Hepatocellular carcinoma, immune, HLA-G, CLU

17986

Association of rs 199254 rs Mir RNA 425 a2 gene polymorphism with non-small cell lung cancer

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Background: Lung cancer is one of the most common cancers among men in the world and is the fifth leading cause of death. It is located on the long arm of chromosome 12 and in the region of HOX C gene 10-C2 and has 78 lethal positions. Any mutation in the sequence of apoptosis pathway and biological process causes disruption. 425 a2 is associated with non-small cell lung cancer in men.

Materials and Methods: Our statistical population in this study included 100 women with lung cancer as a control group and 100 healthy blood samples as a patient group. DNA extraction was performed by ethanol deposition method to amplify the sequence by PCR and to determine the sequence of TAUI shear enzymes were used. Finally, SPSS V.24 software was used to analyze the data.

Results: The mean age of the patient group was 48 8 8 years. The frequency of C allele in the patient group was 78% and the frequency of T allele was 22% that the patient group had a significant relationship with its frequency (P = 0.04). Also, genotypes of heterozygous group (TC) were equal to 42% (P = 0.03) while dominant homozygotes (CC) and recessive homozygotes (TT) were equal to 2% and 32%, respectively, indicating no association with disease. Also, 18% of women who had consanguineous marriages and 42% of women with a family history of this cancer compared to other individuals and groups of the disease (P = 0.04) (CL = 1.19-3.71-OR = 95%

Conclusion: Based on the results, the frequency of heterozygotes compared to homozygotes in the patient group is higher than other groups that this gene can be used in individuals as a pro-factor factor for early detection.

Keywords: Lung Cancer, Polymorphism, Mir RNA 452 a2, rs 199254

16865

The correlation between killer cell immunoglobulin-like receptor-ligand (KIR-L) and breast cancer risk among the Kermanshah women

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Background: Breast cancer (BC) is one of the most common causes of cancer death globally, with a 0.5% increasing incidence per year. Natural killer cells (NK) have a crucial function in immune surveillance mechanisms, which recognize class I human leukocyte antigen (HLA) molecules, expressed on the target cells through their membrane receptors, called killer cell immunoglobulin-like receptors (KIR). Impaired NK cell anti-tumor immunity has particular relevance with BC progression and metastases. KIRs are the most polymorphic receptors of NK cells that modulate NK cell activity against malignant cells through their cognate HLA ligands' interactions. Considering this issue, we conducted this study to survey the impact of some HLA class I variegation on the susceptibility to BC's development in Kermanshah women.

Methods: In our study, the presence of HLA-B Bw4 and HLA-B Bw6 were detected using polymerase chain reaction with sequence-specific primers in 52 patients with breast cancer living in Kermanshah province (Iran) and 40 healthy subjects.

Results: Here, no significant differences were found for HLA-B Bw4, HLA-B Bw6, as well as their genotypes (P: 0.50, P: 0.20).

Conclusion: Our results indicated that the presence of HLA-Bw4 and Bw6 might not be associated with the risk of breast cancer in Kermanshah women.

Keywords: Natural Killer cells, Killer cell immunoglobulin-like receptors ligand, Breast cancer

16747

Elevated Interleukin-37 serum levels in patients with oral squamous cell carcinoma

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Background: Inflammation in oral cavity as well as imbalance of cytokine networks have been implicated in the pathogenesis of oral cancers. IL-37 has been known as an important inhibitor of innate inflammation and immunity, and a tumor suppressor in several kinds of cancers. Anti-inflammatory activity of IL-37 might affect inflammation-related tumors**.** The study aimed to investigate IL-37 serum level in patients with oral squamous cell carcinomas (OSCC), and determine its association with clinical and pathological characterization of the patients.

Methods: In this case control study, serum levels of IL-37 were investigated in 65 patients with OSCC compared with 65 healthy controls. Enzyme linked immunosorbent assay (ELISA) kit was used to investigate IL-37 serum level. The statistical analysis was done by non-parametric tests, Kruskal–Wallis H, and Mann–Whitney U, and pv less than 0.05 considered as significant level.

Results: Statistical analysis showed that serum level of IL-37 was significantly higher in patients than control group. However, there is no significant association between IL-37 serum level and with clinical and pathological factors of disease.

Conclusion: The results of the study show that IL-37 serum level is higher in OSCC cancer patients than in the control group. Increased level of IL-37 might be associated with tumor progression. Although further studies are needed in larger populations, IL-37 targeting might be a successful strategy for treatment of patients with OSCC.

Keywords: Oral squamous cell carcinomas, progression, ELISA, IL-37**.**

16745

Elevated IL-37 serum levels in Iranian women with breast cancer

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Background: Immune cell subsets as well as cytokines are involved in protection and/or progression of breast cancer. Interleukin 37 is one of the cytokines that may be involved in the pathogenesis of breast cancer trough dendritic cell suppression and Tregs activation. The study aimed to investigate IL-37 serum level in patients with breast cancer in comparison to control groups. Additionally, the association between serum IL-37 levels and different stages, tumor grade, nuclear grade, age, TNM stage, lymph node involvement, tumor size and ductal carcinoma in situ were investigated.
Methods: Serum level of IL-37 was measured by enzyme linked immunosorbent assay (ELISA) in 60 patients with breast cancer and 30 healthy individuals as control group. The statistical analysis was done by non-parametric tests, Kruskal–Wallis H, and Mann–Whitney U, and pv less than 0.05 considered as significant level
Results: IL-37 serum level was observed to be significantly higher in the patients than healthy controls. There was no significant association between IL-37 serum levels and different stages of breast cancer, differentiation grade of breast cancer, nuclear grade, age, TNM stage, lymph node involvement, tumor size and ductal carcinoma in situ. Albeit, compared to control group, increase in IL-37 serum level was found in all breast cancer stages. The best cut-off point (highest sensitivity and specificity of the test) for serum IL-37 was 37.94 pg / ml, at which the sensitivity of the test was 88.30% and its specificity was 75.90%.
Conclusion: The results suggest that increase in IL-37 may play a role in pathogenesis of Iranian women with breast cancer. Therapeutic effect of IL-37 should be investigated with more sample size of patients and functional study.

Keywords: Breast cancer, tumor stage, IL-37, ELISA.

16756

Polymorphisms TLR4 and colorectal cancer risk in Iranian population

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Background: Colorectal cancer (CRC) is one of the important leading causes of cancer-related death worldwide. Chronic inflammation has been identified as a major risk factor in CRC. Toll-like receptor 4 (TLR4) is a critical receptor and regulates inflammation. The current study was conducted to investigate the association between two single nucleotide polymorphisms (SNPs) (rs4986790 and rs4986791) in TLR4 gene and susceptibility to CRC.

Methods: The samples including 90 CRC cases as well as 90 matched controls were obtained from South Khorasan, Iran, between 2014 and 2016. Genomic DNA was genotyped using polymerase chain reaction (PCR) method followed by PCR-restriction fragment length polymorphism (RFLP). Data were statistically analyzed based on chi-square test.

Results: No association was observed between TLR4 mutations and CRC risk according to genotype distribution (p = **0. 59). The mutated homozygous genotype was not observed in any cases and it was one in controls. Hardy–Weinberg equilibrium was maintained in the control group.**

Conclusion: According to the results of our study, rs4986790 and rs4986791 polymorphisms are not a risk factor for CRC. However, to confirm these results, more investigations are necessary in a larger population.

Keywords: RFLP, TLR4, polymorphism, colorectal cancer, inflammation

16629

RNA editing sites in interferon alpha and beta receptor (IFNAR) genes of gastric cancer patients

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Background: Tumors need to regulate the immune response in order to survive and expand. It has been reported that RNA editing sites are required to prevent the activation of the innate immune system in cancerous cells. The role of interferon alpha and beta receptor (IFNAR) against viral infections has been studied, but their immunomodulatory functions are unknown. Here we investigate RNA editing sites in IFNAR1 and IFNAR2 genes.
Methods: We used a bioinformatics approach to identify RNA editing sites in gastric cancer patients. RNA-sequencing data of eight patients were retrieved from the GEO database. After variant calling, quality controlling and preprocessing were employed. Reads were mapped to the human reference genome (GRCh38). Differences between RNA and DNA sequences were determined as RDDs. Known SNPs were filtered out from RDDs and several filtering steps were applied to increase the accuracy of identifying actual RNA editing sites. Finally, editing sites in IFNAR1 and IFNAR2 genes annotated.
Results: We identified 15 and 14 RNA editing sites in IFNAR1 and IFNAR2 genes respectively. These editing sites were distributed downstream and 3UTR of IFNAR1 and IFNAR2 genes. Annotating these editing sites with SnpEff software, assigned a modifier impact on all of these editing events.
Conclusion: IFNAR1 and IFNAR2 editing occurs in gastric cancer and the editing event could have immunomodulatory functions.

Keywords: RNA editing, IFNAR1, IFNAR2, immune response

16832

Evaluation of the effects of *Glycyrrhiza glabra*-derived glycyrrhetinic acid on expression of STAT3 signaling pathway-related genes in gastric cancer stem cells

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Background: Gastric cancer is the fifth most common malignancy worldwide. Cancer stem cells (CSCs) are a subgroup of cells in heterogeneous tumors that cause survival, relapse, metastasis, and drug resistance of tumors. Multiple evidence indicated that *Glycyrrhiza glabra*-derived glycyrrhetinic acid (GA) has anti-inflammatory and anti-cancer effects. STAT3 protein regulated epithelial-mesenchymal transition (EMT) process, and interact with CD44, leading to changes in migration, invasion, and metastatic abilities of CSCs. Here, we examined the effects of GA on the expression of STAT3 and Bcl-2 mRNA, EMT-related genes, and CD44 protein in CSCs.

Methods: Gastric CSCs were plated in serum-free medium supplemented with EGF and B-27 under nonadherent conditions, treated with various concentrations of GA at different times, and assessed by using MTT assay. Expression of mRNA levels of STAT3 and Bcl-2, and EMT markers (ZEB-1, Snail-1) using relative quantitative real-time PCR, as well as CD44 molecule using flow cytometry were evaluated after CSCs treatment with IC50 concentrations at different times.

Results: Effects of GA on CSCs using MTT assay showed that CSCs viability decreased in a time and dose-dependent manner. In CSCs treated with IC50 doses of GA after 24 and 48 hours, expression of STAT3, Bcl-2, ZEB-1, and Snail-1 mRNA, and CD44 protein was significantly downregulated compared with untreated CSCs ($P < 0.05$).

Conclusion:

Our findings showed that GA-treated gastric CSCs effectively influenced the STAT3 signaling pathway, EMT, and stemness marker CD44, resulting in inhibition of CSCs growth and killing of them. Therefore, targeting CSCs with GA could be considered as a potential agent for cancer treatment.

Keywords: Cancer stem cells, CD44, glycyrrhetinic acid, STAT3 signaling pathway

16765

The effect of an anti-allergic drug on TGFβ-one of the important inflammatory factors- in colon cancer cell line signaling pathway

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Background: Colon cancer is the second most common cause of cancer deaths around the world. So far, extensive research has been done on the causes and patterns of colon cancer formation and development, as well as on prevention and treatment. Tranilast is a TGF beta_inhibitor and identified as an anti-allergic agent, and used in the treatment of inflammatory diseases, such as bronchial asthma, allergic conjunctivitis. The beneficial effects of tranilast have also been seen in a variety of disease states, such as fibrosis, proliferative disorders, autoimmune disorders, and cancers. In this study, we evaluated the anti-cancer effects of this drug on one of the important signaling pathways in colon cancer cell lines.

Method: CT-26 colon cancer cells were cultured in F12 medium supplemented with 10% FBS and antibiotic streptomycin and penicillin at 37 ° C and 5% CO2. To evaluate the effect of Tranilast toxicity on cells, MTT assay, and spheroid tests were used. The Real-Time PCR technique was also used to examine the expression of cyclinD1, VEGF, VEGFR, and TGF-β genes at the RNA level. For evaluation, the Cyclin-D1protein expression western blotting was used.

Results: The results revealed that the IC50 of the Tranilast on CT-26 cells was about 200µM. consistently, the spheroid test showed that after 7 days, 1mM of Tranilast disturbed spheroid structure and decreased spheroid volume, compared to the control group. The results of Real-Time PCR showed that 200 µm dosage of Tranilast could decrease the expression of Cyclin D1 gene and TGF-beta expression. Also, the expression of VEGF-R was decreased.

Conclusion: This study suggests that Tranilast has anti-cancer properties by decreasing cell proliferation markers, Cyclin D1, and TGF-β levels. These results support the therapeutic potency of Tranilast for colon cancer patients alone or with standard_treatments.

Keywords: Tranilast, Real Time PCR, Cyclin-D1, TGF-β, Colon cancer

16664

Synergistic evaluation of ginger and licorice extracts in a mouse model of colorectal cancer

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Objectives: The use of herbal medicine is necessary to overcome the side effects of conventional treatments. In this study, the anti-cancer activities of ginger and licorice extracts and also the synergistic effect of their combination were evaluated.

Methods: In this study, ginger ethanolic extract (GEE) and licorice methanolic extract (LME) were isolated by a Soxhlet extractor. Next, the anti-proliferative activity of the extracts was examined, and apoptosis induction, tumor growth inhibition, and tumor-infiltrating T lymphocytes were investigated.

Results: The MTT assay showed that GEE and LME decreased CT26 cell viability in a dose-dependent manner; however, the GEE+LME combination was more effective ($P<0.05$). The CT26 cells treated with the half-maximal inhibitory concentration (IC_{50}) of each compound showed a significant increase in Bax/Bcl-2 ratio and caspase-3 gene expression; especially in the GEE+LME group ($P<0.001$). Tumor volume significantly reduced in the GEE+LME group, compared to the negative controls. Finally, mice treated with GEE+LME showed a significant increase in CTL/Treg cell ratio ($P<0.001$) and Bax/Bcl2 ratio ($P<0.05$).

Conclusion: Our results demonstrated that the combination of GEE and LME had synergistic anti-cancer effects on colorectal cancer both in vivo and in vitro; therefore, the prepared mixture can be used in future clinical trials.

Keywords: Ginger ethanolic extract, Licorice methanolic extract, colorectal cancer, Infiltrating T cells, Apoptosis

16853

EL4 small extracellular vesicles express functional TNF-related apoptosis-inducing ligand, which induces apoptosis and necrosis in 4T1 cells

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Background: Tumor-derived exosomes play a crucial role in cancer development. The present study investigates the hypothesis that whether small extracellular vesicles (SEVs) released by EL4 cells are able to carry a functional TNF-related apoptosis-inducing ligand (TRAIL) molecule.
Methods: EL4 cells were cultured and SEVs were separated from the supernatant soup. The EL4-derived SEVs were identified using an anti-CD63 antibody (dot-blot). In addition, the isolated SEVs were characterized based on the shape (scanning electron microscopy), and size (dynamic light scattering). The protein concentration of isolated SEVs was measured and considered as SEVs quantity for in vitro functional assay. Moreover, the expression of TRAIL gene by EL4 cells was studied using cells qRT-PCR. Additionally, TRAIL protein was investigated in EL4-SEVs using dot-blot analysis. In order to evaluate the effect of EL4-derived SEVs on 4T1 (TRAIL-sensitive cell line) apoptosis, the Annexin V/propidium iodide, and acridine orange/ethidium bromide staining was performed.
Results: The results of the in vitro study revealed that EL4 cells constantly and sans stimulation, produce SEVs that carry TRAIL protein. Moreover, the cell death study indicated that the frequency of apoptosis and necrosis induced in cells by SEVs which were treated by 50 µg/mL (32.80 ± 3.36 % and 34.00 ± 3.49 %, respectively) and 100 µg/mL (25.60 ± 4.98 %, $p = 0.009$ and 48.60 ± 6.10 %, $p = 0.009$, respectively) of EL4-SEVs was significantly higher than the controls which were incubated with media.
Conclusion: Finally, it was concluded that EL4 cells produced SEVs, which carry functional TRAIL protein. Besides, the TRAIL-containing SEVs can trigger apoptosis and necrosis in 4T1 cells. Our results pave the way for a better understanding of the potential roles of tumor-derived SEVs in the pathogenesis of cancers.

Keywords: Tumor-exosomes, TNF-related apoptosis-inducing ligand, Apoptosis, Necrosis

16742

Increased serum concentrations of interleukin-37 in patients with bladder cancer

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Background: Bladder cancer is an age related disease, and 3-4 times is more frequent in males than female. IL-37 contributes to tumor progression in various cancer types including melanoma and colon cancer; however, it has not been studied in bladder cancer. The study aimed to investigate IL-37 in serum of patients with bladder cancer, and determine its association with clinical and pathological parameters of disease.

Methods:

In this case control study, IL-37 serum level was measured in 60 patients with bladder cancer for comparison with 50 healthy controls by commercial enzyme linked immunosorbent assay (ELISA) assays. The statistical analysis was performed by non-parametric tests, Kruskal–Wallis H, and Mann–Whitney U, and pv less than 0.05 considered as significant level.

Results:

IL-37 serum level was found to be significantly elevated in male patients and patients aged ≥70 in comparison with male controls and controls aged ≥70 ($p<0.05$). A non-significant trend of an increase in IL-37 serum level was observed in patients with peri neural invasion (PNI) than those without PNI.

Conclusion:

Our results show an increased level of IL-37 in sera of male patients with bladder cancer and those with aged ≥ 70. IL-37 might play an important role in the tumor progression, and might be considered as a new therapeutic target in bladder cancer.

Keywords: Bladder cancer, IL-37, ELISA, Tumor progression.

16678

Tumor suppressor miR-142-3p regulate breast cancer tumorigenicity, invasion and migration by targeting Bach1

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Background: miR-142-3p belongs to the miR-142 family and is involved in pathogenesis and metastasis of various types of malignancies such as breast cancer by targeting several important messenger RNAs (mRNAs) including Bach-1. In this study we aimed to show the regulatory effect of miR-142-3p on breast cancer by targeting Bach-1 expression.
Methods: 24 breast cancer tissues with their adjusted normal tissues have been collected and the expression levels of miR-142-3p and Bach-1 mRNA were measured using quantitative reverse-transcription polymerase chain reaction (qRT-PCR). The targeting Bach1 by miRNA was evaluated using bioinformatics, qRT-PCR and western blot analyses. The cellular proliferation, invasion, and migration were assessed by MTT, transwell matrigel and wound healing assay and the EMT-associated proteins C-X-C chemokine receptor type 4 (CXCR-4 ,(matrix metalloproteinase-9 (MMP9), and vascular endothelial growth factor receptor (VEGFR) were analyzed by western blot analysis.
Results: Analysis of paired specimens of primary malignant and normal tissues showed that miR-142-3p was downregulated, while Bach-1 mRNA and protein both were overexpressed in the breast cancer tumors. This inverse relationship was confirmed by cell line experiments demonstrating that miR-142-3p expression reduced Bach-1 mRNA levels. Furthermore, replacement of miR-142-3p could inhibit the proliferation, invasion, and migration in breast cancer potentially by targeting of Bach-1 mRNA and subsequent inhibition of CXCR4, MMP9, and VEGFR protein expressions.
Conclusion: For the first time, our results revealed that miR-142-3p could target Bach-1in breast cancer cells leading to the reduction of EMT-related proteins and reduced cell proliferation, invasion, and migration. The results also demonstrated that miR-142-3p could regulate important tumor suppressor miRNAs in breast cancer cells. In conclusion, our results suggest that miR-142-3p could be a good candidate for the targeted therapy of breast cancer, especially for the invasive type.

Keywords: Bach-1, breast cancer, invasion, migration, miR-142-3p

16729

Investigation of serum level of IL-27 in endometrial cancer patients

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Background: Endometrial cancer is the most common gynecological cancer in developed countries and seventh most common cancer worldwide. Different investigations have been done about the role of IL-27 in different cancers that suggested dual role for this cytokine. In this study, we investigated and compared serum levels of IL-27 in patients with endometrial cancer and control group and also evaluated the correlations between this serum levels and demographic and clinicopathologic features of the patients.

Methods: In this case-control study we investigated 65 endometrial cancer patients with different stages and tumor sizes. The control group consist of 30 healthy women referred to Fars Blood Transfusion Center. Serum levels of IL-27 measured using ELISA method and results were analyzed with SPSS.

Results: Mean serum level of IL-27 was 330.16±233.04 pg/ml in patients and 315.5 ± 268.25 pg/ml in controls (P = 0.476). Median serum level of IL-27 was 222.73, 268.52 and 258.64 pg/ml in the grade of 1, 2 and 3 of endometrial cancer disease respectively (P =0.51). No significant correlations between serum level of IL-27 and stage, lymph node involvement, and tumor size was found (P = 0.794, 0.475, 0.753 respectively). We also compared serum levels of IL-27 with demographic features of the patients and statistical analysis showed no significant correlations.

Conclusion: Results of this study showed there were no significant differences between serum levels of IL-27 in endometrial cancer patients and controls. No significant correlations found between serum levels of IL-27 and demographic and clinicopathologic features of EC patients. Therefore, the serum levels of IL-27 in endometrial cancer may not be indicative of tumor progression or its high-grade feature, although further studies are needed

Keywords: Endometrial cancer, IL-27, ELISA

16551

Relation between Immune cell response and stemness genes expression in breast cancer; A new approach in NANOG gene and Let7-a expression in breast cancer cell lines

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Background: Failure and recurrence in breast cancer treatment cause a great obstacle in cancer therapy and identifcation of cell population named cancer stem cells (CSCs) in the tumor can be led us to defne it as target in novel therapeutic strategy. The aim of this study is the fnding of correlation between stemness and metastatic characteristic, also knowing CSCs as a potential target of therapy because of its developmental behavior and similarities with normal stem cells.

Materials and Methods: Here, we focus on the expression of NANOG in breast CSCs, a key molecule in the physiological process of stem cells and the Let-7a that is involved in the differentiation of the cells.

Results: In this work, we found that NANOG was highly expressed in SKBR3 and down regulation of let-7a, as a differentiation miRNA, was found in MDA-MB-468 cells.

Conclusion: It will be critical for the developing of effective anti-tumor drugs, utilizing mentioned concepts. Inhibition of NANOG in combination with Let-7a up-regulation can help to decrease the stemness and increase the differentiation of CSCs. The decrease of stemness and increase of differentiation initiate the apoptotic process. So, modifcation in the mechanism of apoptosis beside anti-cancer drugs provide a good preclinical study goal. However, in order to these drugs become clinical, the problems of their side effects and toxicity must be solved. Differentiation of CSCs provides an optimal condition to activity of immune cells which never let them escape from immune cells by alteration of immunogenicity.

Keywords: Breast cancer, Immunologic response, Stemness, Cancer stem cells, Novel cancer therapy

14366

A new labeled allograft in vivo model for analysis of colon carcinoma (micro) metastasis in BALB/c mice

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Background: Colorectal cancer (CRC) is the fourth most common cause of death in the world. The fate of the patients is dependent on the metastatic spread of cancer cells. Therefore, experimental models of (micro) metastasis without any deficiencies in the immune system are necessary for tumor immunotherapy investigations. We have developed a mouse model to evaluate experimental hepatic and pulmonary (micro) metastasis of CT26 colon carcinoma cells in syngeneic BALB/c mice by systemic injection of tumor cells.

Methods: In this study, stable transfected CT26 cells, expressing *Leishmania major GP63,* were intravenously (IV) injected to BALB/c mice for induction of micrometastases. Twelve mice were divided in four groups including one control and three test groups. The test groups were sacrificed on days 3, 7 and 14 of the injection, respectively. The livers, lungs, kidneys and colons were excised and monitored for the presence of micrometastasis. RT-PCR analysis was performed on tissue samples to detect *Gp63* gene.

Results: Our results showed that pcDNA3 *L. major Gp63* was successfully constructed and transfected into CT26 cells. After IV injection, the *Gp63* gene was detected in the liver, lung and kidney but not in the colon as a marker of tumor cells on days 3, 7 and 14 of the injection.

Conclusion: In the present study, due to the importance of (micro) metastasis and the need for establishing simple allograft models for cancer immunotherapy studies, a practical mouse model was developed. CT26 tumor cells stably expressing *Gp63* generated a potent marker for detection of (micro) metastatic cells in the tissues because *Gp63* gene does not exist neither in tumor cells nor in mouse genome. Our data introduces an allograft mouse model of colon carcinoma which leaves the immune system intact and is just like a normal body system. This technique is practical and does not need anesthesia and surgery.

Keywords: Colon carcinoma, (Micro) Metastasis, Mouse model, allograft

15513

Evaluation of Innate Lymphoid Cells (ILCs) Population in Mouse Model of Colorectal Cancer

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Background: Innate Lymphoid Cells (ILCs) are known as mucosal innate immune cells, where they play important roles in initiation of immune responses and chronic inflammation. To shed some lights on potential roles of innate immune system in pathophysiology of colorectal cancer (CRC), this experimental study was designed to evaluate the frequency of ILCs in CRC.
Methods: CRC was chemically induced in a set of Balb/c mice, using AOM and DSS, and orthotopically induced in another set of Balb/c mice via injection of CT-26 cell line into the colon of mice. Normal saline was injected to another set of mice, as a sham group. After 80 days, mice were divided into two groups of dysplasia and reparative change, based on pathological examinations. Frequencies of ILC1, 2, and 3 were then measured in colon tissues, using flow cytometry, and compared with those of the sham group.
Results: Total ILC population was significantly higher in chemically induced reparative change compared with the sham group ($P=0.0071$). While ILC1 in chemically induced reparative change was significantly higher than those in two other groups ($P<0.0001$), chemically induced dysplasia showed more ILC3 population than other groups ($P<0.0001$).
Conclusion: Evidently higher ILC1 population might play a protective role in tumor immunity; ILC2 has no significant impact on malignancy, and inflammation; and finally ILC3 could help the growth and progression of the tumor.

Keywords: Dysplasia, Innate lymphoid cell, Reparative Change

15478

In vitro apoptotic effect of deferoxamine on the glioblastoma cell line

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Background : Deferoxamine is an iron chelator. The anti-proliferative effect of Deferoxamine on erythroleukemia cells was indicated in previous studies. The aim of this study was to investigate the effects of deferoxamine on B92 cells as a model of glial cell carcinoma.
Materials and Methods: In this experimental study, 6×10^4 B92 were cultured with different concentrations of deferoxamine (0, 10, 50 and 100 µM) with or without 10 µmol/l ferric chloride for 24 h. The morphological changes of the treated cells in the comparison sample were evaluated using an inverse optical microscope. The inhibitory and cytotoxic effects of deferoxamine were evaluated by dimethylimidazole-diphenyl tetrazolium bromide (MTT) reduction and neutral red uptake assays. Data were analyzed by using a Kruskal–Wallis test test .P <0.05 was considered as significant level.
Results: The inhibitory effects of deferoxamine on the proliferation rate of B92 cells were determined after 24 hours so that the cells began to accumulate in the presence of deferoxamine. The ferric chloride (10 µmol/L) can prevent these morphological changes. The results also indicated that deferoxamine significantly inhibited B92 cell vitality and viability in a dose-dependent manner. Moreover, the data indicated that ferric chloride can eliminate these effects on B92 cells caused by deferoxamine treatment.
Conclusion: Deferoxamine possesses in vitro anti-proliferative effects on the glial cell line B92.

Keywords: Cell Proliferation, Iron Chelating Agents, Glioma, B92 cells.

14368

Investigation of placental-specific protein 1 (PLAC1) gene and protein expression profiles in bone marrow and peripheral blood of acute and chronic leukemias

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Background: Placenta-specific protein 1 (PLAC1) is one of the cancer-testis antigens family that has no expression in normal tissue except placenta trophoblast and testicular germ cells, but is activated and upregulated in a variety of malignant tissues, including breast, lung, colon, liver, prostate, cervix, and stomach cancers. To the best of our knowledge, there is no reported data on the expression of PLAC1 in acute and chronic leukemias.

Methods: In the present study, we investigated the gene and protein expression of PLAC1 in peripheral blood and bone marrow mononuclear cells of acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) new diagnosed patients, using quantitative Real-Time PCR, western blotting and flow cytometry. Normal healthy subjects with similar age of each group were considered as control.

Results: Our data demonstrated that PLAC1 transcript were expressed in 67.7% of ALLs, 7.8% of CLLs, 48.3% of AMLs and 66.6% of CMLs as judged by quantitative Real-Time PCR. Western blotting and flow cytometry analyses using home-made polyclonal antibody specific to recombinant PLAC1 analysis confirmed expression of PLAC1 in the corresponding samples. PLAC1 expression at the gene and protein levels were totally negative in all included normal healthy subjects.

Conclusion: Our findings showed that PLAC1 could be a proposed marker applicable in the diagnosis and therapy of leukemia patients with complementary studies in the future.

Keywords: PLAC1, Biomarker, Acute leukemias, chronic leukemias

15519

Deterrence of USP14 impel ER stress– Due to autophagy streak A549 in lung cancer cell

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Background: Non-small cell lung cancer is the most common type of lung cancer, accounting for more than 80% of this tumor. Ubiquitin specific protease (USP) 14 is one of the 100 deubiquitinating enzymes that is overexpressed in lung cancer and has been validated as a therapeutic target. The aim of this study is to determine whether the accumulation of ubiquitinated proteins results in endoplasmic reticulum (ER) stress-mediated autophagy. Also found that USP14 inhibitors did not induce apoptosis but actually induced autophagy through accumulation of ubiquitinated proteins/ER stress/unfolded protein response (UPR) axis. Moreover, we have for the first time demonstrated that the USP14 inhibition induces ER stress–mediated autophagy in A549 cells by activation of c-Jun N-terminal kinase 1 (JNK1).

Methods: To inhibit USP-14, A549 lung cancer cells were treated with USP-14 siRNA and IU1-47 (20 μM). The protein level, mRNA expression, and cell cycle analysis were evaluated using Western blot, real-time PCR, and flow cytometry, respectively. We found that treating A549 cells with USP14 inhibitors significantly reduced the proliferation rate and induced cell cycle arrest at G2/Massee.

Results: this investigation proposes new mechanism in which USP14 inhibition induces autophagy via ER stress–dependent upregulation of PERK, IRE1α, and JNK1 pathways, arrests A549 cells at G2/M phase, and does not induce significant apoptosis.

Conclusion: In conclusion, the current investigation represents a new mechanism by which inhibition of USP14 triggers autophagy via ER stress–mediated UPR in A549 cells.

Keywords: Ubiquitin-proteasome, Endoplasmic reticulum stress, UPR, Autophagy, JNK

Congress Abstracts

Cancer Imounotheraphy

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(15518)

PD-1 and Tim-3 blocking dose not improve the apoptosis of leukemic cells by peripheral blood CD8$^+$ T cells in chronic lymphocytic leukemia

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Background: Patients with chronic lymphocytic leukemia (CLL) have profound defects in function of T-cells developing an exhausted phenotype which is recognized by the expression of multiple immune checkpoint receptors such as PD-1 and Tim-3. In the last decade, immunotherapy strategy based on the immune checkpoint inhibitors has achieved invaluable success in tumor therapy. In this in vitro study, the effect of PD-1 and Tim-3 blocking was investigated to restore the function of exhausted CD8$^+$ T-cells in CLL patients.

Methods: Peripheral blood mononuclear cells were isolated from 16 patients with CLL and CD8$^+$ T cells were positively isolated using magnetic beads separation method. Isolated CD8$^+$ T cells were treated with either blocking antibodies against PD-1 and Tim-3 and isotype matched control antibodies and then co-cultured with CLL leukemic cells as target cells. Treated CD8$^+$ T cells were stimulated with anti-CD3/CD28 antibodies and recombinant IL-2. The percentage of apoptotic leukemic cells and expression of apoptotic genes (Bax, Bcl-2 and Caspase-3) were evaluated by flow cytometry and Real-Time PCR, respectively. IFN-γ and TNF-α concentration was also measured using ELISA.

Results: Flow cytometric analysis of apoptotic leukemic cells indicated that the blockade of PD-1 and Tim-3 did not significantly improve the cytotoxicity effects of CD8$^+$ T-cells on CLL cells which then were confirmed by gene expression analysis of Bax, Bcl-2 and Caspase-3 which was similar in blocked and control groups. No significant difference was found between blocked and control groups in term of production of IFN-γ and TNF-α by CD8$^+$ T cells.

Conclusion: We concluded that blockade of PD-1 and Tim-3 is not an effective strategy to restore the function of CD8$^+$ T-cells in CLL patients at the early stages of the disease. Further in vitro and in vivo studies are needed to more address the application of immune checkpoint blockade in CLL patients.

Keywords: Chronic lymphocytic leukemia, PD-1, Tim-3, Immune checkpoint inhibitors

(16861)

Establishment of a murine model of breast cancer expressing human epidermal growth factor receptor 2 (4T1-HER2)

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Background: Nowadays animal models are used to address multitudes questions concerning development, improvement and assessment of novel vaccines or immunotherapy approaches. Given this crucial role in conducting research, we establish a cost-effective animal model for HER-2 positive breast cancer to gain in-depth knowledge about the complexity of this subset of breast cancer.
Methods: 4T1 cells were stably transfected with pCMV6-Neo-Her2 construct**.** Then, immunofluorescence and flow cytometry were conducted to confirm human HER2 expression. Migration and invasion of 4T1-HER2 compared to 4T1 cell line were checked in scratch and trans-well assays. Then, by implantation of 4T1-HER2 cells into Balb/c mice, the tumorgenicity rate and growth rate were measured in comparison to 4T1. The MDSCs population in turmeric mice were analyzed by flow cytometry.
Result: Human HER2 protein was stably expressed on 95% of transfected 4T1 cells using immunofluorescence and flow cytometry. HER2 transcript and protein expressions were also confirmed in tumor mass using RT-PCR and ELISA. Although no significant difference was observed in migration and invasion of 4T1 and 4T1-HER2 cells over 48 hours, the growth of 4T1-HER2 was roughly three times less than 4T1 in challenged mice over 24 days. The rate of tumorigenicity was 90% (9 out of 10) in challenged mice. The level of MDSCs had an increase of 11% and 44/5% in spleen of 4T1-HER2 and 4T1 tumor inoculated mice compared to normal mice.
Conclusion: We describe a murine model for HER-2 positive breast cancer that can be used in immunocompetent mice to shed light on the mechanism of immune evasion in this subset of breast cancer, as well as paving the way to monitor the microenvironment and immune system interaction which can help to make HER2- positive breast cancer more sensitive to novel immunotherapy modalities.
Keywords: Animal model, HER2, Immunotherapy, Breast cancer, 4T1

(17927)

Construction and Functional Characterization of a Fully Human Anti-mesothelin Chimeric Antigen Receptor (CAR) Expressing T Cell

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Background: Chimeric antigen receptor (CAR) T cell therapy is considered as an encouraging approach for the treatment of hematological malignancies. However, its efficacy in solid tumors has not been satisfying, mainly in the immunosuppressive network of the tumor microenvironment and paucity of appropriate target antigens. Mesothelin (MSLN) is a tumor-associated antigen (TAA) expressed in numerous types of solid tumors such as gastrointestinal, ovarian, and pancreatic tumors. Owing to high expression in tumor cells and low expression in normal tissues, MSLN-targeted therapies like monoclonal antibodies have been previously developed.
Methods: In the present study, a CAR T cell harboring the second-generation of a fully human anti-MSLNCAR construct containing CD3ζ and 4-1BB signaling domains was produced and it was functionally evaluated against an MSLN-expressing cell line.
Results: The findings showed potent, specific proliferation, cytotoxic activity, and interleukin (IL)-2, Tumor necrosis factor-(TNF) α, and Interferon-(IFN) γ production in an antigen-dependent manner. Cytotoxic activity was shown in effector-to-target ratio from 1:1 to 20:1, but the most adequate efficacy was observed in the ratio of 10:1. Non-specific activity against MSLN negative cell line was not observed.
Discussion: Our data demonstrated that primary human T cells expressing fully human MSLN-CAR construct are effective against MSLN-expressing cell lines in vitro, suggesting this MSLN-CAR construct as a potential therapeutic tool in a clinical setting.
Keywords: Adoptive immunotherapy; Chimeric antigen receptor; Mesothelin

(18332)

Title: Targeted knock-down of A2a Receptor Enhances the function of anti-mesothelin CAR T cells.

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Background: CAR T cell-based therapies have shown promising results in hematological malignancies. Results of CAR T cell studies in solid tumors have been less impressive, and factors including lack of targetable antigens and immunosuppressive tumor microenvironment (TME) have been suggested as culprits. Adenosine is a highly produced metabolite in TME, known to mediate the suppression of anti-tumor T cell responses via binding and signaling through adenosine 2a receptor (A2aR).
Methods: In the current study, anti-tumor activity of MSLN CAR T cell has been improved using genetic targeting of A2aR. The expression of A2aR and the effects of its activation on the function of fully human anti-mesothelin CAR T cells (MSLN-CAR T), were analyzed. Afterwards, the molecular means to overcome the inhibitory effects of A2aR signaling on CAR T cell function were examined. This was performed by targeting A2aR expression in MSLN-CAR T cells using various anti-A2aR shRNA sequences embedded in the CAR vector. Statistical analyses were performed Prism 7 software.
Results: Our experiments showed significant A2aR upregulation on T cells during the CAR T cell production procedure. Activation of adenosine signaling using adenosine analog (NECA) led to the suppression of all major anti-tumor functions in MSLN-CAR T cells. Interestingly, CAR T cells that carried the anti-A2aR shRNA sequences were resistant to the inhibitory effects of adenosine signaling. Genetic targeting of A2aR reversed the reduction in CAR T cell proliferation, cytokine response, and cytotoxic function of the MSLN-CAR T cells caused by the adenosine analog.
Conclusion: Our results demonstrate that mitigating A2aR signaling by genetic targeting of the receptor might be a promising approach in improving CAR T cell function in an unreceptive microenvironment and could potentially improve the outcome of treatment in clinical settings.
Keywords: Chimeric antigen receptor, Genetic Targeting, Adenosine 2a-receptor, Tumor microenvironment

(18444)

A novel anti-HER2 bispecific antibody with potent in vitro and in vivo tumor inhibitory effects

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Background: Over-expression of HER2 is reported in many types of cancer which makes it a perfect candidate for targeted immunotherapy. Combination of two FDA approved monoclonal antibodies (mAbs), Trastuzumab and Pertuzumab, has more robust anti-tumor activity in patients with HER2-overexpressing breast cancer. Recently, we produced a new humanized anti-HER2 mAb, Hersintuzumab, which recognizes a different epitope than Trastuzumab and Pertuzumab on HER2. This mAb in combination with Trastuzumab exhibits more potent anti-tumor activity than each parental mAb alone. Here we have developed a novel bispecific anti-HER2 antibody (BsAb) designated as TraSintuzumab, composed of Trastuzumab and Hersintuzumab.

Methods: Two BsAbs (BiHT and BiTH) were engineered based on DVD-Ig technology using variable domains of Trastuzumab and Hersintuzumab, which are joined together in tandem with different orientations. Both BsAbs were expressed in conjunction with human IgG1 and Cκ constant domains. These BsAbs were structurally and functionally characterized in vitro and in vivo.

Results: Both variable domains of TraSintuzumab are fully functional and have similar affinities to the parental mAbs and are also able to bind to natural HER2 on surface of several HER2-expressing cell lines. TraSintuzumab was found to inhibit growth of different types of tumor cell lines through suppression of the AKT and ERK signaling pathways as efficiently as the combination of the parental mAbs. It also induced tumor regression as potently as the combination of the two mAbs in nude mice bearing ovarian and gastric cancer xenografts.

Conclusion: Our data suggest that TraSintuzumab may be a promising therapeutic candidate for treatment of HER2-overexpressing cancers.

Keywords: Bispecific antibody, HER2, DVD-Ig, Monoclonal antibody, Cancer immunotherapy

(18467)

Highly Efficient Generation of Transgenically Augmented CAR NK Cells Overexpressing CXCR4

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Background: Based on the natural cytotoxicity behavior of NK cells, genetically modifying NK cells is among the prime goals in immunotherapy. We show efficient gene delivery of huCAR19 to primary NK cells using lentiviral vectors.huCAR19 NK cells displayed specific potent cytotoxic activity against target cells. To improve the homing of NK cells, we augmented huCAR19 NK cells with the human CXCR4 gene, resulting in transgenically augmented CAR NK cells (TRACKs). TRACKs exhibited enhanced migration capacity in response to the ligand while retaining functional.

Methods: A fully human, second-generation CD19 CAR construct (huCAR19), and huCAR19 - huCXCR4 were used to transduce isolated primary NK cells from healthy donors. CFSE-based cytotoxic assay applied for measuring the specific cytolytic activity of gene-modified huCAR NK Cells. Migration of both kinds of huCAR19 NK cells was investigated in a transwell migration assay in the presence or absence of SDF-1. Mimicking the bone marrow environment and homing, migration assay was performed seeding BMSCs in the lower wells. Fluorescent microscopic imaging and quantification by flow cytometry of migrated cells were performed.

Results: semi-equivalent transduction rates were achieved for both CAR constructs (huCAR19-LV=87.11% and huCAR19.CXCR4-LV=85.25%). huCAR19.CXCR4 cells significantly expressed CXCR4 (average= 81.5%). Specific cytolytic activity of huCAR19 NK cells demonstrated efficiently killing of tumor cells in all applied ratios. In Chemotaxis, the number of migrated huCAR19.CXCR4 NK cells were nearly two-fold and three-fold enhanced compared to huCAR19 NK and untransduced cells correspondingly. Fluorescent microscopic imaging and quantification of migrated cells toward BMSCs revealed more than 4-fold chemotaxis of TRACs compared to other cells.

Conclusion: We could show efficient overexpression of native human CXCR4 on primary CAR NK cells upon genetic engineering. These *TRACKs* displayed a strong specific anti-tumor activity besides enhanced chemotaxis towards specific ligands. TRACKs may become a novel candidate for immunotherapeutic strategies in clinical applications.

Keywords: natural killer (NK) cell, huCAR19, transgenically augmented CAR NK cell (TRACKs), chemokine receptor 4 (CXCR4)

(18575)

PLAC1: a potential biomarker for targeted immunotherapy of melanoma

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Background: Melanoma incidence is increasing worldwide prompting scientists to find new biomarkers for targeted immunotherapy of melanoma. Placenta specific 1 (PLAC1) is one of the members of cancer-testis antigens which is widely expressed in variety of cancers. The aim of this study was expression profiling of PLAC1 in human skin cancers.

Methods: Anti-PLAC1 polyclonal and monoclonal antibodies were generated and fully characterized. One of the antibodies with higher reactivity in immunohistochemical (IHC) staining was applied for tissue microarray (TMA)-based IHC profiling of PLAC1 expression in skin cancer tissues including cutaneous melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in comparison with normal skin and nevus tissues. SN38 was conjugated to an anti-PLAC1 antibody and conjugation efficacy was evaluated by HPLC and UV spectrophotometry. Post-conjugation reactivity was then tested using ELISA and flow cytometry. *In vitro* cytotoxicity profiling of anti-PLAC1-SN38 conjugate was examined in melanoma cell lines, A-375 and A-2058.

Results: It was observed that 100% of melanoma tissues highly expressed PLAC1 in cytoplasmic and surface expression pattern. SCC cancer cells showed very weak staining and analysis of PLAC1 expression in BCC tissues showed negative results. Nevus samples and normal skin tissues showed no expression of PLAC1. The generated anti-PLAC1 antibodies specifically reacted with a wide variety of human cancer cells. Conjugation of anti-PLAC1 antibody to SN38 did not negatively affect reactivity of the antibody with cognate native antigen. Anti-PLAC1-SN38 exerted a substantial cytotoxicity in melanoma cells expressing surface PLAC1 in a time- and dose-dependent manner.

Conclusion: Our results support the idea of embryonic/placental tissue antigens re-expression in cancer and highlights the probability of melanoma targeted therapy using anti-PLAC1 antibody.

Keywords: PLAC1, Immunotherapy, Melanoma, SCC, BCC

Poster

(15452)

"Suppression of PD-L1 Inhibits Tumor Progression and Upregulate the Production of Pro-inflammatory Cytokines by T-lymphocytes"

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Background: Triple Negative Breast Cancer (TNBC) is known as invasive tumor with high incidence of distant metastasis and poorer prognosis than other subtypes. High PD-L1 expression by TNBC cells have immunosuppressive effect on tumor infiltrating T-Lymphocytes (TILs). Although several FDA-approved anti-PD-1/PD-L1 axis are suggested as the therapeutic methods, immune-related adverse events (irAEs) induced by these therapies in many cases it has been become a critical problem. Furthermore, siRNAs as regulator of gene expression was used to directly target PD-L1 on breast cancer cells. We initiated the study with bioinformatics analysis, the results indicated that PD-L1 is significantly upregulated in TNBC rather than other breast cancer subtypes and also its upregulation among TNBC cell lines showed increased PD-L1 expression on MDA-MB-231 cell line. Further investigation displayed that silencing of PD-L1 significantly reduced PD-L1 expression at mRNA and protein levels in MDA-MB-231 breast cancer cells. Moreover, it was shown that PD-L1 knockdown reduced breast cancer cells proliferation and induced apoptosis via intrinsic and extrinsic pathways. We observed that silencing of PD-L1 successfully inhibited metastatic and invasion of cancer cells. Further investigation also displayed that silencing of PD-L1 in breast cancer cells, induced T-cell cytotoxic function by increased expression of pro-inflammatory cytokines genes in co-cultured system.

Key words: Triple Negative Breast cancer; PD-L1; siRNA; silencing

(15467)

A novel multi-epitope peptide vaccine consisted of immunodominant epitopes of MUC1, MAGE-1 and MAGE-A3 against breast cancer: An insilico approach

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Background: Cancer immunotherapy has an outstanding position in breast cancer (BC) prevention and treatment. Researches on tumor-associated antigen have become a hot target in immunotherapy, but it stagnated in the pre-clinical/clinical stages. In the present study, we have implemented various strategies to design an efficient multi-epitope vaccine including the epitopes of Mucin 1, MAGE-1 and MAGE-A3 to use in diagnostic or therapeutic applications.

Methods: In silico techniques were launched to characterize the properties and structure of the multi-epitope peptide vaccine. In this study, physicochemical property immunogenic potency and safeness of the designed vaccine were assessed. After homology modelling, the 3D structure was refined and validated as quality assurance. Besides, disulphide engineering also improved the stability of the chimeric vaccine. The vaccine protein was then subjected to molecular docking to evaluate its binding efficiency followed by dynamic simulation for stable interaction. Furthermore, higher levels of cell-mediated immunity and rapid antigen clearance were suggested by immune simulation and repeated-exposure simulation, respectively. Finally, the optimized codons were used in in-silico cloning to ensure higher expression within the E. coli BL21DE3.

Results: The designed multi-epitope peptide vaccine retained high stability and the same immunogenicity as of the original proteins. Bioinformatics data indicated that the epitopes of the multi-epitope peptide vaccine might induce B-cell- and T-cell-mediated immune responses.

Conclusion: The designed multi-epitope peptide vaccine may be useful as a breast cancer diagnostic tool and for developing a protective vaccine against breast cancer.

Keywords: Cancer immunotherapy, molecular docking, molecular dynamic, vaccine

(15515)

Inhibition of HIF-1α/EP4 axis by hyaluronate-trimethyl chitosan-SPION nanoparticles markedly suppresses the growth and development of cancer cells

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Background: Increased expression of Hypoxia-inducible factor-1α (HIF-1α) in the tumor microenvironment, mainly due to tumor growth, plays a major role in the growth and spread of cancer. Tumor cells induce the expression of cyclooxygenase 2 (COX2) and its product, prostaglandin E2 (PGE2), through overexpression of HIF-1α. It has been shown that ligation of PGE2 with its receptor, EP4, robustly promotes cancer progression. It seems that an increasing cycle consisting of HIF-1α/COX2/PGE2/EP4 increases tumor growth. Therefore, we decided to block the expansion of cancer cells by blocking the initiator and end of this pathway, the HIF-1α and EP4 receptor.

Methods: In this study, we used hyaluronate (HA), and trimethyl chitosan (TMC) recoated superparamagnetic iron oxide nanoparticles (SPIONs) loaded with HIF-1α-specific siRNA and the EP4 antagonist (E7046) to treat cancer cells and assessed the effect of combination therapy on proliferation, angiogenesis, apoptosis, and tumor growth.

Results: The results showed that optimum physicochemical characteristics of NPs (size 126.9 nm, zeta potential 27 mV, PDI <0.2) and linkage of HA with CD44 molecules overexpressed on cancer cells could significantly deliver siRNAs to cancer cells and suppress the HIF-1α in them. Combination therapy of cancer cells by using HIF-1α siRNA-loaded SPION-TMC-HA NPs and E7046 also impressively prevent proliferation, migration, invasion, angiogenesis, and colony formation of the cancer cells.

Conclusion: These findings imply that targeting HIF-1α/EP4 can be a novel target for cancer therapy, which should be examined in future studies in animal models.

Keywords: superparamagnetic iron oxide nanoparticles; HIF-1α; EP4; siRNA; Cancer

(16533)

Comparison of anti-proliferative effects of leaf Hydroethanolic extract and gum of *Ferula assa foeitida* on MDA-MB-468 triple negative cell line of breast cancer

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Background: Cancer is the second leading cause of death in the world. Breast cancer is responsible for 33% of all gynecological cancers and 20% of cancer deaths. The triple negative tumor lacks estrogen receptors, progesterone, and epidermal growth factor HER2. This tumor is highly resistant to the immune system defense mechanisms, hormone therapy or drugs designed for the HER2 receptor.
Methods: MDA-MB-468 cells were cultured in DMEM with 10% FBS and 1% streptomycin penicillin at 37 ° C in an incubator at 5% CO2 humidity. MTT test was used to evaluate the anti-proliferative effects of *Ferula assa foeitida* extract. For this purpose, the cells were exposed to different concentrations of *Ferula assa foeitida* extract for 24, 48 and 72 hours.
Results: After 24 hours, we observed a significant difference in the anti-proliferative effects of the extracts. The IC50 value was 223.12 ± 12.35 µg/ml for leaf extract and more than 1000 µg/ml **(P<0/0001)** for gum extract. After 48 hours, The IC50 value was 102.15 ± 18.53 µg/ml for leaf extract and more than 1000 µg/ml **(P<0/0001)** for gum extract. After 72 hours, The IC50 value was 71.62 ± 17.19 µg/ml for leaf extract and more than 1000 µg/ml **(P<0/0001)** for gum extract.
Conclusion: The widespread prevalence of breast cancer and severe malignancy due to triple negative tumors have highlighted the need for research into new drugs. The present study showed that the hydroalcoholic extract of *Ferula assa foeitida* leaves has a high ability to inhibit the proliferation of cancer cells. It is recommended to evaluate the content of chemical compounds of this plant in future studies. Doing animal studies under the influence of this plant product will be helpful.
Keywords: *Ferula assa foeitida*, IC50, MTT, anti-proliferative

(16534)

Tumor-derived exosome: a promising candidate for cancer immunotherapy?

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Background: Cancer, as one of the important diseases caused by abnormal cell growth and proliferation, is a leading reason for mortality worldwide. According to GLOBOCAN data in 2018, 18 million new cancer cases were identified in the world and roughly 9.5 million died of the disease. Despite existing therapies (chemotherapy, radiotherapy and surgery), cancer treatment remains one of the major challenges in the clinic. Therefore, searching for novel therapies against cancer is an urgent need. Recently, cancer immunotherapy has opened a new window to kill malignant cells. However, because of the poor immunogenicity of most tumor antigens, its therapeutic efficacy has been limited. To this end, tumor-derived exosomes (TDEs) which are the nanosized type of extracellular vesicles have received a lot of attention to overcome this limitation due to their important properties. The aim of this study is to review the potential of TDEs in cancer immunotherapy.
Methods: This research is a narrative review that is performed by studying related articles in PubMed and Google Scholar databases.
Results: There is ample evidence that TDEs have a great potential to stimulate immune responses against tumor cells because they are a rich source of the whole panel of tumor antigens. Besides, the high stability of their contents due to the lipid bilayer membrane, as well as their easy isolation and purification from the patient's body fluids (serum, blood and etc.) are other advantages of TDEs in cancer immunotherapy. However, despite the high potential of TDEs, it should be noted that they act as a double-edged sword and can also induce immunosuppression caused to unsatisfying anti-tumor immune effects in vivo.
Conclusion: Overall, it is expected that further studies on TDEs open a new way in the field of cancer immunotherapy but the efficacy of TDEs needs to be improved by a variety of strategies before their widespread clinical use as a cancer vaccine.

Keywords: Tumor-derived exosomes, Immunotherapy, Cancer vaccination

(16588)

Effect of conditioned medium of mesenchymal stem cells treated of metformin and curcumin on 4T1

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Background: mesenchymal stem cells have different responses to tumor cells under the influence of their surroundings. Therefore, the purpose of this study was to evaluate the effects of conditioned medium derived from mesenchymal stem cells with anti-cancer metformin and curcumin on breast cancer cells of the 4T1.

Methods: For this purpose, mesenchymal stem cells were isolated from the leg of female mice. After 14 days of culturing these cells, these cells were treated with curcumin in concentrations of 5mM, 10mM, 15mM, and 2.5µM, 5µM, 10µM, respectively. Also, in the presence of half of maximum concentrations of 5µM Curcumin and 7.5mM Metformin Were treated at the same time. After disposing of the conditioned medium, they were incubated for 24 hours by adding a non-serum-incubated medium. After collecting the supernatant, 50% was used in the culture medium of 4T1 cancer cells. The survival of 4T1 cells was measured by MTT assay and the apoptosis rate in the4T1 cells was evaluated by staining with acridin orange and propidium iodide.the survival of cancer stem cells in the population of breast cancer cells was investigated using flow cytometry technique.

Results: This study showed that the conditioned medium of mesenchymal stem cells treated of metformin and curcumin increases the lethality of mesenchymal stem cells against mouse breast cancer cells4T1, and this property depends entirely on the dose of metformin and curcumin.

Keywords: Mesenchymal Stem Cells, 4T1, Metformin, Curcumin,

(16594)

Cell vaccine for cancer treatment: current state and future perspective

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Background: Cancer as a complex and less-understand disease characterized by uncontrollable cell growth and invasion that cause to high mortality worldwide. Common therapeutic approach such as surgery, chemotherapy and radiotherapy had achieved some cure in cancer patient along with significant side effects and challenges. Hence, the improvement of new strategies for management the challenge is essential. Immunotherapy as a promising approach has been developed to target specific molecular and cellular objects of cancer. Cancer vaccines may prevent or treat the tumor by provoke the guiding immune responses. Cell- based vaccines have formulated as the antigen processing cells (APCs) such as dendritic cells (DCs) or agents that present tumor antigens to the APCs. DC- vaccine, Tumor cell vaccine and induced pluripotent cell (iPSC) vaccine are the examples of cell- based vaccine experiencing preclinical or clinical trials. Here, we reviewed the application, advantages and disadvantages of cell-based vaccine for cancer treatment based on pervious experiments.
Method: As a narrative review, we studied the research papers by searching the phrase "cell vaccine and cancer treatment" in Google scholar and Pubmed databases.
Results: DC vaccine as preventive or therapeutic agent may induce long-term anticancer immune responses via memory cells. The preclinical and clinical evidences demonstrated the promising effect of DC vaccine to provide anti-tumor immunity. Tumor cell/lysate vaccines and iPSC-based vaccine present all known or unknown tumor antigens to the APCs revealing more potent and effective immunity than specific anti-tumor responses created by strategies with presenting one or two identified antigen(s). Application of cell- based vaccines can be optimized while accompanied with adjutants to induce APCs, but the toxicity of treatment will increase.
Conclusion: The development of cell- based vaccines and further clinical trials are required to optimize the effect of these approaches for cancer therapy.
Keywords: cell vaccine, cancer, tumor antigens, immunotherapy

(16621)

SSX2IP, a promising target for gastric cancer immunotherapy

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Background: The primary concept of cancer immunotherapy is to distinguish tumor cells from normal non-tumor tissues. Any successful immunotherapy must minimize off-target attacking to normal tissues. The SSX2IP gene is located on chromosome 1p22.3 and it was identified as a leukemia-associated antigen through the immunoscreening of a testes cDNA library. The aim of this study was to evaluate the expression of SSX2IP in normal and gastric cancer tissue.
Methods: Tissues from the patients who underwent surgery were used. Twenty cancerous and normal tissue obtained from gastric cancer patients. Tissues were lysed and the mRNAs were extracted using the RNA extraction Kit. The first-strand cDNA was synthesized according to the Easy cDNA Synthesis Kit protocol. The expression of SSX2IP was quantified by real-time PCR. We also performed a data mining study to determine the SSX2IP expression in TCGA gastric cancer patients.
Results: Our results showed that the expression of SSX2IP in gastric tumor samples was increased 3.18 fold relative to adjacent normal tissues. Bioinformatic analysis of TCGA patients showed a significant increase in gene expression in cancerous samples ($p<0.01$).
Conclusion: Targeting SSX2IP might be a promising approach for gastric cancer immunotherapy.

Keywords: SSX2IP, Expression, Gastric cancer, Immunotherapy

(16632)

Title: Emerging targets in cancer immunotherapy

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Background: Ipilimumab and Pembrolizumab as the first generation of immune checkpoint inhibitors targeted natural immune homeostasis pathways to drive anti-tumor immune responses. However, these agents are effective in only a minority of patients and alternative pathways and novel strategies were needed. Numerous studies have been performed on the identification of new targets associated with tumor immunity. TIM3 is an immune-inhibitory molecule first identified on helper T-cells and cytotoxic T-cells. This transmembrane protein plays an immunosuppressive role. Immediately after TIM3 binds to its ligand, inhibits the cell-mediated immune response by inducing apoptosis in TIM3-expressing T cells. LAG3 is another transmembrane protein and it is mainly expressed in activated T and natural killer cells. Expression of LAG3 induces a T cell exhaustion state, which results in diminished cytokine secretion. Studies showed that the blockade of LAG3 improves cytotoxic T lymphocyte proliferation and effector function. VISTA is a type I immunoglobulin membrane protein, which predominantly expressed in myeloid cells, monocytes, macrophages, and dendritic cells. VISTA negatively regulates T cell responses and it acts as an immunosuppressive receptor and ligand on T-cells by decreasing IFN-γ and TNFα. Activating co-stimulatory pathways is another promising approach to enhance antitumor immune responses. This approach employs agonist antibodies to target members of the tumor necrosis factor receptor superfamily (TNFRSF), consisting of OX40, 4-1BB, CD40, GITR, ICOS, and B7-H6 molecules. The inhibition of these molecules by monoclonal antibodies is being investigated.

Keywords: cancer immunotherapy, CTLA-4, PD-1, monoclonal antibody

(16676)

Engineering Exosomes as Biological Tools for Cancer Therapy

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Background: Exosomes, a subgroup of extracellular vesicles, have been recognized as important mediators of long-distance intercellular communication and are involved in a diverse range of biological processes. Exosomes are engineered at the cellular level under natural conditions. Furthermore, exosomes can selectively accumulate in cancer site through modification of their surface in order to express targeting molecules that bind to receptors on cancer cells. Engineering of exosomes can either be carried out on the parental cells which will secrete exosomes carrying the desirable therapeutics or directly on the exosomes after they are isolated.

Methods: A literature review was conducted on the exosome. Eligible studies were identified via an electronic search through various databases including PubMed, Scopus, and Web of Science using the following keywords: exosome, exosome engineering, and cancer. The search was limited to articles studying the role of exosome published in English languages. The validated combination of MeSH terms and keywords was used.

Results: Exosomes have great potential to be drug delivery vehicles due to their natural material transportation properties, intrinsic long-term circulatory capability, and excellent biocompatibility, which are suitable for delivering a variety of chemicals, proteins, nucleic acids, and gene therapeutic agents. Exosomes can be engineered to present various targeting/therapeutic molecules on their surface, incorporating hydrophobic compounds in the lipid bilayer membrane and, encapsulating hydrophilic compounds or macromolecules inside their aqueous core. The combination of therapeutic drugs and exosomes exhibits increased cytotoxicity and more effective killing efficacy on cancer cells. Therefore, engineered exosomes show promise in cancer therapy.

Conclusion: Exosomes are of great clinical value due to their strong biocompatibility, offering a new frontier in drug delivery. Exosome engineering and the production of designer exosomes are entering a new phase. The previous phase of exosome engineering was based on the curiosity of the researchers about the engineering of exosomes. In recent years, the development of biological therapeutics has been steadily pursued, and some companies have been founded to manufacture the engineered exosome therapeutics.

Keywords: Cancer therapy, engineering exosomes, nanocarriers

(16688)

A review of the relationship between the Breast Cancer and Herpes Simplex Virus

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Background: Herpes Simplex Viruses (HSV) is a group of pathogenic viruses for humans that in most instances the immune system can never remove them from the body. Although these sexually transmitted DNA viruses mostly infect the nerve cells, but there is some evidence that determined this group of viruses can be a potential risk factor for breast carcinomas. on the other hand, recent investigations expressed a contradictory association. Therefore, in the current study, we reviewed the relationship between HSV and breast cancer to investigate the possible oncogenic or oncolytic role of HSV on breast cancer.

Methods: A comprehensive search was done through electronic databases including PubMed, Scopus, Embase, and Web of Science with the keywords “Breast Cancer”, “Herpes Simplex Virus” and other related MeSH terms. Original studies, review studies, and the references of the review studies were included. Finally, the related studies which investigated the possible relationship between HSV and breast cancer were reviewed.

Results: Some studies indicated the oncolytic HSV can targeting the tumor cells and killing the cells by cytopathic actions. These cytotoxic activities determined by the G47 delta, oncolytic HSV vector, which plays an anti-tumor role for malignant breast cells but not normal cells, in-vitro. As several studies demonstrated the presence of HSV in breast cancer cells, there are some guesses that this virus can cause breast neoplasms. This phenomenon could be due to the higher rate of cell development by the effect of the HSV.

Conclusion: According to our findings, specific HSV vectors can be used as an oncolytic tool for tumor lysis, but it is important to take attention to its possible side effects and the presence of this virus in some breast malignant tissues which demonstrated in several studies. Therefore more studies needed to exactly determine the oncolytic or oncogenic role of the HSV in breast cancer cell lines.

Keywords: Breast Cancer, Herpes Simplex Virus, Cancer Immunotherapy, Oncogenesis, Oncolysis

(16708)

Cloning, Expression and Characterization of a fusion protein to deplete myeloid derived suppressor cells in 4T1-HER2 breast cancer model

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Background: Myeloid Derived Suppressor Cells (MDSCs) are an immature heterogeneous population of myeloid lineage that accumulate in tumor-bearing hosts. MDSCs can inhibit the anti-tumor immune responses using the different mechanisms. Thus, a variety of strategies have been develop to limit the immunosuppressive function of MDSCs in cancer immunotherapy settings. The main goal of this study is to produce and characterize a MDSC specific recombinant peptibody in CHO-K1 cell line.

Methods: The peptibody consists of a MDSC binding peptide linked to FC domain of mouse IgG2a using glycine-serine linker. In designed construct, codon pair bias in GS linker and signal peptide optimization were employed for increase the protein expression. Construct was cloned in *E.coli* DH5a and transformed clones confirmed by colony PCR, enzymatic digestion and sequencing. Then, midiprepes of final clones were utilized to transfect CHO-K1 cell line by lipofectamine3000. Peptibody concentration in cell supernatant was measured by home-made ELISA. At last, the peptibody was characterized by flow cytometry.

Results: Remarkably, the optimized construct contains codon optimized linker as well as codon pair bias optimization increased the peptibody production from 30ng/ml to 250ng/ml in the cell supernatant. After 4 round selection, final stable clone generated 1µg/ml of peptibody in serum free medium. Flow cytometry data was shown that the purified peptibody can bind to spleen $CD11b^+$ $Gr\text{-}1^+$ MDSCs isolated from 4T1-HER2 mouse model.

Conclusion: Produced the FC-fusion recombinant peptibody could specifically bind to murine MDSCs.

Key words: MDSCs, peptibody, codon pair bias, recombinant protein, cancer

(16716)

Bioengineered Exosomes as New Achievement for Cancer Immunotherapy

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Background: Exosomes are nano-sized (30-100 nm) membrane vesicles with endocytic origin, which communicate with other cells by transferring proteins, lipids, DNA, RNA, and microRNA (miRNA). Exosomes are ideal nano-carriers for clinical application because of their naturally biocompatible characteristics. Exosomes are engineered at the cellular level under natural conditions, but the successful modification of exosomes requires further exploration. Patient-derived exosomes have been employed as novel cancer immunotherapy in several clinical trials, but at this point lack sufficient efficacy. Still, many researchers have focused on modifying the content and function of exosomes in various ways, toward the end-goal of specialized therapeutic exosomes.
Methods: This research was done by studying the articles related to exosome engineering and cancer immunotherapy in PubMed and Scopus databases from 2017 to 2020.
Results: Exosomes are potential immunotherapeutic agents, with promising results in pre-clinical studies of cancer immunotherapy where exosomes derived from B-cells, monocytes, macrophages and dendritic cells (DCs), loaded with peptide or whole protein antigens, have demonstrated the ability to induce systemic antigen-specific T- and B-cell responses. In separate research efforts, several groups have worked to directly bioengineer exosome contents through the use of exogenous immune-stimulating proteins that are sorted into exosomes during formation or attached to exosomes after secretion.

Three distinct approaches focused on loading exogenous proteins in exosomes have shown promising results: 1) Some cell-type-specific transmembrane proteins are observed or enriched within exosomes such as antigen-presenting HLA-A2 or G protein-coupled receptors (GPCRs), induced expression of these transmembrane proteins in exosomes, and multiple other locations in cells. 2) Exogenous protein loading into exosomes involves the fusion of exogenous peptides onto the surface of a known exosomal protein LAMP-2b. 3) Loading exogenous proteins into exosomes depends upon the generation of recombinant proteins with exosome binding domains.
Conclusion: The future of exosome-based cancer immunotherapy may lie in bioengineering exosomes toward increased immunostimulation in order to boost clinical response rates.

Keywords: Bioengineering exosomes, cancer, immunotherapy

(16732)

Endogenous Over-expression of OCT4B1 in Bone Marrow-derived Mesenchymal Stem Cells Makes Them Resistance to Anticancer Dose of Curcumin

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Background: Dysregulation of pluripotency genes was observed in some cancers so targeting these genes promises a new approach in cancer therapy. Pluripotency genes are normally expressed in stem cells. Therefore, anti-cancer drugs that are designed to target these genes may negatively affect stem cell repertoire. Recently, scientists interested in herbal anticancer extracts due to their safety. Curcumin is an anti-cancer agent extracted from the rhizome of curry. In our previous job, we found that in a dose effective for cancer cells, no cytotoxic effect was connected to normal cells. Down regulation of OCT4, SOX2, and Nanog was also observed following treatment by curcumin. Owing to the anti-apoptotic role of these genes, here, we evaluated OCT4, SOX-2, and Nanog expression after curcumin treatment.

Methods: MTT assay was performed to calculate the effective dose of curcumin. Annexin-V-FLUOS was applied to quantify apoptosis. Real-time PCR was used to analyze the expression of OCT4, SOX-2 and Nanog.

Results: Curcumin could not induce apoptosis in normal cells even after 48h treatment. Following treatment with curcumin, OCT4B1 was significantly overexpressed in stem cells.

Conclusion: Curcumin differentially targets cancerous and normal cells and this variation partly attribute to different gene expression patterns among cells. Possibly, OCT4B1 seem to involve in this way.

Keywords: Dendrosome, Curcumin, Cancer cells, OCT4B1

(16738)

Cancer Immunotherapy:Systemic analysis

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Background: Much progress has been made in the field of tumor immunology in the last decade. Cancer immunotherapy can elicit a long-term response in patients with metastatic cancers from a wide range of histologies. The expansion of the clinical application of these therapies requires a better understanding of the mechanisms by which the immune system restricts cancer therapy.Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. After decades of frustration, due to the success of recent clinical trials proving the concept, the trend has finally changed. The aim of this study was to evaluate cancer immunotherapy

The present study is a systematic review study whose information has been collected and analyzed with a comprehensive review of research texts, journals and numerous articles in reputable information databases. The interactions between the immune system and cancer cells are continuous, dynamic, and evolving from the initial onset of the cancer cell to the development of metastatic disease, which is dependent on the escape of the immune system. Because the molecular mechanisms of immunotherapy resistance have been identified, practical strategies for their prevention or treatment may be developed to improve clinical outcomes for patients.

Emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies. These observations suggest that neoantigen loading may be a biomarker in cancer immunotherapy and may be an impetus for the development of new therapeutic approaches that selectively increase T cell response to these antigens.

It is antibodies that release T cell secretion and give them the ability to fight tumors. Another involves genetically modifying a person's T cells outside the body for a better ability to target the cancer and then re-inject it so they can do so. Experts emphasize that these techniques have only been tested in small experiments and do not always work.

But the results have raised hopes that the immune system may provide doctors with new treatment options in the future.

Keywords: Immunotherapy, cancer,Cancer Immunotherapy,T cell,tumor immunology

(16786)

Enhanced anti-tumor immune responses by nano liposomes encapsulated anti PD-1 small interference RNA in melanoma tumor model

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Background: Tumor cells have several mechanisms to suppress anti-tumor activity of immune cells. PD-1 is one of the most important immun-checkpoit molecules that regulate T cells activity and has a role in T cell exhaustion. Small interference RNA molecules with high specificity to target mRNA have great potential in cancer therapy as they can silence genes that contributed to immune suppression. siRNA delivery to target cells is the most limitation in siRNA therapy approach. The aim of this study was to preparing of liposomal formulation as a siRNA carrier to silencing PD-1 expression in T cells and investigating its anti-tumor efficacy in in-vivo and in-vitro condition.
Methods: after preparing lipid thin layer, liposomal siRNA was prepared with ethanol injection method and characterized in size, Zeta potential and biodistribution. Uptake assay and mRNA silencing was evaluated at mRNA and protein level in in-vitro condition. Liposome containing PD-1 siRNA injected to B16F0 tumor bearing mice to evaluate tumor growth, mice survival and tumor Lymphocyte infiltration.
Results: Uptake assay, MTT assay, and PD-1 mRNA expression indicated that liposomal PD-1 siRNA efficiently silenced PD-1 mRNA expression in T cell lymphocytes and did not have cytotoxicity in these cells. The liposome size and percent of siRNA encapsulation were evaluated and it was approximately about 200 nm and 93.5 %, respectively. Flowcytometry analysis demonstrated that PD-1 siRNA enhanced T helper 1 and Cytotoxic T lymphocyte infiltration in tumor site in B16F0 tumor bearing mice. liposome- PD-1 siRNA treated group monotherapy and PD-1 siRNA- Doxil (Liposomal Doxorubicin) combinational therapy, remarkable improve survival in compare to control group.
Conclusion: According to the results of this study, liposomal PD-1 siRNA reduced tumor volume and improve survival in tumor bearing mice. Anti-tumor effect of liposomal siRNA was not due to direct toxicity of liposome on B16F0 melanoma cells, and it was due to maintaining lymphocyte activity.

Keywords: PD-1, Liposome, T lymphocyte, Immunotherapy, immune-checkpoint.

(16834)

Evaluation of hydroalcoholic extract effects of Ferula assa-foetida on expression change of EMT and CD44-related genes in gastric cancer stem cell

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Background: Gastric cancer (GC) with high incidence is a life-threatening malignant tumor in humans. Cancer stem cells (CSCs) due to tumor-initiating capacity, ability of invasion, metastasis, recurrence, and chemoresistance may be utilized for cancer treatment. *Ferula assa-foetida* as a herbal remedy in ancient Iranian medicine was shown to have various biological activities, including anti-cancer. Epithelial-mesenchymal transition (EMT) markers play an important role in migration, invasion, and metastatic dissemination of CSCs. The gastric CSCs-surface glycoprotein CD44 also responsible for high tumorigenicity, self-renewal, and metastasis through EMT. In this study, we investigated the hydroalcoholic extract effects of *Ferula assa-foetida* on the expression of EMT-related genes, anti-apoptotic factor BCL-2 and CD44 cell-surface molecule in CSCs.

Methods: CSCs were cultured in serum-free medium containing EGF and B-27 and exposed to different concentrations of *Ferula assa-foetida* hydroalcoholic extract and for different time durations. Cytotoxic effects of the extract compounds were evaluated using MTT assay. After CSCs treatment with IC50 dose of the extract, expression of EMT markers vimentin, Snail1, and Zeb1 and anti-apoptotic marker BCL-2 using relative quantitative real-time PCR as well as marker CD44 using flow cytometry were measured.

Results: Our MTT assay results demonstrated that cytotoxicity effect of extract compounds was significantly dependent on time and concentration. After exposing CSCs to IC50 doses of extract in different times, mRNA expression levels of EMT markers (vimentin, Snail1, Zeb1) and anti-apoptotic marker BCL-2, as well as protein expression of stemness marker CD44 in treated CSCs significantly reduced compared with untreated CSCs ($P < 0.05$).

Conclusion: Our data demonstrated that extract compounds of *Ferula assa-foetida* were able to decrease EMT markers, BCL-2 anti-apoptotic factor, and stemness marker CD44, leading to inhibition of CSCs proliferation as well as killing of them. Therefore, isolation and purification of anticancer effective compounds of *Ferula assa-foetida* hydroalcoholic extract could be used as a potential agent for cancer treatment.

Keywords: Cancer stem cells, CD44, EMT, *Ferula assa-foetida*

(17938)

Optimization of In Vitro Expansion and Activation of Human Natural Killer Cells against Breast Cancer Cell Line

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Background: Regarding to the increase of cancer deaths in recent years and disability of common therapies to eradicate cancers, as well as expansion of Natural Killer (NK) cell therapy, it seems so vital to find new useful therapies against cancers. Breast cancer is the second main cause of cancer death among women. As it is impossible for a majority of patients to receive NK cell therapy, an attempt was made to establish a low-cost and efficient method for expanding and activating NK cells against breast cancer cell line (MCF7).

Methods: NK cells were isolated from Peripheral Blood Mononuclear Cells (PBMCs) applying either MACS based NK cell enrichment kit or antibodies and complement as cytotoxic method. Then, the NK cells were cultured in Stem Cell Growth Medium (SCGM) with feeder layer (irradiated PBMCs) along with PHA or OKT3. IL-2, IL-15 and IL-21 were used to expand NK cells and finally their cytotoxic activity was investigated by flow cytometry.

Results: Highly pure NK cells were obtained and no significant difference between the two isolation methods was found. Using IL-2 plus IL-15, the number of NK cells in-creased up to100 fold after 16 days. No significant effect was observed after IL-21 treatment.

Conclusion: Our data indicated that cytotoxicity method can be considered a low-cost alternative for NK cell isolation kits. It seems that culturing NK cells for 14 days in either PHA or OKT3 supplemented SCGM medium would be more effective than culturing for 16 days in the presence of IL-21.

Keywords: Interleukins (IL), Immunotherapy, Natural killer cells

(17949)

Reprogramming of tumor-associated macrophages for cancer treatment: Challenges and opportunities

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Background: Tumor-associated macrophages (TAMs) refer to the macrophages in tumor microenvironment, which are mainly composed of M2 type. TAMs as major component of innate immune cells in neoplastic tissue play a significant role in further growth, progression, tumor metastasis and even drug resistance. Currently, repolarization and targeting of this type of immune cells, due to their cancer supportive role in the tumor microenvironment, have attracted considerable attention.

Methods: A systematic search was performed in various databases including Scopus, PubMed and Google Scholar, to find review and original articles from the last five years with different keywords such as TAM, reprogramming TAM, Macrophage repolarization and Macrophage targeting and tumor.

Results: Evidence shows that tumor cells express CD47، CD24, PD_L1 and MHC I molecules, which bind to their receptors and/or ligands on macrophages and in turn *inhibit* their phagocytotic clearance by *phagocytes*. Therefore, targeting these molecules has been used as a novel strategy to promote the phagocytic activity of macrophages and inhibit tumor growth. In other hands, TAMs have been effectively repolarized by various compounds including TLR agonists, Interleukin, microRNA and *reactive oxygen species-inducing nanoparticles*, which led to enrichment of proinflammatory *M1 subset* relative to M2 *subset* in cancer tissue. This reprogramed TAMs demonstrated effective tumor growth suppression and increased survival.

Conclusion: It seems that although TAMs targeting strategies are effective in inhibiting metastasis and tumor growth, they are unable to *regress tumor* volume alone. But simultaneous repolarization of M2 to M1 macrophages, and increasing phagocytic capability macrophage, may lead to tumor regression. Moreover, targeting the innate and adaptive immune systems together will pave the way toward successful cancer immunotherapy.

Keywords: TAM , Tumor microenvironment , reprogramming TAM ,macrophage

(17954)

Prolonged Persistence of Chimeric Antigen Receptor (CAR) T Cell in Adoptive Cancer Immunotherapy: Challenges and Ways Forward

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Background: CAR T cell qualities, such as persistence and functionality play important roles in determining the outcome of cancer immunotherapy. In spite of full functionality, it has been shown that poor persistence of CAR T cells can limit an effective antitumor immune response. **Methods:** Here, we outline specific strategies that can be employed to overcome intrinsic and extrinsic barriers to CAR T cell persistence. We also offer our viewpoint on how the growing use of CAR T cells in various cancers may require modifications in the intrinsic and extrinsic survival signals of CAR T cells. **Results:** We anticipate these amendments will additionally provide the rationales for generation of more persistent, and thereby, more effective CAR T cell treatments. CAR T cell qualities, such as persistence and functionality play important roles in determining the outcome of cancer immunotherapy. In spite of full functionality, it has been shown that poor persistence of CAR T cells can limit an effective antitumor immune response. Here, we outline specific strategies that can be employed to overcome intrinsic and extrinsic barriers to CAR T cell persistence. We also offer our viewpoint on how the growing use of CAR T cells in various cancers may require modifications in the intrinsic and extrinsic survival signals of CAR T cells.
Conclusion: We anticipate these amendments will additionally provide the rationales for generation of more persistent, and thereby, more effective CAR T cell treatments.

Keywords: chimeric antigen receptor, persistence, tumor microenvironment, cancer immunotherapy

(17956)

Biomarkers for predicting the outcome of various cancer immunotherapies

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Background: Cancer immunotherapy has appeared as a well-known therapeutic modality for different cancers. Yet, only a subset of patients derive clinical benefit. It is thus critical to understand the determinants driving response, resistance and adverse effects. Predictive biomarkers in different modalities of cancer immunotherapy offer novel information about the effect of a therapeutic intervention. These biomarkers and their patterns may not only operate similarly across different tumor types that are amenable to these therapies, but also assist to identify patients who will benefit from the treatment and subsequently leading to tailored immunotherapy with the wider-successfully-targeted patient population. In this review, we will outline a variety of predictive biomarkers in various cancer immunotherapies and their clinical utility. It is anticipated that the incorporation of biomarker studies in the clinical practice will help optimize therapeutic decision making and realize the potential clinical benefit of biomarker-guided therapy.

Keywords: Predictive biomarkers, Cancer immunotherapy, Clinical outcome, CAR T cell therapy

(17978)

Using nanoparticles as a delivery vehicle for mature DCs

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Background: Dendritic cells (DCS) are the most powerful antigen-presenting cells for T cell activation. DCs can be pulsed with tumor antigen and subsequently administered as a cellular vaccine to elicit a specific antitumor response. PLGA is an excellent component for the immune system due to its low toxicity and high degradability compared to other polymer systems. Most studies of PLGA nanoparticles for cancer immunotherapy are based on DC targeting.
The PLGA nanoparticle vaccine can provide stable antigen release, which is crucial for inducing strong immune responses.
Methods: 5mg of the prepared nanoparticles were dissolved in 1 ml of phosphate buffer saline (PBS, pH = 7.4). The solution was then placed in a shaker incubator at 37 ° C. After 24 hours supernatant was collected and stored at -20 ° C until protein was assayed. The nanoparticles were redissolved in 1 ml of new PBS solution and placed back in a shaker incubator to repeat these steps and after 24 hours the supernatant was collected again. Nanoparticle's supernatant was collected for seven days (Equivalent to functional half-life of adult dendritic cells). The collected supernatants were used to measure the protein concentration released from the nanoparticles.
Results: To estimate the release of protein from PLGA nanoparticles, the release rate was measured over seven days. The release was two-phase and had an initial phase with high speed and the second phase with slow and controlled release. The nanoparticles released large amounts of loaded protein during the first days and then continued for the following days until the maximum release of protein on day 7.
Conclusion: Due to antigen releasing phases by nanoparticles and considering that PLGA nanoparticles have a maximum of release on the seventh day which coincides with DC maturity day, these nanoparticles can be used to deliver cancer antigens to dendritic cells.

Keywords: PLGA nanoparticle, Dendritic cell, Cancer vaccines

(18004)

Dendritic cell-derived exosomes, a novel approach in cancer immunotherapy

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Background: Dendritic cells are professional antigen presenting cells that can present antigens to other types of immune cells by their surface Major Histocompatibility Complex (MHC) molecules [1][2]. These cells have a crucial role in identifying cancer antigens and initiating anti-tumor immune response [3]. Previously, it was thought that antigen presentation is only possible by direct delivery of antigens to the other types of immune cells via dendritic cells' surface MHC-antigen complexes. But, with the discovery of extracellular vesicles, this view underwent fundamental changes [1]. Extracellular vesicles are nano-sized particles which can be secreted from almost all cells [4]. These particles have a key role in many physiological and pathological pathways [5]. Exosomes, as one of the major types of extracellular vesicles, are 50-150 nanometer particles that have gained much attention during the recent years [6]. Dendritic cells, like other types of cells, can secrete exosomes [7]. But the interesting point is that it has been shown that dendritic cells can remotely deliver antigens to other types of immune cells by placing MHC-antigen complexes and costimulatory molecules on the surface of exosomes [8][9]. This feature can be used to boost the anti-tumor immune response in cancer patients [10]. In this regard, dendritic cells (or monocytes) are taken from the patient and co-cultured with tumor cells or tumor antigens. This process can lead to the maturation of dendritic cells. After maturation, dendritic cells secrete MHC-cancer antigen enriched exosomes that can be isolated and injected to the patient and boost the anti-tumor immune response [10][11]. Given the stimulation of immune system against cancer cells, this procedure can be called a novel approach in cancer immunotherapy.

Keywords: Cancer Immunotherapy, Dendritic cells, Extracellular vesicles, Exosomes

(18006)

CAR T cells: The next pioneers of cancer immunotherapy

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Background: Cancer is one of the most lethal diseases around the world[1]. In the past decade, extensive advances in immunotherapy have led to improved survival rates for patients diagnosed with cancer[2]. Chimeric antigen receptor (CAR) T cell therapy is one the novel adoptive immunotherapy methods based on enhancing a patient's T cells anti-tumor toxicity using a genetically engineered T cell that expresses CAR receptor on the cell surface[3]. CARs are bioengineered receptors with the ability to head towards a targeted antigen[4].To date, four generations of CAR T cells have been designed and the efficacy is enhanced by further genetic modification throw-out the time[5].CD-19 targeted CAR T cells has shown promising therapeutic results in patients with hematologic malignancies[6][7]. In spite of high rates of complete remission following CAR T cell therapy in different blood cancers, still much remains to be done in the area of CAR T cell therapy for solid tumors[8] CAR T cells have demonstrated tremendous success in eradicating hematologic malignancies (e.g., CD19 CARs in leukemias.In this review, we aim to discuss different generations of CAR T cell, opportunities and challenges facing the field of CAR T cell therapy and the innovative designs of novel CAR T cell products.

Keywords: Cancer Immunotherapy, CAR T cell Therapy, Immunotherapy, Chimeric Antigen Receptor

(18013)

Tim-3 and PD-1 blocking cannot restore the functional properties of NK cells in patients with Chronic Lymphocytic Leukemia; an in vitro study

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Background: Inhibition of immune checkpoint receptors has been introduced as a promising area in cancer immunotherapy. Programmed death-1 (PD-1) and T cell immunoglobulin- and mucin-domain-containing molecule-3 (Tim-3) are among the major immune checkpoint receptors over-expressed on immune cells in chronic conditions and their up-regulation is related to the exhaustion phenotype of immune cells. In this in vitro study, blockade of PD-1 and Tim-3 molecules was performed on isolated NK cells from chronic lymphocytic leukemia (CLL) patients in order to restore their functional characteristics.

Methods: Fresh peripheral blood was obtained from 18 CLL patients and NK cells were positively isolated from the PBMC fraction by magnetic beads. Isolated NK cells were treated with blocking anti-PD-1, anti-Tim-3 and their Isotype-matched control monoclonal antibodies and then co-cultured with K562 cells as target. Apoptosis rate of K562 cells was assessed by Annexin V-PI method and the anti-CD107a assay was applied to evaluate the degranulation properties of NK cells. The level of TNF-α and IFN-γ secretion by NK cells was also measured using the ELISA method.

Results: The results of the present study showed no significant changes in functional properties of NK cells isolated from CLL patients neither in degranulation nor in apoptosis of K562 target cells in PD-1/Tim-3 blocked and control groups. Moreover, it was shown that blocking of PD-1 and Tim-3 could not improve the secretion levels of pro-inflammatory TNF-α and IFN-γ cytokines by isolated NK cells from CLL patients.

Conclusion: Altogether, our results suggested that pre-treatment of NK cells with anti-PD-1 and anti-Tim-3 blocking antibodies cannot improve their functions in CLL patients at early clinical stages of the disease. More investigations are needed to declare the possible application of immune checkpoint inhibitors in CLL patients.

Keywords: chronic lymphocytic leukemia, Tim-3, PD-1, immune checkpoint inhibitors, NK cells

(18038)

Blockade of PD-1 and Tim-3 immune checkpoints fails to restore the function of exhausted CD8+ T-cells in chronic lymphocytic leukemia; an in vitro study

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Background: Common treatment protocols have improved overall survival in patients with chronic lymphocytic leukemia (CLL), but they continue to relapse and progress. In the present study, the application of anti-PD-1 and anti-Tim-3 blocking antibodies was assessed to investigate their effects on restoration of the function of exhausted CD8+ T-cells in CLL patients.

Methods: CD8+ T-cells were isolated from peripheral blood of 20 patients with CLL and treated with blocking anti-Tim-3 and anti-PD-1 antibodies and then were co-cultured with target cells (mitomycin-freezed non-CD8+ T-cells fraction). Stimulated cultures with anti-CD3/CD28 antibodies were assessed for the proliferation of CD8+ T-cells by MTT assay. Degranulation, CD107a expression, and cytokines production of CD8+ T-cells were analyzed on PMA/ionomycin stimulated co-cultures with flow cytometry and ELISA methods, respectively.

Results: Our results showed that the blockade of PD-1 and Tim-3 receptors does not improve the proliferation capacity and degranulation properties of CD8+ T-cells in CLL patients. Besides, blocking of PD-1 and Tim-3 had no significant effects on the production of IFN-γ, TNF-α, IL-2, and IL-10 by CD8+ T-cells from CLL patients.

Conclusion: Our study showed that pre-treatment of exhausted CD8+ T-cells with anti-PD-1 and anti-Tim-3 blocking antibodies in CLL patients was not effective to restore the function of these cells. To more explore the application of checkpoint inhibitors for CLL patients, complementary in-vitro and in-vivo studies are required.

Keywords: Chronic lymphocytic leukemia, CD8+ T-cells, Immune checkpoints, Anti-Tim-3, Anti-PD-1

(18039)

The effect of miR-142a-3p replacement and Taxol on inhibition of proliferation, metastasis and apoptosis in osteosarcoma

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Background: Osteosarcoma (OS) is the most common primary malignancy of bone tumor that mainly occurs in adolescents and young adults. MicroRNAs are pivotal post-transcriptional regulators of gene expression. Various studies suggest that miR-142a-3p acts as a tumor-suppressor microRNA in different types of cancers, but precisely how has remained unclear. In this study, we investigate miR-142a-3p expression in osteosarcoma by studying how normalization of miR-142a-3p expression affects osteosarcoma cellular phenotypes such as viability, apoptosis, proliferation, and migration.

Methods: we cultured MG-63 cell line in RPMI 1640 with10% FBS and 5% co_2 condition. mimic miR-142a-3p was transfected by JetPEI into the MG-63 cell line, total RNA was extracted using Trizol kit, to examine the effect of miR-142a-3p on cell proliferation, MTT assay and cell cycle arrest with flow cytometry and colony formation was performed. In the following to evaluate rate of apoptosis of the MG-63 cells analyzed by Annexin V-FITC apoptosis detection kit and flow cytometry, at the end, metastasis rate of MG-63cells analyzed by wound healing assay.

Result: The MTT assay , analyzing cell proliferation and apoptosis by flow cytometry showed that transfection of miR-142a-3p combined with Taxol reduced cell proliferation, survival and induced apoptosis in MG-63 cell line. The wound healing scratch assay showed that miR-142a-3p replacement inhibited cell metastasis in MG-63 cell lines compared to control groups.

Conclusion: Our research show that miR-142a-3p can have anti-cancer and anti-metastatic effect in MG63- cell line. In addition, our studies showed that miR-142a-3p combined with Taxol could be a new therapeutic small molecule to inhibit proliferation, survival, and metastasis of osteosarcoma cells in MG-63 cell line compared with control groups.

Keywords: miR-142a-3p, replacement therapy, osteosarcoma, apoptosis, metastasis

(18048)

Inhibitory effects of Pycnogenol® (French maritime pine bark extract) on Myeloid-derived suppressor cells in a murine model of breast cancer

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Background: Myeloid-derived suppressor cells (MDSCs) in the tumor environment play an important role in inhibiting anti-tumor immune responses and induce tumor cells' angiogenesis and invasion. Pycnogenol® (PYC), as a powerful antioxidant, is naturally obtained from the bark of European coastal pine (Pinus pinaster). Various studies have shown that pycnogenol has a variety of beneficial effects, including anti-inflammatory effects, strong antioxidant properties, and modulatory effects on the immune system. Therefore, this study aimed to investigate the anti-tumor effects of PYC on MDSC obtained from breast cancer-bearing mice.

Methods: Female BALB/c mice were injected with 4T1 cells subcutaneously. After two weeks of injection, MDSCs were isolated from the spleen by magnetic-activated cell sorting. MDSCs were treated with PYC at noncytotoxic doses (0, 10, 25, 50, and 100 µM) for 24 h and 48 h. Gene expression of S100A8, S100A9, Arg-1, iNOS, STAT3/5, IRF8, and CEBP/B in MDSCs was evaluated by SYBR Green real-time PCR technique. Supernatants were collected to measure TGFβ, IL-10, and IL-13 by the enzyme-linked immunosorbent assay (ELISA). Analysis of variance (ANOVA) followed by Tukey's post-hoc test was performed to analyze the significance of the differences among various formulations.

Results: iNOS, S100A8, and S100A9 expression was reduced significantly in the treated MDSCs groups compared with the control group ($P<0.05$). Arg-1 levels were slightly lower in the treated group than the control group ($P>0.05$). Supernatant concentrations of TGFβ significantly decreased in the treated MDSCs groups compared with the control group ($P<0.05$).

Conclusion: This study showed that the use of pycnogenol could possibly reduce the inhibitory function of MDSCs. However, more studies are needed to confirm the effectiveness of pycnogenol as a supplement in cancer.

Keywords: Pycnogenol, MDSCs, S100A8, S100A9, TGFβ.

(18051)

Evaluation of the effect of miRNA-124 –modified tumor derived exosomes in the induction of cytotoxicity and apoptosis in CT-26 cell lines

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Background: in the recent years, exosomes have been presented as a new delivery system for the transmission of small noncoding RNAs. In addition to having tumor-specific antigens, Tumor derived exosomes (TEXs) can act as a suitable carrier for miRNA. The goal of the current investigation was to assess the efficacy of miR-124-3p-loaded TEX (TEXomiR) as a cell free nano vaccine in the induction of antitumor responses in the in vitro system.

Methods: Briefly, CT-26 cells were cultured and adapted to FBS free medium through sequential adaptation. Subsequently, the exosomes were isolated from conditioned media applying Exocib kit. Isolated exosomes were characterized by electron microscopy, Nano zetasizer, and flow cytometry. After that, modified calcium chloride method was used to deliver miR-124-3p mimic into the exosomes. MTT assay and FITC Annexin V apoptosis Detection Kit were conducted for evaluation of cell cytotoxicity and apoptosis, respectively.

Results: The results of quantitative Real Time PCR showed that miR-124 expression in TEXomiR group compare to unloaded TEX group was significantly increased. Moreover, treatment with TEXomiR significantly downregulated the expression of STAT-3 and SP-1 in TEXomiR group compared to TEX and control groups. The viability of CT-26 cell lines following treatment with TEXomiR and TEX considerably decreased and increased, respectively. Moreover, TEXomiR significantly increased the apoptosis percentage of CT-26 cell lines.

Conclusion: Taken together, our findings showed that TEXs can efficiently deliver miR-124-3p mimic and TEXomiR exerts its cytotoxic effects on CT-26 cell lines by suppressing miR-124 target genes.

Key Words: Tumor-derived exosomes, miR-124-3p, anti-tumor response, colon cancer, CT-26.

(18064)

Effect of Transfection of Recombinant shPD1 Gene on Cytotoxicity of CD8- T Cells

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Background: Program cell death protein-1 (PD-1) / ligands (PD-Ls) pathway is one of the important immune-checkpoints pathways for inhibition of cytotoxicity of $CD4^+$/$CD8^+$T cells. $CD4^+$T cells induce apoptosis in the $PD\text{-}Ls^+$ cells such as $PD\text{-}Ls^+$ breast or colorectal tumor cells. In some animal and clinical studies, anti PD-1/PD-Ls antibodies or soluble PD-1 showed induction of cytotoxicity of T cells. In this study, we designed a new recombinant form of PD-1, human soluble PD-1 expressing gene, for blocking PD-1/PD-Ls pathway between T cells and $PD\text{-}Ls^+$ cell line, in the in-vitro model.
Methods: New recombinant PD-1 gene, shPD1 pcDNA-hygro, was designed for expression in hypoxic condition. This structure was transfected into PD-L1+ cell line, MDA-MB-231 cell line. Concanavalin-A stimulated PBMCs were co-cultured with transfected and non-transfected MDA-MB-231 cells for 6 hours, in hypoxic condition. Cytotoxicity of $CD8^-$T cells was evaluated by flowcytometry via anti CD107a, CD3 and CD8 antibodies.
Results: Cytotoxicity of $CD8^-$T cells was evaluated by measuring the lysosome degranulation using detection of CD107a expression on $CD8^-$T cells. CD107a expression was significantly increased on $CD8^-$T cells in co-culture of transfected MDA-MB-231 cells (20%±1.1) and PBMCs.
Conclusion: In the present study, in transfected group, the cytotoxicity of $CD8^-$T cells was significantly increased than non-transfected group. In fact, secreted PD-1 from transfected cells masked PD-L1 on MDA-MB-231 cells and prevented activation PD-1 signaling pathway in $CD8^-$T cells. Blockade of PD-1/ PD-L1interactions by shPD-1 along with recognition of MDA-MB-231 cells (tumor antigens) could improve cytotoxicity of $CD8^-$T cells population and might induce apoptosis in the target cells via affecting perfurin/granzyme and Fas/FasL interaction. Therefore, shPD1 pcDNA-hygro structure might be a potential candidate for restoring the cytotoxicity of T cells in PDLs+ solid (such as breast and colorectal) tumors.

Keywords: Breast Cancer, $CD8^-$T cells, CD107a, Cytotoxicity, PD-1 Ligands, Soluble PD-1, Transfection.

(18074)

slc26a3 as a new target therapy in colorectal cancer

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Background: Colorectal cancer (CRC), a malignant neoplasm that occurs in the mucosa of the colon. Decreased expression of CAs in Cancer cells disrupt the pH due to the production of large amounts of CO_2 and lactic acid. extracellular acidosis weakes the extracellular matrix, and weakes the immune system and encourage tumor progression. Carbonic anhydrase SLC26A3 regulates pH of cells through Cl^-/HCO^{3-} exchange, and also acts as a tumor suppressor. In addition, SLC26A3 involves in neutralizing the acids, increasing the expression and function of CFTRs as well as in the reabsorption of NaCl in the intestine. The expression of this CAs in CRC is reduced and impairs the maintenance of epithelial membrane integrity and cell acidification, which ultimately stimulates CRC and metastasis.
Results:The results of literature review showed that JAK/STAT signaling pathway, is activated due to expression of cytokines such as IFNɣ or EGFR, and Activated STATs by binding to gene promoters reduces the expression of SLC26A3 in CRC. Moreover, activated NFκB signaling pathway due to the effect of some cytokines such as TNF-α and IL-1β or PTEN and EGFR, which their expressions change in CRC, or by up-regulated of PI3K/AKT signaling, which result in the secretion of P65 subunit and reduces the expression of SLC26A3.
Other factors of SLC26a3 down regulation in CRC are miR-494-3P and miR-142-5P which reduce SLC26A3 expression by targeting SLC26A3 mRNA or by affecting PTEN expression. Acetazolamide increases the down-regulated slc26a3 in CRC, due to its effects on reduce the increased-expression of NF KB and PI3K/AKT signaling pathways.
Conclusion:Our goal is to increase the effect of acetazolamide on reducing the expression of SLC26A3, in combination with oxaliplatin to increase the ability of SLC26A3 as a tumor suppressor and to modulate the pH of the tumor environment to prevent acidification and metastasis.

Keyword: SLC26A3, CRC, NF KB, JAK / STAT, PI3K / AKT, miR-142-5P, miR-494-3P, PTEN, oxaliplatin, acetazolamide

(18086)

Anti-inflammatory and Cytotoxic Activities of Sea Cucumber *(Holothuria leucospilota)* Extract in Colorectal Cancer Cell Line.

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Background: Sea cucumbers possess a wide range of biological and pharmacological properties. The objective of the present study was to evaluate the anti-inflammatory effects of the Persian Gulf sea cucumber (*Holothuria leucospilota*) through inhibiting the expression of cyclooxygenase-2 (*COX-2*) in colorectal cancer cell line SW742.

Methods: The methanolic extracts of the body wall, body fluid, and internal viscera of *H. leucospilota* were prepared, and their cytotoxicity was assessed. Moreover, the cell line was further cultured to extract their mRNA in order to, measure the expression of *COX-2* and Vascular endothelial growth factor (*VEGF*) by Real-Time PCR, and to determine the production of Prostaglandin E2 (PGE2) and VEGF by ELISA.

Results: The body-wall extract significantly downregulated the expression of *COX-2* and VEGF and reduced the level of PGE2 and VEGF production, whereas body fluid and the viscera extract revealed no effect.

Conclusion: the outcomes suggest that the body-wall could be useful in food and pharmaceutical industries to prevent inflammation and colorectal cancer as well.

Keywords: Biological activity, Sea cucumber, *Holothuria leucospilota,* Persian Gulf.

(18183)

Pediatric Cancer Immunotherapy and Oncolytic viruses

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Background: Pediatric cancers are often resistant and reversible cancers that are less likely to be treated with chemotherapy, radiation, and surgery. Oncolytic viruses (OVs) are designed to infect and kill cancer cells, which do so through intracellular proliferation and subsequent oncolysis. Approval of Talimogene laherparepvec (T-VEC), an oncolytic herpes virus, in the treatment of metastatic melanoma has made it possible to use other oncolytic viruses in the treatment of cancer.
Methods: Relevant literature was identified by a PubMed search (2017-2020) of English language papers using the terms "**:** Oncolytic viruses," "Pediatric cancers", and "Immunotherapy".
Results: Oncolytic viral infection directly kills cancer cells, leading to the release of damage-associated molecular signals (DAMPs) and pathogen-associated molecular signals (PAMPs).These antigens, called neoantigens, are detected by pattern recognition receptors such as toll-like receptors (TLRs), which trigger the expression of inflammatory cytokines, which in turn activate the innate and adaptive immune system especially NK cells to identify and destroy these antigens.
Conclusion: Unfortunately, virus treatments performed on children have not been accompanied by an objective response, but this treatment is a safe method for children and due to their low toxicity, this method can be combined with other cancer treatment methods, especially with immunotherapy methods. This type of treatment is still under investigation. Considering that the maximum tolerated dose has not been used in the studies and also due to the fact that a small number of oncolytic viruses and a small number of cancers have been studied, the hope for the development of this treatment can be considered high.

Keywords: Oncolytic viruses, Pediatric cancers, Immunotherapy.

(18187)

Evaluation of the effects of TIM3/GAL9 autocrine loop in acute myeloid leukemia cell line (U937)

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Background: Acute myeloid leukemia (AML) is a malicious leukemia. Recent studies have shown that AML cells secrete a large amount of galectin-9 (Gal-9) in to serum which binds to T-cell immunoglobulin and mucin 3 (TIM-3) molecule as its receptor. The autocrine loop of TIM-3/Gal-9 induces activation of the signaling pathways of NF-KB and β-catenin in leukemia cells and plays a crucial role in their chemotherapy resistant and self-renewal and therefore could be a novel target for leukemia treatment. In this study, we studied the effects of oridonin and doxorubicin on proliferation of U937 cells (as AML cell line) and their simultaneous inflammatory responses.

Methods: CCK-8 assay was applied to measure the cytotoxicity of oridonin and doxorubicin as chemotherapy drugs and to determine the impact of galectin-9 on proliferation of U937 cells. The effects of the studied chemicals on galectin-9, TIM-3 and IL-1B gene expression were measured by quantitative PCR and the secretion level of galectin-9 was measured by ELISA. Finally, NF-kB pathway was assessed by western-blotting.

Results: In a dose-dependent manner, oridonin and doxorubicin were capable to eradicate U937 cells but galectin-9 expanded them. Following treatment of U937 cells with oridonin, the expression of galectin-9, TIM-3 and IL-1B genes were lowered, and the galectin-9 secretion and NF-kB phosphorylation were reduced. However, doxorubicin acted reversely and increased the levels of the mentioned factors.

Conclusion: Doxorubicin as a chemotherapy agent can exacerbate the disease through inducing inflammation and increasing TIM3/Gal-9 autocrine loop and consequently may enhance the possibility of the leukemia relapse. Meanwhile, oridonin was capable to reduce inflammation and inhibited the leukemia cells signaling pathways and reduced the inflammation rate and expansion of tumor cells which may consequently stop leukemia recurrence.

Keywords: Acute myeloid leukemia; Oridonin, Doxorubicin; Galectin9; NF-kappa B; T-cell immunoglobulin and mucin 3

(18188)

Chemotherapy as a double-edged sword may induce cancer promotion and recurrence

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Background: Cancer is a multifactorial diseases and is regarded as the second leading cause of death worldwide. Different types of therapies such as chemotherapy have been applied to its treatment up to now; however, none of them were capable to completely eradicate cancer cell and avoid its recurrence. It seems that chemotherapy may alter tumor microenvironment features and increase systemic and local inflammation. It was shown that multiple inflammatory signaling pathways are activated following the administration of chemotherapy drugs and consequently various inflammatory mediators are released which may worsen the situation. Although inflammatory response can help to eradicate the tumor cells, it may conversely induce cancer promotion by providing appropriate situation for tumor growth. Therefore, we hypothesized that the control of the inflammation during chemotherapy may increase the possibility of cancer treatment. Here in, we will introduce this idea and will compare the available treatments in this context.

Keywords: Cancer, chemotherapy, microenvironment, Inflammation

(18214)

Viruses against Viruses: A glance at the oncolytic effects of Adenovirus on the EBV

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Background: Today Epstein–Barr Virus (EBV) has been determined as the cause of some malignancies including hematologic and solid neoplasms. On the other hand, several studies indicated the similar functions of the EBV and Adenovirus genes. Therefore, there is an opinion that expresses the possible oncolytic role of the Adenovirus against EBV- associated malignancies. In this study, we review the current knowledge and developments about this relationship.
Methods: A comprehensive search was done through electronic databases including PubMed, Scopus, Embase, and Web of Science with the related keywords. All types of studies that were published up to 2020 November were included for the review.
Results: Based on the similarities between EBV and adenovirus in terms of genomic functions, some in-vivo and in-vitro studies suggested that adenovirus vectors could be a potential tool for targeting EBV infected malignant cells. In detail, Virus-associated I (VAI) RNAs-deleted adenovirus is determined as a potential vector for targeting EBV infected cells. Moreover, several studies indicated that the hybrid vectors which consist of both adenovirus and EBV can due to the instability of the EBV genome in infected cells.
Conclusion: According to the reviewed studies, using adenovirus vectors could be a potential therapeutic either preventional method against EBV-associated tumors. It is important to note that although some studies determined the current method as an efficient way to battle with some neoplasms, but we should take attention to the possible controversies and side effects that can occur during using this unproven method. Therefore, further studies are needed to make these kinds of oncolytic methods more clear for ous.

Keywords: Cancer, Adenovirus, EBV, Immunotherapy

(18225)

Assessment of the anti-proliferative impacts of genetically modified mouse mesenchymal stem cells in the expression of chicken anemia virus oncolytic protein on A549 cell line (Lung carcinoma)

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Background: Recently, lung cancer, as one of the most prevalent types of cancer, is a leading death factor assigned to cancer. In recent years, as mortality and morbidity of lung cancer has increased, the research on its treatment has been increased. Encoded by Chicken Infectious Anemia Virus' VP3 gene, Apoptin is a protein rich in proline with the capability of apoptosis induction selectively in cancerous cells. The current research was carried aid for specifying the anti-proliferative impacts of genetically modified mouse mesenchymal stem cells for expression of chicken anemia virus oncolytic protein on A549 cell line (Lung carcinoma) in cell culture.

Methods: Enzymatic digestion was conducted and extracted in this study on a plasmid carrying the Apoptin gene. Cloning of Apoptin gene into Adenovirus (Ad) vector was done. The subcloned plasmid was concentrated and precipitated. Using Lipofectamine, it was transmitted to MSCs. We evaluated protein production and Apoptin gene expression using western PCR and blot methods. Then, we evaluated anti-proliferative effects of the Apoptin-modified MSCs on A549 cell line.

Results: According to the results **of s**equence determination, the secretory plasmid Subcloning process has acceptable accurateness. PCR method showed apoptin gene expression in transfected MSCs, and results of western blots verified production of its protein. Moreover, as revealed by MTT findings, the Apoptin-modified MSCs showed an anti-proliferative impact on the A549 cell line.

Conclusion: According to this research, an experimental basis is provided for a new in vivo drug delivery way by stem cells as the means, leading to resolving immune rejection caused by duplicated administration of the drug with direct delivery by Ad vectors and reducing costs for purification and production of exogenous drugs at large scale.

Keywords: Lung carcinoma, Apoptin, Mesenchymal stem cells, Anti-proliferative

(18235)

Synergistic antitumor effect of PI3K/AKT inhibitor and Tumor environment cytokines on MDA-MB-231 breast cancer cells

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Background: Breast cancer is the most common malignancy among the world and Iran. Two cytokines TGF-β1 & IL-6 through PI3K/AKT & JAK-STAT3 signaling can lead to increase the transcription of CXCR4 gene. CXCR4 plays an important role in metastasis of tumors, including breast cancer. Also, tumor environmental cytokines play a key role in inducing genes that promote breast cancer stem cells (BCSCs). The purpose of this research is finding the role of TGF-β1 and IL-6 in combination with NVP-BEZ-235 (PI3K/AKT inhibitor) on expression of the stem cell inducing genes including the Snail, Twist-1, and C-myc, induction of apoptosis and surface expression of CXCR4 in metastatic breast cancer cells.

Methods: MDA-MB-231 breast cancer cells treated with different concentrations of NVP-BEZ-235 alone or in combination with cytokines TGF- β1 and IL-6. Cell proliferation and growth inhibition were investigated using MTT test. After breast cancer cell treatment with IC50 concentration of NVP-Bezz 235 alone and in combination of two cytokines for 24 and 48 hours, flowcytometry method was used to study the percentage of apoptosis, CXCR4 positive cells and BCSCs (CD24-/CD44+). Also Twist-1, Snail and C-myc genes expression were assayed by Real-time PCR method.

Result: The results showed that NVP-BEZ-235 has a time and dose-dependent manner in inhibition of cancer cell growth and also in induction of apoptosis in breast cancer cells. Also NVP-BEZ-235 plus TGF-β1 and IL-6 could decrease the percentage of stem cells more than NVP-BEZ-235 in alone form. On the other hand, the percentage of CXCR4+ cells was increased significantly in MDA-MB-231 cells treated with cytokines and drug after 24 and 48 hours. Gene expression analysis showed that expression of Snail, Twist-1, and C-myc in were decreased significantly after treatment.

Conclusion: Although treatment with NVP-Bezz 235 resulted in increased expression of CXCR4, it was able to increase apoptosis and decreased BCSCs and their related genes, which, with further studies, seems to be a proper drug. for breast cancer, especially for late stage cancers that IL-6 and TGF-β1 presence in tumor micro-environment.

Key words: TGFβ1, IL-6, NVP-BEZ-235, PI3K/AKT

(18237)

Bioinformatics evaluation of KRAS gene signaling pathway related to hsa-miR-143-3p in patients with acute lymphoblastic leukemia (AML).

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Background: AML is the most common genetically heterogenous cancer in adult, which both B and T cell progenitors participate in its formation. The treatment is based on chemotherapy; while Unfortunately , most of the patient will die less than five years after diagnosis. Nowadays, immunological methods have influential roles in their treatment. This study aims to demonstrate one of the essential pathways of creating cancer in order to help find the best cure. PI3K-AKT signaling pathways is one of the pivotal hallmarks of cancer, and KRAS is an oncogene protein that can lead the cell to cancer. In this study, miRwalk, miRbase and DAVID databases were used to accomplish targeted genes by hsa-miR-143-3p. Signaling pathway was evaluated in KEGG pathway. A reduction in the amount of the hsa-miR-143-3p increase KRAS, RAF-1, MEK and ERK activity. This process activates the MAPK signaling pathway. This pathway is involved in proliferation, differentiation and migration, which seems that it can lead to AML. Thus, if this abnormality was diagnosed in a patient, immunological targeting of these cells could be a way to prevent AML.

Keywords: Acute lymphoblastic leukemia, miRNA, hsa-miR-143-3p, KRAS

(18256)

In vitro Effect of Pentoxifylline on the Breast Tumor-Infiltrating Regulatory T Cells

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Background: Triple-negative breast cancer (TNBC) is the deadliest type of BC with a poor response to common therapies. Since TNBC has the most tumor-infiltrating Lymphocytes (TILs) among BCs, TIL therapy would be a promising candidate for immunotherapy of TNBC. Re-education or depletion of immunosuppressive cells such as regulatory T cells (Tregs) in TILs can optimize the anti-tumor function of TIL therapy. Pentoxifylline (PTXF) is a xanthine derivative that can alter the NF-kB signaling and block the Tregs function.
Purpose: The effect of PTXF on the proportion of Tregs in TILs derived from a mouse model of TNBC was examined due to in vitro treatment of TILs with PTXF.
Methods: TILs were isolated by enzymatic digestion of 4T1-inoculated BALB/c mouse tumors. TILs were cultured with 4T1 cells for 24, 48, and 72h in the presence of IL-2 with different concentrations of PTXF. PTXF toxicity and its effects on Tregs proportion were evaluated using MTT assay and flowcytometry, respectively. TGF-β and IFN-γ production of TILs was measured by ELISA.
Results: PTXF did not significantly decrease the TILs viability. Both 500 and 1000 µg/mL of PTXF reduced the proportion of Tregs in a dose-dependent manner. The level of TGF-β and IFN-γ in PTXF-treated TILs supernatant was decreased and increased, respectively.
Conclusion: Our data suggest that in vitro treatment of TILs with PTXF could reduce the Tregs proportion in the conventional TIL expansion and alter the cytokine balance of TILs in favor of anti-tumor response.

Keywords: Breast cancer, Tumor-infiltrating lymphocyte, Pentoxifylline, Regulatory T cells

(18270)

Pediatric Cancer Immunotherapy and Its Challenges

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Background: Pediatric cancers are resistant and reversible cancers that are difficult to treat. Immunotherapy is one of the treatment methods for these patients. Monoclonal antibodies (mAbs), checkpoint inhibitors, bispecific T-cell engagers (BiTEs), chimeric antigen receptor T cells (CAR-Ts) are among the approved treatments in children and vaccines and oncolytic virotherapy are being studied. There are many problems and challenges in this direction.

Methods: Relevant literature was identified by a PubMed search (2006-2020) of English language papers using the terms ": Pediatric Cancer," "Immunotherapy", and "Challenging".

Results: One of these challenges is to identify prognostic or diagnostic biomarkers in these patients so that patients can be placed in the appropriate group for diagnosis or treatment. The appropriate target for CAR-Ts, BiTEs and mAbs therapies should also be strongly expressed on tumor cells and weakly expressed on normal cells of the body, which is unfortunately rare. mAbs and T-cell therapy kill all the cells that express the target, regardless of whether they are normal or cancerous. In addition, T-cell therapy may cause cytokine storms and death. Oncolytic virotherapy has not produced any objective response despite the approval of this treatment as a low-risk method for children.

Conclusion: In general, immunotherapy seems to be less toxic than long-term chemotherapy and radiation therapy and is easily tolerated by children. Also, most of its side effects can be easily controlled. However, the existence of the mentioned challenges limits the use of these methods, which need to be studied and solved.

Keywords: Pediatric cancers, Immunotherapy , Challenging

(18278)

IL-15 activated natural killer cell cytotoxicity against human ovarian cancer spheroid cells

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Background: Ovarian cancer stem cells (OCSCs) as a small population of tumor cells are responsible for drug-resistance, metastasis and recurrence of tumors. However, the effect of the immune system on this type of tumor cells is unknown. Natural killer (NK) cells as the effector lymphocytes of the innate immune system can eliminate the tumor and the infected cells. There are increasing data demonstrating that NK cells can selectively identify and lyse CSCs; hence, the aim of the present study was to evaluate the effect of the activated peripheral blood NK cells on the OCSCs derived from SKOV-3 tumor cells and the patient's tumor biopsy.
Methods: To generate the ovarian cancer spheroid culture, as a model of CSCs, 3×10^4 cells/well were seeded in a 12-well low attached plate. The tumor spheroids reached a solid state in 5 days following the initial seeding and the stem cell markers were then assayed at the molecular level through qRT-PCR. Primary tumor cells, were obtained immediately after surgery through mechanically dissociation and then expanded for several days in the medium containing EGF and bFGF.
The NK cells were isolated from the peripheral blood of the healthy donors using CD56 enriching MACS kit. Pure NK cells were activated with IL-15 (10 ng/ml) for 24 hours and then co-cultured with SKOV-3 cells in 2D and 3D models at 1:3 ratio for 48 hours. Finally, the cell cytotoxicity was evaluated through live/dead flow cytometry assay.
Results: The SKOV-3 spheroid cells were assessed for cancer stem cell markers expression through flowcytometric analysis and demonstrated a high expression of CD44 which was about 99% and a low expression of CD24 and CD177. The NK cell cytotoxicity against SKOV3 cells was about 21% with the inactive NK cells and 81 % with the active NK cells. on 3D culture of the SKOV3 spheroid cells, the cell lysis rates were about 29% and 14.2% for the inactive and active NK cells respectively. The primary tumor cells were assessed for expression of cancer stem cell markers through flowcytometric analysis and the results demonstrated that the expression of CD44, CD117and CD133 markers were about 93%, 81% and 23% respectively. The NK cell cytotoxicity against the primary tumor cells were about 10.9% with the inactive NK cells and 67.1% with the active NK cells
Conclusion: according to the results obtained in this study, the activated NK cells compared to the inactive group demonstrated a better cytotoxic effect on SKOV-3 cancer cells and the primary tumor cells derived from the patient's biopsy. However, no significant difference in cell lysis was observed between the activated and non-activated NK cells in 3D model of SKOV3 cell line. Finally, it can be concluded that NK cells possess a desirable antitumor potential for immunotherapeutic purposes.

Keywords: Ovarian cancer, Cancer stem cell (CSC), Natural killer Cell (NK), Immunotherapy

(18306)

Cancer and immunotherapeutic strategies

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Background: Suppression of immune cell activation and function in the tumor microenvironment has long been considered as one of the crucial factors in regulating tumor progression. Therefore, inducing immune responses to tumors is of great benefit to prevent tumor progression. Compared to conventional cancer therapies including radiation therapy and chemotherapy, the cancer immunotherapy primarily targets the immune system or tumor microenvironment rather than tumor cells, and can have a synergistic effect in combination therapies. Monoclonal antibody, tumor vaccine, immunosuppression blockade, and recently CAR-T cell and bispecific antibody (BsAb) are powerful tools for immunological treatment of cancer. There are also newer types of bsAbs that are more stable, easier to produce, and less immunogenic, called bispecific T-cell engager (BiTE). The use of antibodies to block pathways inhibiting the endogenous immune response to cancer, known as checkpoint blockade therapy, has stirred up a great deal of pleasure among scientists. Clinical trials evaluating the safety and efficacy of antibodies that inhibit T cell inhibitory molecules, cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death 1(PD-1), have reported success in treating cancer. Adoptive cell transfer (ACT) is a highly personalized cancer therapy that involves administration to the cancer bearing host of immune cells with direct anticancer activity. In addition, the ability to genetically engineer lymphocytes to express conventional T cell receptors or chimeric antigen receptors has further extended the successful application of ACT for cancer treatment. Here is a brief overview of the most advanced antibody engineering technologies used in the production of therapeutic antibiotic drugs such as monoclonal antibodies, checkpoint inhibitors and adoptive cell transfer. Finally, future applications and perspectives are discussed.

Keywords: cancer, immunotherapy, adoptive cell transfer, antibody based therapy

(18342)

Oncolytic Viruses in Cancer Immunotherapy

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Background: The use of immunotherapy to treat cancer has gained substantial attention in the past decade and different approaches have been developed to induce strong anti-tumor immune responses, such as the use of cancer vaccines, adoptive T-cell transfer, monoclonal antibodies against tumor antigens, checkpoint inhibitors, and Oncolytic viruses (OVs). OVs immunotherapy is a new therapeutic strategy for cancer treatment that utilizes native or genetically modified viruses that selectively replicate within tumor cells, resulting in antitumor effects by a variety of mechanisms. The antitumor effect of OVs acts in two main ways: by directly infecting and lysing tumor cells, or by arousing the immune system to generate an immune attack. OV-infected tumor cells die in situ, releasing viral and tumor antigens that are phagocytosed by macrophages, transported to regional lymph nodes, and presented to antigen reactive T cells, which proliferate before dispersing to kill uninfected tumor cells at distant sites. These functions of OVs result in potential directions for therapeutic improvement. OVs can be administered locally or intravenously and spread to a variable degree at sites of tumor growth. Many types of viruses have been tested as potential oncolytic viruses, including herpesvirus, poxvirus, picornavirus, adenovirus, paramyxovirus, parvovirus, reovirus, Newcastle Disease virus, and rhabdovirus. Talimogene Laherparepvec (T-VEC), a genetically modified herpes simplex virus expressing granulocyte macrophage colony- stimulating factor (GM-CSF), is the only OV that has been successfully tested in phase III trials. Compared with traditional administration routes, immune system activating agents produced by OVs enable the infected tumor cells to be localized and concentrated, reducing the apparent side effects. These features make them ideal candidates against diverse malignancies. Despite the potential of OVs, there are still some limitations that should be tackled to improve their efficacy in virotherapy. These include viral tropism, delivery platforms, viral distribution, dosing strategies, antiviral immunity, and oncolysis by the OVs.

Keywords : Oncolytic Viruses; Immunotherapy; Virotherapy

(18343)

A natural bispecific hybridoma monoclonal antibody with inhibitory effects on HER2/HER3 expressing tumor cells

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Background: The human epidermal growth factor receptor (HER/ErbB) family-targeted therapies result in a significant improvement in cancer immunotherapy. To date, several monoclonal antibodies (MAb) against EGFR and HER2 such as cetuximab and trastuzumab demonstrated a survival benefit for patients, however, drug resistance occurs in a significant number of patients. HER3, a member of the HER family, which is overexpressed in various human cancers, acts as a major cause of treatment failure. Effective inhibition of HER3 and HER2 is thought to be required to overcome resistance and enhance therapeutic efficacy.

Methods: In this study, we produced and characterized a hybridoma MAb, designated 1G5D2, which naturally acts as a bispecific antibody targeting extracellular domains of both HER2 (subdomain III+IV) and HER3 (subdomain I+II). Structural and functional characteristics of this MAb were studied by a broad series of methodologies, including enzyme linked-immunosorbent assays, flow cytometry, immunoblotting, cell signaling and cell proliferation assays.

Results: Our results showed that 1G5D2 specifically binds to both HER2 and HER3 expressed on tumor cells, and these receptors compete with each other for binding to this MAb. Competition flow cytometry experiments demonstrated that our MAb does not compete with heregulin and binds to an epitope out of HER3 ligand-binding site. We evaluated the inhibitory effects of this MAb in tumor cell lines co-expressing HER2 and HER3. Interestingly, 1G5D2 synergizes with trastuzumab to inhibit both PI3K/AKT and MAPK/ERK signaling pathways and potently downregulates the proliferation of these tumor cell lines, more efficiently than each MAb alone.

Conclusion: This MAb is the first reported hybridoma antibody, which acts as a natural HER2/HER3 bispecific antibody. It might potentially be a suitable therapeutic candidate for HER2/HER3 overexpressing cancer types.

Keywords: Hybridoma, Bispecific antibody, HER2-HER3 heterodimer, Cancer immunotherapy

(18355)

Exosomes in cancer treatment

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Background: Cancer is one of the important problems in the word. Although there are a lot of advances in treatment of cancer, most of the therapeutic methods are not effective. Cancer therapy by using exosomes as vehicles can be suitable strategies. Exosomes are biological extracellular vesicles secreted by various cells that contain a plenty of specific proteins, lipids, and RNA. Given that specific ligands and proteins express on the surface of exosomes, as well as exosomes are low immunogenic and toxic and be more homogeneous and biocompatible , therefore they have considered as the great potentials for therapy of cancer . There are promising new results in transferring genes or agents whereby exosomes . We have introduced several applications of exosomes in cancer therapy.

Keywords: Exosomes; Cancer; Therapy;

(18361)

An in silico epitope-based peptide vaccine design against the HPV16-E7 Protein

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Background: Cervical cancer is one of the most common cancer worldwide that leading cause of death, related to human papillomavirus (HPV). Peptide-based vaccines being safe, stable, highly selective, multivalent and easy to produce, and transport have demonstrated great potential in developing therapeutic HPV vaccine.

Methods: In this investigation, an immunoinformatics method were used to predict and determine the major histocompatibility complex (MHC) class I, class II T cell epitopes of HPV16-E7. To find the potential peptides, retrieving protein sequences, conserved region identification, phylogenic tree construction, T cell epitope prediction, epitope-predicted population coverage calculation, and molecular docking were performed consecutively.

Results: Totally, six CD8+ T cells and six CD4+ epitopes were selected Based on different tools index. This combination of 12 epitopes created a putative global vaccine with a 95.06% population coverage.

Conclusion: These identified peptides can be employed further for peptide analysis and can be used as a peptide or poly-epitope candidates for therapeutic vaccine studies to treat HPV-associated cancers.

Keywords: Human papillomavirus 16, E7 protein, Peptide vaccine, Epitope prediction

(18364)

In silico epitope-based peptide vaccine design against HPV16-E6 through Immunoinformatic Approaches

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Background: Cervical cancer is second of the most leading causes of death globally that related to high-risk human papillomaviruses (HPVs), particularly type 16. The E6 therapeutic vaccines can promote appropriate anti-tumor T cell-mediated immune responses such as cytotoxic T lymphocytes that have key roles in current therapeutic vaccine development.
Methods: In this study, we applied bioinformatics approaches such as retrieving protein sequences, conserved region identification, phylogenic tree drawing, T cell epitope prediction, population coverage calculating of predicted epitopes, and molecular docking to predict the major histocompatibility complex (MHC) class I and class II T cell epitopes of HPV16-E6.
Results: Considering scores from different tool index, six CD8+ T cells and three CD4+ epitopes were selected. A combination of selected epitopes creates a global potential vaccine with 86.41% population protection coverage.
Conclusion: Selected peptides in the present study can be utilized for further peptide analysis and for assessing their potential as a peptide or poly-epitope therapeutic vaccine for HPV-associated cancers.

Keywords: Human papilloma virus 16, MHC class I, MHC class II, E6 protein

(18370)

Recombinant Cytotoxin II from *Naja naja oxiana* venom, a potent protein for inducing apoptosis in melanoma cancer cells

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Background: Melanoma is the most lethal skin-associated cancer. Due to the undesirable results of the current therapeutic strategies, more efficient treatments are required. Venom-based components have shown a variety of pharmaceutical functions and the ability to kill cells such as tumoral cells. Cytotoxin I and cytotoxin II from *Naja naja oxiana* (Caspian cobra) give rise to significant cytotoxic outcomes in tumoral cells. In this study, the recombinant cytotoxin-II (rCTII) was expressed in SHuffle® T7 Express cells, and its effects on cancerous melanoma cells were assessed.
Methods: SHuffle® T7 Express Competent E. coli was applied to express rCTII. After treating SK-MEL-3 and HFF-2 cells with rCTII, the MTT assay was performed to evaluate the viability of cells and to determine the effect of rCTII on underlying pathways of apoptosis. The expression levels of caspase-8 and caspase-9 was assessed in tumoral and non-tumoral cell lines by real-time PCR.
Results: The MTT assay demonstrated that rCTII suppresses cell proliferation in a dose-related manner. The half maximal inhibitory concentration (IC50) value of rCTII in the HFF-2 cell line as a non-cancerous cell was 24.76 µg/mL, but in SK-MEL-3 cancer cell line was 17.7 µg/mL. Also, real-time PCR has shown that the expression level of caspase-8 and caspase-9 in treated SK-MEL-3 cell line was mainly enhanced (both $p < 0.01$). The rational mRNA expression of caspase-8/caspase-9 after treating melanoma cells with 17.7 µg/mL rCTII was 2.513.
Conclusion: According to the results, rCTII can greatly suppress cell proliferation. Also, lower IC50 of rCTII in SK-MEL-3 cancer cell line in comparison with HFF-2 cells ($p < 0.0001$) can bring an opportunity for administrating rCTII as a drug. Upregulated caspase-8 and caspase-9 have indicated that rCTII by activating both intrinsic and extrinsic pathways of apoptosis can kill tumoral cells. These findings highlighted the promising anti-cancer function of rCTII in order for cancer therapy.

Key words: Melanoma, recombinant cytotoxin-II, apoptosis, cancer therapy.

(18394)

Title: Pharmacological Targeting of A2a Receptor Improves Function of Anti-Mesothelin CAR T Cells

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Background: CAR T cell-based therapies have shown significant results in hematologic malignancy. Due to the hostile tumor microenvironment (TME), CAR T cell therapy in solid tumors was not completely successful. Adenosine is a metabolite product in hypoxic TME that suppresses T cell antitumor function by binding to adenosine 2a (A2aR) receptor in T cells. In the present study, A2ar was targeted in CAR T cells using the adenosine antagonist to enhance the antitumor activity of mesothelin CAR T cells.

Methods: At first, the expression of A2aR and the effects of its signaling on the function of fully human anti-mesothelin CAR T cells (MSLN-CAR T) were analyzed using flowcytometry. Afterwards, an A2aR pharmacological antagonist, SCH-58261, were used to diminish the inhibitory effects of A2aR signaling on CAR T cell. The Anti-tumor activity of MSLN-CAR T cell including proliferation, cytokine secretion (IL-2, IFN.γ, and IL-2 secretion), and cytotoxic potency of MSLN-CAR T cells were analyzed against both Mesothelin positive (Ovarian Cancer cell lines) and negative cells (NALM-6), in the absence and presence of SCH-58261. To simulate TME, CAR T cell functional analyses were also performed in the absence and presence of an A2aR specific agonist. Statistical analyses were performed Prism 7 software.

Results: Present study determined that Adenosine suppressed proliferation, cytokine secretion and cytotoxic potency of MSLN-CAR T cells against mesothelin positive cells. Pharmacological inhibition of A2aR reversed the reduction in CAR T cell proliferation and cytokine response caused by the adenosine analog; however, it failed to rescue the cytotoxic function of the cells.

Conclusion: Altogether, our results determined that pharmacological targeting of A2aR signaling improves CAR T cell function in the hostile microenvironment of solid tumors. Inhibition of A2aR in CAR T cells can be used as a translatable strategy in clinical trials.

Keywords: Pharmacologic Targeting, Ovarian cancer, Adenosine 2a-receptor, Tumor microenvironment, Adenosine

(18417)

Investigating the effect of Pycnogenol supplementation (French maritime pine bark extract) on tumor growth rate and immunological factors in a murine model of breast cancer

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Background: During the past decades, anti-oxidants attracted much attention due to their anti-tumor properties. Several studies have reported anti-oxidant activity of the Pycnogenol extracted from French maritime pine in the past decades, focusing on the polyphenols. However, additional surveys are needed to clarify the underlying mechanisms behind the anti-tumor activity of Pycnogenol.
Methods: Two groups of BALB/c 10 mice receiving Pycnogenol (100 mg/kg/day) and tap water were determined. On day 10, both groups were inoculated with 1×10^6 4T1 cells subcutaneously. On day 30, when tumors had been grown, 4 mice from each group were sacrificed to evaluate T cell subsets by flow cytometry and cytokine gene expression by QRT-PCR.
Results: Flow cytometry analysis showed that subsets of CD8+ T cell population were significantly increased in the Pycnogenol-receiving group ($P < 0.05$). The population of regulatory T cells and CD4+ T helper 1 and 2 cells were not altered. The expression of IFN-γ, perforin, and granzymes genes was statistically enhanced in the intervention group. However, the levels of IL-2, IL-4, IL-13, and TGF-β were not changed.
Conclusion: The results showed that in addition to its anti-oxidant properties, the use of Pycnogenol can also strengthen lymphocyte cells.

Keywords: Pycnogenol, Cancer, Immune-responses, Anti-oxidants

(18430)

Suppression of CD73 and Cisplatin combination: A new strategy for treatment of lung cancer

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Background: In the treatment of lung cancer, the number of clinical protocols evaluating combination therapies including immune chekpoint inhibitors and chemotherapies are currently growing. The effectiveness of cancer treatment based on cisplatin is restricted by several factors such as side effects. In the development of several cancer types, CD73 (ecto-5′-nucleotidase) is involved. For the treatment of cancer, CD73 inhibitors are already being evaluated in clinical trials. The key to developing this line of therapy is understanding the molecular and cellular activities of CD73 inhibitors. Given that, the present study was purposed to discover the potential therapeutic role and underlying mechanism of CD73 in human lung cancer cell line in combination with cisplatin.

Methods: The specific siRNA of CD73 transfected into A549 cells via electroporation and then treated with cisplatin, then their impact was assessed on several gene expressions related with metastasis, apoptosis, and cell cycle. The inhibitory effect of this combination therapy on cell cycle, and apoptosis were assessed by flow cytometry. Scratch assay was performed to evaluating the migration.

Results: Functional analyses displayed that the combination therapy inhibited migration of A549 cells. Moreover, siRNA transfection in combination with cisplatin induced apoptosis on the A549 cells. q-RT PCR results also revealed that siRNA transfection in combination with cisplatin decreased the expression levels of c-Myc, MMP-9, CXCR4, and ROCK in treatment groups compared to the controls.

Conclusion: The findings of our study suggest that the specific siRNA of CD73 in combination with cisplatin effectively decreases the viability of lung cancer cells. Thus, suppression of CD73 expression in combination with cisplatin may be recommended as a potential therapeutic goal in the treatment of lung cancer patients.

Keywords: Lung cancer, CD73, Cisplatin, combination therapy

(18432)

Combination of B7-H6 siRNA with cisplatin inhibit the growth of lung cancer cells

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Background: One of the most challenging aspects of lung cancer therapy is drug resistance and side effects of chemotherapies. In patients with lung cancer, the B7 family is considered to be a negative regulator of immune responses. B7-H6 has been found to cause natural killer (NK) cell cytotoxicity as a newly identified member of the B7 family. The goal of this study was to identify the potential therapeutic function and underlying mechanism of B7-H6 in cell line of human lung cancer in combination with cisplatin.

Methods: B7-H6 siRNA was transfected via electroporation into H1299 cells and then treated with cisplatin, and its effect was assessed on several gene expressions related to metastasis, apoptosis, and the cell cycle. Flow cytometry technique was performed to evaluate the inhibitory effects of this combination therapy on cell cycle and apoptosis of cells. In order to evaluate migration, the scratch assay was performed.

Results: In particular, siRNA transfection in combination with cisplatin induced apoptosis on H1299 cells. Functional analysis showed that the combination therapy prevented migration of H1299 cells. The results of q-RT PCR also showed that siRNA transfection in combination with cisplatin reduced Rock, c_myc, CXCR4, and MMP9 expression levels in the treatment groups relative to the controls.

Conclusion: The results of our research indicate that the specific siRNA of B7-H6 in combination with cisplatin, effectively reduces the viability of lung cancer cells. Thus in the treatment of patients with lung cancer, suppression of B7-H6 expression in combination with cisplatin may be suggested as a possible therapeutic method.

Keywords: Lung cancer, B7-H6, Cisplatin, combination therapy

(18447)

CAR T cell therapy and hurdles: a review

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Background: Hematological malignancies include various types of leukemia that effect blood, bone marrow, and lymph nodes. Chimeric antigen receptor T (CAR T cell) therapy has shown exciting clinical efficacy for hematological malignancies. It is a US Food and Drug administration (FDA) approved method that revolutionized tumor elimination. CAR T cell therapy success rate is about 30% to 40% for lasting remission. Despite its significant responses, it has been associated with unique toxicities, which can be severe or even lethal. This study is a review of the obstacles that are faced during CAR T cell therapy.

Methods: This research was based on articles which were published from 2016 to 2020. PubMed, Scopus, and google scholar were searched using keywords: "CAR-T cell", "cytokine release syndrome", "neurotoxicity", "solid tumors", and "hematological malignancies".

Results: The most frequently reported toxicity associated with CAR-T cell therapies are cytokine release syndrome (CRS) and consequently neurotoxicity (NT) due to efficacy of cytokines like IL-6 in CNS. Clinical trials suggest the centrality of monocytes (major sources of IL-6), endothelial dysfunction, and blood brain barrier in expansion of CAR T cell-associated neurotoxicity. In addition, solid tumors have been hampered by countless obstacles such as CAR T cell expansion, inadequate trafficking, and immunosuppressive microenvironment which is characterized by hypoxia, and etc.

Conclusion: In this study, we describe the current state of the CAR T cell therapy and its high response rates observed in blood cancer patients treated with anti-CD19 CAR-engineered T cell. While it is considered a major breakthrough, the clinical success is blemished by life-threatening side effects that have led to some CAR-associated deaths in clinical trials. We emphasize some ways to improve this method and solve current challenges.

Keywords: CAR-T cell therapy, cytokine release syndrome, neurotoxicity, solid tumors, hematological malignancies.

(18452)

Enrichment of breast cancer derived exosomes with miR-34a can induce anti-proliferative and apoptotic effects on 4T-1 cell line

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Background: Breast cancer is the most prevalent cancer type in women. Finding new therapeutic agents is always a priority in this field. MiR-34a has shown anti-tumor effects in different cancers. Exosomes can be used as a carrier for miRNAs. In this study we evaluate the effects of miR-34a enriched tumor derived exosomes (TEXs) on 4t1- cells.
Methods: 4T1 cells cultured in standard cell culture condition and when they reached to 85% confluency, the cells serum starved for 24 hrs. Afterwards the conditioned media gathered and purified by commercial kit. The purified exosomes characterized by TEM, DLS and BCA. miR-34a inserted in TEXs by CaCl2 0.1M and the successful insertion verified by real-time pcr. MTT and Annexin/PI flowcytometry performed for evaluation of anti-proliferative and apoptotic effects with different doses (0, 5,10,25,50, 100 µg/ml) of miR-TEX and TEX after 24 and 48 hrs.
Results: The purified exosomes morphology (bilayer), size (average of 68 nm) and concentration confirmed by TEM, DLS and BCA, respectively. miR-34a expression significantly upregulated in miR-enriched -TEXs in comparison to non-enriched TEXs. miR-34a-TEXs showed a dose and time dependent pattern of anti-proliferative and apoptotic effects on 4T1 cells compared to non-treated and TEX only groups in 48hrs ($p<0.05$) and no changes observe at 24 hrs groups.
Conclusion: miR-34a-TEXs can induce time-dose dependent anti-proliferative and apoptotic effects on 4T1 cells, which may have therapeutic application in cancer immunotherapy.

Keywords: miR-34a, breast cancer, 4T1, exosome

(18457)

Investigation of the expression pattern of MHC class I chain-related protein A, microRNA-106b and microRNA-20a in gastric cancer cells treated with linoleic acid and docetaxel

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Background: Considering that microRNAs (miRNAs) are involved in response to anti-cancer and supplementary agents, they are considered as biomarkers for monitoring therapy outcome. MHC class I chain-related protein A (MICA) is up-regulated during tumor growth and is considered a dangerous signal for immune system activation against tumor cells. Here, we studied the effect of LA and docetaxel on MICA and its regulating miRNAs, miR-106b and miR-20a expression level in gastric cancer (GC) cell line, MKN-45.

Methods: MKN-45 cells were cultured and treated by 18.5 µM docetaxel and 50 µM LA. Subsequently, cells were harvested and then RNA extraction and cDNA synthesis were done. The expression level of MICA and miRNAs were evaluated using quantitative real-time PCR for both treated and untreated cells.

Results: Expression level of MICA was decreased significantly by docetaxel (100 fold and *P*-value<0.0001), LA (7.14 fold and *P*-value<0.0001), and their combination (3.03 fold and *P*-value=0.0002). Furthermore, miR-106b was increased in docetaxel-treated cells alone (0.65 fold, *P*-value=0.01) and was decreased in LA- and LA/docetaxel-treated cells (2.77 fold and *P*-value<0.0001, 1.08 fold and *P*-value=0.002). Although miR-20a was decreased in docetaxel- and LA/docetaxel-treated cells (2.43 fold and *P*-value<0.0001, 4.76 fold *P*-value<0.0001), it was increased in LA-treated cells (0.89 fold and *P*-value=0.02).

Conclusion: Higher expression level of MICA on cancer cells would elicit more potent immune responses. LA in combination with docetaxel restored the expression of MICA on gastric cancer cells and would be used as effective supplementation in patients' therapeutic regimen.

Keywords: Linoleic acid, Docetaxel, MICA, miR-106b, miR-20a

(18486)

Potential Role of MicroRNAs in Cancer Immunotherapy

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Background: In the past decade, cancer immunotherapy has represented as a promising new era in cancer management due to the high safety border and selectivity, compared to the common cancer chemotherapeutic methods. Interestingly, microRNAs (miRNAs) have been shown to function as crucial regulators of immune response in cancer immunology. In this article we aim to review the latest findings on immune pathways that regulated by miRNAs in cancer.
Methods: In this study, the articles were searched in electronic databases including pubmed/medline, scopus and web of science by following keywords: cancer immunotherapy, miRNAs, biomarker and immune system.
Results: miRNAs are small regulatory non-coding RNA molecules that inhibit the translation and stability of messenger RNAs (mRNAs). They are ~22 nucleotides in length and control the physiological and pathological processes. So, altered expression of these small molecules is often associated with some human diseases. A complex system of miRNAs regulates the gene expression at transcriptional and post-transcriptional level and plays an important role in the regulation of many pathways of cancer and immune system cells. In cancer immunotherapy studies, the expression profile of immune-regulatory miRNAs as a predictive biomarker could be beneficial for the clinical results.
Conclusion: In summary, understanding the role of miRNAs in regulating cancer immunity is important, as it can contribute to determine mechanisms that can be modulated to ameliorate the success of immunotherapy in cancer patients.

Keywords: cancer immunotherapy, miRNAs, biomarker, immune system

(18505)

Effects of TLR4 on inflammatory and cancer factors during cancer; A systematic review

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Background: Toll-like receptor 4 (TLR) receptors, due to their association between innate and specific immunity, play an essential role in the development of inflammation and cancer, and if TLR binds to its receptor, it causes inflammatory effects in the body that trigger immunity and tumor growth. Meanwhile, TLR4 has received more attention and testing. Therefore, we decided to study the effects of TLR4 on inflammatory and cancer factors during cancer.

Methods: This article is a review by searching reputable databases including PubMed, Scopus, Cochrane Library, and Web of science with the keywords "TLR4", "cancer" and "Inflammation" which were examined to ensure the completion of search results of article sources and After removing duplicate titles from endnote software and reviewing the titles and abstracts, articles related to JBi tools were reviewed.

Results: Different studies indicate that the expression of TLR4 is the same in tumors with different degrees of tissue differentiation and at different stages of the disease, and its clinical and pathological indices did not affect its rate. Studies have also shown that TLR signaling increases tumor growth, invasive phenotypes, and metastasis in tumor cells and the expression of inhibitory molecules such as XIAP, Bcl-2, and Bcl-XL, which ultimately induce metastasis growth. Depend on MyD88- and TRIF used to include the following: Curcumin, 6-gingerol, 6-shogaol, 1-dehydro-10-gingerdione, epigallocatechin gallate (EGCG), luteolin, quercetin, resveratrol, caffeic acid phenethyl ester, xanthohumol, genistein, berberine, and sulforaphane.

Conclusion: Due to the destructive effects and effects of this TLR in cancer and inflammation, it's non-production and secretion can play a positive role in the treatment of cancer and inhibition of its growth.

Keywords: toll-like receptor4، Inflammation، cancer

(18523)

Modulatory effects of TMZ, IFN-γ, TMZ+IFN-γ on TNF-α and IL-10 level in c6-induced glioblastoma in rats

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Background: This study aimed to assess the anti-glioma effect of separated and combination of Temozolomide (TMZ) and Interferon-gamma (IFN-γ) in rat C6 glioma model.
Methods: Forty male Sprague-Dawley rats bearing intracerebral C6 inoculation were randomly divided into four groups of seven rats including intraperitoneal administration of PBS, TMZ (15 mg/kg for 3 days), IFN-γ (1x IU for 3 days), and a TMZ + IFN-γ combination. On day 28 after tumor implantation, rats were sacrificed and brain tissues were collected for cytokines (TNF-α, IL-10) assessment by ELISA assay.
Results: Our results indicated that TNF-α level increased significantly in serum and nonsignificantly in brain tissue compared with culture medium group. Administration of TMZ, IFN-γ, TMZ+IFN-γ could significantly reduce TNF-α level in serum compared to tumor group. IL-10 level increased significantly in brain and nonsignificantly in serum compared with culture medium group. Administration of TMZ, IFN-γ could significantly reduce IL-10 level in brain compared to tumor group.
Conclusion: The drug treatments could reduce TNF-α level in serum and IL-10 in brain tissue. Taken together, it can be concluded that c6-induced glioblastoma causes increase of TNF-α and IL-10 which may be ameliorated through TMZ, IFN-γ, TMZ+IFN-γ.

Keywords: Glioblastoma, Temozolomide, Interfron-γ, rat

(18525)

Docosahexaenoic acid compensates adverse effects of paclitaxel on the expression level of vascular endothelial growth factor, microRNA-126, and microRNA-30a in breast cancer cell line

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Background: Angiogenesis is an essential stage in tumor progression and is considered as a poor prognostic factor in breast cancer (BC). Vascular endothelial growth factor (VEGF) and its regulating microRNAs including miR-126 and miR-30a are some important players in angiogenesis. In this study, we aimed to evaluate the effect of docosahexaenoic acid (DHA) and paclitaxel alone or in combination on the expression level of VEGF, miR-126, and miR-30a in BC cell line, BT-474.
Methods: BT-474 cells were cultured and treated with 19nM paclitaxel and DHA. Then, RNA extraction and cDNA synthesis was done and the expression level of VEGF, miR-126, and miR-30 were determined by quantitative real-time PCR for both treated and untreated cells.
Results: VEGF expression level was increased significantly in paclitaxel- (20.74 fold) and paclitaxel/DHA-treated cells (6.36 fold), and was decreased in cells treated with DHA (0.28 fold). MiR-126 was significantly decreased in cells treated with paclitaxel (0.30 fold) and was significantly increased in DHA- (1.58 fold) and paclitaxel/DHA-treated cells (1.18 fold). MiR-30a was increased significantly in all treatments (1.19 fold, 3.25 fold, and 1.39 fold in paclitaxel, DHA, and paclitaxel/DHA, respectively).
Conclusion: While paclitaxel showed adverse effects on the expression level of VEGF and tumor suppressor miR-126 and miR-30, DHA demonstrated the opposite effect and compensates for such unwanted gene expression patterns. DHA showed a promising effect to be used as a supplementary regimen in the treatment of BC patients.
Keywords: Docosahexaenoic acid, Paclitaxel, VEGF, miR-126, miR-30a

(18528)

Anti-tumor effects of anti-PLAC1 antibody-SN38 conjugate in a xenograft model of human breast cancer

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Background: Placenta-specific 1 (PLAC1) is one of the oncoplacental genes ectopically expressed in a wide variety of cancers. Antibody drug conjugates (ADC) have the potential to substantially improve efficacy and reduce toxicity compared with cytotoxic small-molecule drugs and are being employed for treatment of cancers.

Methods: Anti-human PLAC1 monoclonal antibodies were produced and fully characterized. SN38 was conjugated to an anti-PLAC1 antibody (clone: 2H12C12) and conjugation efficacy was evaluated by HPLC and UV spectrophotometry. Post-conjugation reactivity was then tested using ELISA and flow cytometry. *In vitro* cytotoxicity profiling of 2H12C12-SN38 was examined on MDA-MB-231 breast cancer cells using a flourimetric assay. The effect of 2H12C12-SN38 on MDA-MB-231 tumor growth and angiogenesis *Ex vivo* was tested by chorioallantoic membrane (CAM) assay followed by immunohistochemical analysis of cancer cell seeding. Pharmacokinetics of 2H12C12-SN38 in mice bloodstream was measured by successive venipuncture after ADC administration. Inhibitory effects of anti-PLAC1 ADC on tumor growth was assessed in nude mice xenograft model of human breast cancer.

Results: The generated anti-PLAC-1 monoclonal antibody specifically reacted with a wide variety of mouse and human cancer cells**.** Conjugation of anti-PLAC-1 antibody to SN38 did not negatively affect reactivity of the antibody with cognate native antigen. Anti-PLAC1 ADC exerted a substantial cytotoxicity on MDA-MB-231 cells starting from a concentration of about 33 nM. ADC also signifi-

cantly decreased the growth of MDA-MB-231 tumors on CAM assay but did not show a significant effect on tumor angiogenesis. Pharmacokinetics of anti-PLAC1 ADC in mice showed an average half-life (t1/2) of about 80 hours. Treatment of nude mice with ADC resulted in a significant decrease in tumor size compared to isotype-matched antibody-SN38 conjugate, unconjugated anti-PLAC1 antibody or free SN38.

Conclusion: This is the first therapeutic application of anti-PLAC1 ADC in a xenograft model of human breast cancer. Our results reinforce on embryonic origin of cancers and sheds light on the potential therapeutic benefits of targeting oncofetal antigens in human breast cancer.

Keywords: Placenta-specific 1 (PLAC1), SN38, CAM, Tumorigenesis, Breast cancer

(18539)

Synergism between Liposomal-CpG and PD-1 Blockade: Effects of *ex vivo vs in vivo* Administration as DC Vaccine

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Background: Induced acquired resistance have limited the clinical outcomes of PD-1 immune checkpoint therapy and led to low response rate. Pre-existing of tumor-specific T cells is one way for solving this problem that can be achieved by combination therapy with anticancer vaccines. Here we compared the efficacy of *ex vivo* delivery *vs in vivo* direct administration of liposomal-CpG formulation to dendritic cells (DCs) as DC-based anticancer vaccine in combination with PD-1 blockade in murine melanoma model.

Methods: In the present study, gp100 melanoma antigen was conjugated to the DOTAP cationic liposome and mixed with CpG. Melanoma tumor-bearing mice were treated with *in vivo* subcutaneous administration or *ex vivo* DCs pulsed with this formulation alongside anti PD-1 monoclonal antibody. Induced immune responses were evaluated in tumor microenvironment (TME) followed by tumor growth progression and survival rate.

Results: *Ex vivo* DC vaccination with liposomal-CpG yielded a significant increase in antigen-specific CD8+ TILs proliferation and IFN-γ secretion over *in vivo* administration of liposomal-CpG which resulted in highest cytotoxic activity. Remarkably, *ex vivo* DC vaccination resulted in an increase in the frequency of antigen-specific CD4+ TILs and IFN-γ secretion in TME relative to *in vivo* vaccination which clearly show the critical role of CpG co-delivery with antigen to DC and antigen presentation. Furthermore, therapeutic *ex vivo* DC vaccination in combination with anti PD-1 antibody significantly controlled the tumor growth ($P<0.001$) and increased mice survival time compared to *in vivo*-treated mice.

Conclusion: Our results show that in combining liposomal antigen with CpG and simultaneous co-delivery to DC as *ex vivo* DC-based vaccine, specific-antitumor immune responses can be significantly increased which results in enhanced efficacy of PD-1 blockade regium.

Keywords: Liposome, PD-1 antibody, CpG, DC-based Vaccine

(18548)

In silico modeling of a 3rd generation chimeric antigen receptor against Mesothelin

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Background: Chimeric antigen receptor (CAR) T cells known as newly developed immunotherapy approaches that showed promising results in controlling cancer progression. Mesothelin (MSLN) is the most targeted antigen in pancreatic cancer. In this study, MSLN binding moiety of a humanized Ab (Morab-009) combined with CD8α transmembrane, intracellular domain of CD28, CD137 and CD3 zeta were used to design a 3rd generation CAR T cell. The interaction of a designed molecule was investigated against its target, MSLN, via in silico tools to validate the design strategy and confirm the true energetic condition of the complex harnessing. The hotspots in the interaction network of the complex were evaluated. The energetic frustration of all contact in the free molecule was assessed.

Methods: The amino acid sequences of MSLN, Morab-009, CD8α, CD28, CD137 and CD3 zeta were obtained from UniProtKB. The structures were taken from the Protein Data Bank (PDB). The sequence of the humanized anti-mesothelin was used to modify CDRs of Morab-009 and other parts were retained by their sequences. A HHpred search against Protein Data Bank revealed the existence of homologous structures to the C-terminal and N-terminal of the construct sequence. Therefore, the homology modeling approach was selected to build the 3d structure of the construct. I-tasser, Phyre 2, Swissmodel, and rosetta were used. The quality of the resulting structures was evaluated by Molprobity. The satisfactory structure in terms of maximal ramafavored residues, allowed angles, minimal poor rotamers was selected for the docking approach. The tertiary structure of mesothelin (PDB ID: 4F3F) was docked into the designated construct using chimera software and HADDOCK server. The network of interactions was extracted from the complex by Cytoscape 3.8.2. The energetic frustration of all residual contacts was measured by frustratometer server.

Results: The most appropriate structure was built by rosetta (with 358 favored rotamers 98.9%, no poor rotamer, 1 Ramachandran out layer 0.23%, 425 Ramachandran favored residues 97.03%, bad bonds 3/3463 0.09%, and bad angles 11/4689). The minimal delta G belonged to the interaction of VLCDR1,2 and VHCDR1,2 with initial N-terminal residues of both helixes of mesothelin. The highly frustrated interactions were mostly distributed in the CDR regions suggesting a high level of flexibility of aforesaid motives which might propel the motives to the binding. Moreover, the interaction of hotspots in the complex was limited to hydrogen bonds.

Conclusion: The interaction of the designed construct herein with mesothelin predicts a high affinity and true orientations for all moieties. The comparison of the predicted complex to mesothelin-MORAb-009 through structural alignment confirmed the accuracy of the designing approach. With a view to the energetic state of different parts of the complex and free receptor along with the orientation of receptor and ligand, it is expected that the interaction would be prone to happen in vivo.

Keywords: Cancer Immunotherapy, CAR T cells, Pancreatic Cancer, Mesothelin, In silico studies

(18553)

In silico modeling of a 3rd generation chimeric antigen receptor against Mesothelin

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Background: Chimeric antigen receptor (CAR) T cells known as newly developed immunotherapy approaches that showed promising results in controlling cancer progression. Mesothelin (MSLN) is the most targeted antigen in pancreatic cancer. In this study, MSLN binding moiety of a humanized Ab (Morab-009) combined with CD8α transmembrane, intracellular domain of CD28, CD137 and CD3 zeta were used to design a 3rd generation CAR T cell. The interaction of a designed molecule was investigated against its target, MSLN, via in silico tools to validate the design strategy and confirm the true energetic condition of the complex harnessing. The hotspots in the interaction network of the complex were evaluated. The energetic frustration of all contact in the free molecule was assessed.

Methods: The amino acid sequences of MSLN, Morab-009,CD8α , CD28, CD137 and CD3 zeta were obtained from UniProtKB. The structures were taken from the Protein Data Bank (PDB). The sequence of the humanized anti-mesothelin was used to modify CDRs of Morab-009 and other parts were retained by their sequences. A HHpred search against Protein Data Bank revealed the existence of homologous structures to the C-terminal and N-terminal of the construct sequence. Therefore, the homology modeling approach was selected to build the 3d structure of the construct. I-tasser, Phyre 2, Swissmodel, and rosetta were used. The quality of the resulting structures was evaluated by Molprobity. The satisfactory structure in terms of maximal ramafavored residues, allowed angles, minimal poor rotamers was selected for the docking approach. The tertiary structure of mesothelin (PDB ID: 4F3F) was docked into the designated construct using chimera software and HADDOCK server. The network of interactions was extracted from the complex by Cytoscape 3.8.2. The energetic frustration of all residual contacts was measured by frustratometer server.

Results: The most appropriate structure was built by rosetta (with 358 favored rotamers 98.9%, no poor rotamer, 1 Ramachandran out layer 0.23%, 425 Ramachandran favored residues 97.03%, bad bonds 3/3463 0.09%, and bad angles 11/4689). The minimal delta G belonged to the interaction of VLCDR1,2 and VHCDR1,2 with initial N-terminal residues of both helixes of mesothelin. The highly frustrated interactions were mostly distributed in the CDR regions suggesting a high level of flexibility of aforesaid motives which might propel the motives to the binding. Moreover, the interaction of hotspots in the complex was limited to hydrogen bonds.

Conclusion: The interaction of the designed construct herein with mesothelin predicts a high affinity and true orientations for all moieties. The comparison of the predicted complex to mesothelin-MORAb-009 through structural alignment confirmed the accuracy of the designing approach. With a view to the energetic state of different parts of the complex and free receptor along with the orientation of receptor and ligand, it is expected that the interaction would be prone to happen in vivo.

Keywords: Cancer Immunotherapy, CAR T cells, Pancreatic Cancer, Mesothelin, In silico studies

(18558)

A Review on Bruton tyrosine kinase & chronic lymphocytic leukemia

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Background: Chronic lymphocytic leukemia is more common in adults than other leukemias. BTK is an essential mediator of B cell receptor signaling in growth and immune function and considering the importance of lymphocyte cells in the body's immunity and the prevalence and severity of the disease. This study aimed to determine the tyrosine kinase receptor's potential therapeutic role in reducing treatment costs and improving adults' health.

Methods: This study reviews the effect of BTK on CLL disease by analyzing articles from scientific databases, including Science Direct, Pubmed, and Scopus. This research has been done with keywords "BTK,"" BCR," Chronic lymphocytic leukemia," "IBRUTINIB" from 2012 to 2020.

Result: Bruton is a kinase that acts downstream of multiple receptors in various blood cells. B-cell receptor signaling is an essential pathway in the pathogenesis of several B-cell malignancies, including chronic lymphocytic leukemia, and can be targeted by BCR associated kinase inhibitors such as BTK. B-cell receptor signaling in leukemia is suddenly activated, and BRUTON is essential for BCR signaling, and BRUTON protein is overexpressed in CLL compared to normal B-cells. BTK is a tyrosine kinase receptor and a significant player in BCR signaling.

Conclusion: BTK plays a fundamental role in several signaling pathways in B cells, especially BCR, and targeting it can be a treatment for a variety of B cell malignancies in clinical trials. Inhibition of BTK alone can be a treatment, but today there are studies for combination therapies to improve the disease.

Keywords: Chronic lymphocytic leukemia, CLL, Bruton tyrosine kinase

(18564)

Interleukin 27; a novel candidate for cancer cytokine therapy

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Background: Interleukin 27 (IL-27) is a new member of the IL-12 cytokine family, which is composed of Epstein-Barr Virus-Induced 3 (EBI3) and IL-27p28 subunits. IL-27 has potent anti-tumor features that suppress the tumor progression through various pathways with fewer side effects compared to conventional cytokines such as IL-6 and IL-12. High efficacy and low toxicity of IL-27 indicate the potential ability of this cytokine to serve as a promising agent in cancer immunotherapy.

IL-27Rα subunit of IL-27 receptor activates the STAT1 pathway and induces the anti-tumor responses through the induction of T-bet and CXCR3, which leads to Th1 activation and cytotoxic responses. Indeed, IL-27 inhibits the GATA-3 and Th2 responses consequently. Moreover, IL-27 suppresses angiogenesis by expressing the CXCL9 and CXCL10. It has been shown that IL-27 avoids tumor metastasis by inhibiting the associated genes with the endothelial mesenchymal transition (EMT). It should be noted that IL-27 is less toxic compared with other cytokines such as IL-12. Various studies have revealed the anti-tumor and anti-metastatic responses of IL-27 particularly in Non-small-cell lung cancer (NSCLC), breast, colorectal, prostate, and hematologic cancers, and melanoma.

Conclusion: IL-27 is a potent anti-tumor agent, which suppresses the progression and metastasis of tumors, through various pathways. Toxic side effects of IL-27 are significantly less compared with conventional cytokines, which suggests IL-27 as an efficient alternative for conventional cytokines. Taken together, we conclude that IL-27 can be a promising candidate for cancer cytokine therapy.

Keywords: Interleukin-27, cancer, immunotherapy, cytokine therapy

(18580)

Profiling of RTL1 expression in human breast cancer tissues and cell lines

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Background: Breast cancer (BC) is the most occurring malignancy in females and recognition of molecules driving BC is needed for developing more effective immunotherapeutic medications. In this study we investigated the expression of Retrotransposon-like 1 (RTL1), a placenta-specific protein, in a series of BC tissues and cell lines.

Methods: A polyclonal anti RTL1 antibody was produced in rabbit and characterized. RTL1 expression was investigated in a total of 147 BC and 36 non-malignant breast tissues using immunohistochemistry on tissue microarray samples and association of its expression with patient's clinicopathological parameters was then assessed. Flow cytometric analysis was applied for RTL1 expression in BC cell lines.

Results: A mixture pattern of cytoplasmic and nuclear RTL1 expression in most of examined tissues were observed, however nuclear expression was dominant pattern of expression. The nuclear RTL1 expression level was significantly higher in BC tissues ($p \leq 0.001$). A statistically significant association between nuclear RTL1 expression and histological grade and vascular invasion was found ($p \leq 0.001$ and $p \leq 0.05$). All of four examined cell lines expressed RTL1 at their surface with varying degree. MDA-MB-231, the most invasive BC cell line, compared to MCF7, SKBR3 and T47D expressed higher levels of RTL1 at their surface. Cells with low level of RTL1 expression on their surface, expressed high levels of intracellular RTL1 expression.

Conclusion: Our results showed for the first time that RTL1 is differentially expressed in BC compared to non-cancerous breast tissues and associated with higher grade and vascular invasion. It seems that metastasis is associated with nuclear to cell surface translocation of RTL1, an event that highlights the potential application of anti-RTL1 antibodies for immunotherapy of advanced metastatic BC patients.

Keywords: RTL1, Breast cancer, Expression, Tumor grade, Vascular invasion

(18595)

Improving antitumor efficacy and safety of CAR T cell therapy by universal and programmable chimeric antigen receptors

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Background: CAR T cell therapy is one of the most promising and innovative approaches to treat cancers. Antitumor activity of CAR T cells needs to be improved to increase efficacy in both hematologic and solid tumors. Limitations of this therapy include 'On-target/ Off-tumor' toxicity, poor persistence, insufficient migration to solid tumors and inactivation of T cells due to local secretion of inhibitory factors. The safety, efficacy and antitumor activity of CAR T cells could be enhanced by different strategies.

In this review, we will discuss the latest developments in this rapidly evolving area including targeting two tumor-associated antigens by TanCARs, combining a suicide gene with CAR T cells (iCARs) and approaches to remote control of T cell location and dosage. Moreover, we will describe the universal CAR platform: (SUPRA CAR, BBIR CAR, anti-FITC CAR, anti-5B9 CAR, anti-PNE CAR) which are designed to avoid the costly manufacturing process of engineered T cells for each new target and evade antigen escape, and to broaden the targeting of complex tumor antigens. Finally, gene editing technologies for generation of universal CAR T cells from healthy donors are reviewed.

All these efforts promote the development and evolution of CAR T cell therapy and move toward curing cancer with high safety and efficacy, and low cost.

Keywords: Chimeric antigen receptor, CAR T cell therapy, Universal CARs, gene editing

(18597)

Evaluation of CETUXIMAB Consumption in non-small cell lung cancer(NSCLC)

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Background: Lung cancer is a disease with significant burden, with nearly 2.5 million new diagnoses in 2011 contributing to almost 1.5 million deaths worldwide However, no longer is lung cancer managed by distinguishing non-small cell lung cancer (NSCLC) and the associated subtypes from small cell lung cancer (SCLC), but as variety of distinct, although related, diseases each with requiring their own treatment options. NSCLC make up approximately 85% of lung cancers, which is then further broken down into three distinct histological subtypes; adenocarcinoma, squamous cell carcinoma and large cell carcinoma (LCC). Adenocarcinoma comprises the majority of all new lung cancer diagnosed with an associated fall in the proportion of squamous cell cancers. Epidermal growth factor receptor (EGFR), is one of several somatic mutations, in NSCLC, which is seen more frequently in certain population groups. This population group is classically described as non-smoking females with adenocarcinoma. The interest in these mutations is due to the small molecule targeted therapies (such as erlotinib and gefitinib) available and in development, which can have significant prognostic benefits.
Methods: By examining the words of Cetuximab, Lung cancer, non-small cell lung cancer (NSCLC) in the of Google Scalar and Pubmed from 2018 to 2020, and mesh of NSCLC, EGFR find related articles.
Results: According to the articles and clinical sections of the trial, it is thought that the drug Cetuximab can be effective in the treatment of lung cancer by acting on EGFR and increase its lifespan in a multidrug regimen.Evaluation of this requires clinical evaluation.
Conclusion: EGFR mutations are an important factor in NSCLC. Examination of non-small lung cells and history have shown that it puts you at risk, while longevity is not necessary, which is why it interferes with your choice Dysregulation of the EGFR leads to increased intracellular pathways activity, via tyrosine kinase autophosphorylation, resulting in directly or indirectly, cell proliferation, angiogenesis, invasion and metastasis .Overexpression of the EGFR gene has been identified in a variety of other cancers including: head and neck, ovary, cervix, bladder, oesophagus, stomach, brain, breast, endometrium, colon and lung .EGFR overexpression has been identified in between 40% to 89% of NSCLC , with highest rates seen in squamous tumors (89%) and lowest in adenocarcinomas (41%) .
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Keywords: EGFR, Cetuximab, non-small cell lung cancer, Lung cancer

(18599)

Effectiveness of intraoperative radiotherapy targeted to anigiogenesis in patients with breast cancer

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Background: The standard of breast cancer treatment is based on breast conserving surgery with administration of adjuvant whole breast radiotherapy. It is shown that in-breast relapse is most likely to occur in the tumor bed, i.e. around the scar. The wound healing process after surgery alters the area surrounding the original tumor and around the scar, and the modified microenvironment is more favorable for tumor recurrence. Intraoperative radiotherapy (IORT) is one of the novel strategies in breast cancer treatment. Irradiation during surgery has effects on the tumor microenvironment, abrogating the proliferative cascade induced by surgical wound healing. The aim of the present study was to determine the effect of IORT on angiogenesis factors, recurrence and overall survival of patients with breast cancer.

Methods: We collected serum and surgical wound fluids from 400 patients who underwent IORT and from patients after breast conserving surgery alone. Finally, TGF-β, EGF, FGF, DLL4 and VEGF were measured using ELISA.

Results: Our results demonstrated that IORT effect on angiogenesis factors especially DLL4 and improved recurrence-free and overall survival. It seems that TGF-β and EG can predict late stages in patients before surgery.

Conclusion: Delivery of IORT to the tumor bed alters the molecular composition and biological activity of surgical WF. This novel antitumoral effect could, at least partially, explain the very low recurrence rates. We suggest that inhibition of angiogenesis factors directly after surgery can increase survival and postpone recurrences.

Keywords: IORT, Angiogenesis, Survival, TGF-β, EGF, FGF, DLL4, VEGF

(18612)

Human amniotic epithelial cells exert anti-cancer effects through secretion of immunomodulatory exosomes

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Background: Human amniotic epithelial cells (hAECs) are among placenta-derived cells with known immunomodulatory properties mediated mainly through their secretome. We showed earlier that vaccination of mice with hAEC confer effective protection in a mice model of colon cancer. Here, we extended our previous observation by examining the potential anti-cancer effects of hAEC-derived exosomes in murine models of colon, breast and melanoma cancers.

Methods: hAECs were isolated from termed placentas and characterized by immunophenotyping with a panel of stem cells markers. Different sets of experiments performed to assess anti-cancer effects of hAECs including vaccination with live hAEC cells and hAEC lysate followed by tumor induction and orthotopic and heterotopic administration of hAEC and tumor cells. Exosomes were derived from cultured hAEC and the anti-proliferative and pro-apoptotic properties of hAEC exosomes were performed by colorimetric and flow cytometric assays, respectively. Protective vaccine and therapeutic effects of hAEC-derived exosomes were also assessed in cancer models mentioned above. Enhancement of CTL responses in mice and percentage of CD4+ and CD8+ spelenocytes following exosome injection was evaluated by Calcein AM (cAM) assay and flow cytometry.

Results: Isolated hAEC showed high purity and expressed stem cells markers. Live hAEC conferred effective protection against colon cancer and melanoma but not breast cancer in orthotopic administration. Heterotopic injection of hAEC and tumor cells abolished anti-cancer effect of hAEC. Mice vaccinated with hAEC lysate showed no protection against melanoma and colon cancer.hAEC-derived exosomes induced apoptosis in CT26 cells and inhibited their proliferation. Administration of Exosomes with tumor cells considerably reduced tumor size and substantially increased CTL responses in vaccinated mice. Exosomes did not alter frequency of spleen CD4+ and CD8+ cells.

Conclusion: It is mostly probable that hAEC mediate their anticancer effects through immunomodulatory exosomes. These findings shed light to the potential therapeutic application of hAEC-derived exosomes for cancer immunotherapy in the future.

Keywords: Stem cells, Human amniotic epithelial cell, Cancer, Exosomes, Cytotoxic T lymphocyte

(18614)

The role of Therapies directed to specific molecular targets in improving outcomes for patients with TNBC a systematic review

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Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease that accounts for 15-20% of all breast cancers. This represents the most challenging molecular subtype of breast cancer with higher rates of relapse, greater metastatic potential, and shorter overall survival compared with other major breast cancer subtypes.

Methods: By searching in related site Pubmed and google scholar and whit filter year 2016 to 2020

Results: This article will make a comprehensive review of standard therapies in the treatment of TNBC and seek to review the most recent efforts to classify TNBC based on the comprehensive profiling of tumors for cellular composition and molecular feature.

Characterization of genomic, transcriptomic, proteomic, epigenomic, and micro environmental alterations has expanded our knowledge of TNBC. According to this classification we will discuss about innovative drugs that have been effective for this particular kind of cancer, trying to compare their effectiveness with the standard therapies to help guiding treatment decisions and surveillance and improve risk stratification of patients.

Conclusion: Therapies directed to specific molecular targets have rarely achieved clinically meaningful improvements in outcomes of patients with TNBC and chemotherapy is still the common standard treatment of TNBC but other agents deserve our attention as well. For example TRPV2 expression based drugs like: Cannabidiol and Doxorubicin and the poly-ADP-ribose polymerase (PARP) inhibitors.This disease usually gains rapid resistance and unresponsiveness to chemotherapeutic drugs Active research tries to find actionable targets or other molecules to treat this aggressive disease with higher levels of success

Keywords: Cannabidol, Doxorubicin, the poly ribose polymerase(PARP)inhibitors, TNBC

(18615)

Optimization of anti-PSMA nanobody expression in E.coli and evaluation of its binding to prostate cancer cells

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Background: Nanobodies show attractive characteristics for tumor targeting in cancer diagnosis and therapy. Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer (PCa), so it is a promising target for molecular imaging and therapy. Nanobodies (single-domain antibodies, VHH) are the smallest antibody-based fragments possessing ideal properties such as high target specificity and rapid penetration in tumor sites. In the present study, we carried out a detailed study to find the optimal condition for expression of an anti-PSMA nanobody.

Methods: The construct was designed and synthesized by Biomatik company. The nanobody sequence contains c-myc and his-tag sequences for nanobody detection and purification, respectively. The construct was transformed into Top10 cells, confirmed by restriction enzyme digestion, and sub cloned into PET28a vector. The expression level of the anti-PSMA nanobody was evaluated at different hours (4, 8 and 16 hours), two host strains (Rosetta DE3 and Rosetta Gami2), different temperatures (30˚c and 37 ˚c), and different concentrations of IPTG (0.5mM,1mM,1.5mM). Then the expressed protein was analyzed SDS-PAGE and western blot with anti-c-myc mouse antibody and purified by Ni-NTA chromatography. After protein dialysis, LNCaP (PSMA +) and Du145 (PSMA-) cell lines were used for binding evaluation.

Results: SDS-PAGE and Western blot analysis demonstrated a protein band in the desired range, with a molecular weight of about 27 KD. Our findings showed that the highest nanobody expression was observed in Rosetta DE3 after 16 hours post-induction by 1mM IPTG, and in 37 ˚c. Flow cytometry results confirmed the nanobody binding to the target cell line, LNCaP.

Conclusion: The favorable biophysical and pharmacological properties of nanobodies, together with the ease of formatting them into multifunctional protein therapeutics leaves them ideal antibody-based therapeutics. The anti-PSMA nanobody was successfully expressed in E. coli expression system and is able to detect target antigens on cancer cells. This recombinant nanobody could be useful in cancer cell therapy approaches.

Keywords: PSMA, nanobody, expression optimization

(18616)

The Clinicopathological and Prognostic Value of immune checkpoints expression in colorectal cancer: A Meta-Analysis

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Background: blockade of immune checkpoint (ICP) has emerged as one of the most potential treatments for solid tumors. Programmed cell death ligand 1(PD-L1), a member of the B7 family of molecules, plays a crucial role in tumor immunobiology. However, the prognostic significance of ICP in colorectal cancer (CRC) patients remains controversial. This study aimed to inquire into the prognostic and clinicopathological significance of ICP in CRC via a meta-analysis.

Method: Articles in the field of immune checkpoint (Receptors and Ligands) related to CRC, was retrieved from Web of Science-Core Collection, Pubmed, Scopus, EMbase, Cochrane and Proquest without any limitation in language, publication year and document type. Synonyms of the concepts were defined according to MeSH (Medical Subject Headings) and EMTree (EMbase Subject Headings). Finally, in all of the subgroups (B7-CD28 superfamily, Immunoglobulin superfamily and TNF-superfamily), 121 and 24 articles imported in qualitative and quantitative synthesis respectively. The meta-analysis was performed using "metaprop" program in STATA version 15 (STATA, College Station, TX, USA). The meta-analysis resulted in pooled (overall) frequencies with a 95% confidence interval (95% CI). We also reported overall p-value. Heterogeneity of the included studies was assessed using Higgins' I^2 statistic and expressed as percentage.

Results: According to our meta-analysis, there was a significant association between TNM stage and TIM-3 (overall p-value=0.0013), PD-L2 (overall p-value=0.0213), PD-L1 (overall p-value<0.0001), PD-1 (overall p-value=0.0047), and Galectin-3 (overall p-value=0.0029). Association between TNM stage and CTLA-4 (overall p-value=0.92), B7H3 (overall p-value=0.36) was not significant.

Conclusion: Our meta-analyses revealed that expression of some ICP (such as Tim-3 and PD-L1) in CRC tissue was significantly correlated with the AJCC TNM stage of CRC, raising the possibility of the use of targeted anti-ICP therapy for CRC patients. In contrast, expression of CTLA-4 did not seem to be associated with patient outcome in our study.

Keywords: colorectal cancer, immune checkpoint, TNM stage

(18630)

Cancer immunotherapy strategy to strengthen Iran's position in international health services

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Introduction: Cancer immunotherapy is any therapeutic intervention that forces the immune system to eliminate malignancies and produces an anti-cancer response that is systemic, specific and tolerable and overcomes the basic limitations of traditional therapies. One of Iran's most prominent initiatives in this field has been the research and development of recombinant products and the establishment of active centers in bone marrow transplantation with the aim of improving the health of patients, which has put safety and treatment at the forefront of cancer research for several years. Cancer immunotherapy today, as one of the targeted therapies as opposed to chemotherapy, uses the body's own immune system, targeting only tumor cells and causing less damage to healthy cells and therefore fewer therapeutic side effects.

Methods: In this article, we try to review the latest achievements of Iran in the field of cancer immunotherapy and the priorities of presenting the patient market with the greatest impact and a new perspective for branding and marketing this type of treatment at the international level.

Results: A review of scientific papers and scientific and research data shows that Iran is the first and one of the top countries active in the field of immunotherapy in the region.over the years, clinical trials of various types of "cancer immunotherapy" have shown promising results that could be used to treat patients in the future. One type of cancer immunotherapy is called T-cell therapy, which involves taking the patient's T cells and using genetic engineering to modify their genetic code so that they can identify and target the cancer cells. This treatment was approved in early 2017 for the treatment of children with acute lymphoblastic leukemia. This new method has also been effective in treating other solid tumors such as breast and clone cancers, and Iran has been one of the leading countries in this field due to the efforts of researchers and the establishment of more than 17 bone marrow transplant centers in the country.

Conclusion: Many centers in different cities of Iran, including Tehran, Urmia, Shiraz, Mashhad, Kerman, Sari, Babol, Kermanshah, Tabriz, Ahvaz and Isfahan are set up and are engaged in bone marrow transplantation, which performs 1000 stem cell transplants annually. The results of research show that up to 96% of patients have a positive response to this treatment and among foreign patients it is one of the most popular treatments in the treatment of some cancers and can be attracted by attracting foreign patients to the country in addition to development Branding and strengthening Iran's position in international health services while earning foreign exchange earnings for the country took an effective step in increasing the number of active centers in other cities of the country and the budget for new research.

Keywords: Cancer immunotherapy, T cell therapy, Iran

(18656)

Third-generation nanobody-based VEGFR2-CAR T cells containing the long spacer improve immune response and kill VEGFR2+ tumor cells.

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Background: Cancer therapy with T cells expressing chimeric antigen receptors (CARs) has produced remarkable clinical responses in recent trials. Most of researches focused on optimized intracellular signaling domain to activate CAR T cell function. It was appreciated that for optimal CAR-T-cell recognition, the sequences between the scFv and the T-cell membrane should provide flexibility, and the length of this spacer region may need to vary depending on the target molecule. Here we analyze the influence of length of extracellular spacer domains on the function of CARs.

Methods: We constructed a third generation of nanobody based VEGFR2-CARs from VHH camelid that containing extracellular IgG1-Fc spacer domains of different lengths, CD28, OX40 and CD3ζ as the costimulatory and activating domains, in a lentiviral vector. T cells from healthy individuals were transduced efficiently with two different CARs.

Results: The VEGFR2-CAR T cell proliferated efficiently and produced more inflammatory cytokines, such as IL-2, IFN-γ when activated. VEGFR2-CAR containing a long 'Hinge-CH2-CH3' extracellular spacer conferred superior cytokines release of VEGFR2 tumor cell and induction of T-cell effector functions compared to CARs with short 'Hinge-only' spacers. The VEGFR2-CAR T cell effectively lysed VEGFR2+ cell line.

Conclusion: These results demonstrate that the VEGFR2-CAR T cell containing long 'Hinge-CH2-CH3' extracellular spacer induced superior T cell functions compared to CAR with short 'hinge only' spacer. This is a promising approach for the treatment of solid tumors.

Key words: VEGFR2, Chimeric Antigen Receptor (CAR), CAR T-cell, nanobody, Solid tumor, Spacer, Transduction

(18662)

Overcoming the UCB HSCs –Derived NK cells Dysfunctionality through Harnessing RAS/MAPK, IGF-1R and TGF-β Signaling Pathways

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Background: Natural killer (NK) cells differentiated from umbilical cord blood (UCB) hematopoietic stem cells (HSCs) may be more suitable for cell-based immunotherapy compared to NK cells from adult donors. This is due to opportunity to choose alloreactive donors and potentially more robust *in vivo* expansion. However, the cytotoxicity of UCB-HSC derived NK cells against cancer cells might be suboptimal. To overcome this obstacle, we attempted to generate NK cells with potent antitumor activity by targeting RAS/MAPK, IGF-1R and TGF-β signaling pathways.

Methods: The CD34+ cells isolated from human UCB mononuclear cells through MACS with purity of (≥90%) were used to be differentiated into NK cells. After 21 days of induction with SFTG36, IS721 and IL-15/Hsp70 media, NK cells phenotype was studied and their cytotoxicity against K562 human erythroleukemia cell and SKOV3 ovarian carcinoma cells was analyzed.

Results: The induced NK cells treated with SFTG36/I721 and SFTG36/IS721 growth factor cocktail expressed a phenotype with CD56+16+CD3- and NKG2D+ with mean fluorescence intensity (MFI) of 92.7%±1.45-168.00±19.20 and 93.23%±0.75-168.66±20.00 respectively. These NK cells once activated by IL-15, demonstrated a higher cytotoxicity against K562 (≥90%) ($P \leq 0.001$) and SKOV3 tumor cells (≥65%) ($P \leq 0.001$) compared to IL-15/Hsp70 activated NK cells.

Conclusion: The differentiation of ex vivo-expanded CD34+ cells through manipulation of RAS/MAPK, IGF-1R and TGF-β signaling pathways is an efficient approach for generating functional NK cells that can be used for cancer immunotherapy.

Key words: Umbilical Cord blood, Natural killer cells, Differentiation, Cytotoxicity, Cancer Immunotherapy

(18686)

AMG- 427 AND Immunotherapy in Acute Myeloid Leukemia

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Background: Acute myeloid leukemia is one of the hematological malignancies with poor prognosis. To date, therapy approaches to this leukemia has been chemotherapy and in some cases Hematopoetic stem cell transplantation (HSCT); Due to therapy-related complications like drug toxicity, Graft versus Host Disease(GVHD) and even leukemia relapse,novel therapies with more durable and deeper response like immunotherapy seems critical. One type of immunotherapy approaches is Bispecific T cell Engager (BiTE).It seems that AMG-427,as a BiTE, can correlate CD3 marker of host Tcells and FLT3 on the surface of leukemic blasts, activate host T cells against leukemic cells without MHC complex and eliminate the leukemic blasts.

Methods: To collect the data related to this article, we searched the Databases PubMed, Google Scholar, Science Direct, and Scopus. Among articles between 2018-2020 , 4 related articles were selected for abstract preparation.

Result: In our review, it became clear that a BiTE, anti FLT3/CD3 (AMG-427) is currently being evaluated in a clinical study (NCT03541369). In a normal bone marrow, FLT3 expression is restricted to a subset of HSC s, which makes FLT3 an attractive BiTE target. Studies show that FLT3 BiTE molecules have potent T dependent cell cytotoxicity (TDCC) in FLT3 positive cell lines cultured at a 1:10 ratio with human pan T cells for 48 hours. In animal studies, among mices injected with AML cells and intraperitoneally AMG-427, tumor growth was inhibited by 90 %.($n=10$, $P<0.0001$)

Conclusion: Despite advances in field of immune-oncology, many patients with cancer; specially leukemia still have critical unmet needs. BiTE therapies have the potential to provide deep and durable response by eliminating MRD. It seems that AMG-427,as a BiTE, might be an appropriate therapy to acute myeloid leukemia.

Keywords: Acute myeloid leukemia, AML, BiTE, immunotherapy,FLT3

(18688)

Interleukin 27; a novel candidate for cancer cytokine therapy

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Background:
Interleukin 27 (IL-27) is a new member of the IL-12 cytokine family, which is composed of Epstein-Barr Virus-Induced 3 (EBI3) and IL-27p28 subunits. IL-27 has potent anti-tumor features that suppress the tumor progression through various pathways with fewer side effects compared to conventional cytokines such as IL-6 and IL-12. High efficacy and low toxicity of IL-27 indicate the potential ability of this cytokine to serve as a promising agent in cancer immunotherapy.
IL-27Rα subunit of IL-27 receptor activates the STAT1 pathway and induces the anti-tumor responses through the induction of T-bet and CXCR3, which leads to Th1 activation and cytotoxic responses. Indeed, IL-27 inhibits the GATA-3 and Th2 responses consequently. Moreover, IL-27 suppresses angiogenesis by expressing the CXCL9 and CXCL10. It has been shown that IL-27 avoids tumor metastasis by inhibiting the associated genes with the endothelial mesenchymal transition (EMT). It should be noted that IL-27 is less toxic compared with other cytokines such as IL-12. Various studies have revealed the anti-tumor and anti-metastatic responses of IL-27 particularly in Non-small-cell lung cancer (NSCLC), breast, colorectal, prostate, and hematologic cancers, and melanoma.
Methods
This review article uses articles from PubMed, Google Scholar, Scopus, and web of science from 2004 to 2020. The primitive number of related articles was 74 from which 42 articles were reviewed.
Conclusion:
IL-27 is a potent anti-tumor agent, which suppresses the progression and metastasis of tumors, through various pathways. Toxic side effects of IL-27 are significantly less compared with conventional cytokines, which suggests IL-27 as an efficient alternative for conventional cytokines. Taken together, we conclude that IL-27 can be a promising candidate for cancer cytokine therapy.

Keywords: Interleukin-27, cancer, immunotherapy, cytokine therapy

(18752)

Title: LncRNA NEAT1 Knockout by using CRISPR/Cas9 strategy in cells derived from gastric, renal and prostate cancers

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Background: Long non-coding RNAs (LncRNAs) have been identified as important gene regulators and prognostic marker in diverse cancers. Although overexpression of lncRNA nuclear enriched abundant transcript 1 (NEAT1) has been demonstrated in several cancers such as gastric cancer (GC), renal cell carcinoma (RCC) and prostate cancer, up to now, its downregulation effect on cancer cells has not been elucidated. In this study we investigated the effect of NEAT1 systemic deletion by using CRISPR/Cas9 in three AGS, ACHN and PC-3 cell lines.

Methods: A plasmid system was designed to use CRISPR/Cas9 and E.coli strain TOP10F was used for cloning and plasmid propagation. After replication of the bacteria, new CRISPR-Cas9 vectors were extracted and delivered to the cells by using liposome-based transfection. NEAT1 and its associated gene's expression levels were evaluated by quantitative real-time PCR. Once liposome transfection was done, apoptosis of cancer cells was determined using Annexin test. Additionally, MTT and wound healing assays were applied for assessing cytotoxic effects of CRISPR-Cas9 vectors and migration of the cells, respectively.

Results: Our results showed that lncRNA NEAT1 is up regulated in the cancer cells and its knocking-down by CRISPR-Cas9 system decreased cancer cells survival and migration to a great extent. In addition, NEAT1 reduction increased apoptosis significantly. Evaluation of NEAT1 associated genes showed reduction in P21, BCL2 and BIRC5 expression after NEAT1 inhibition and increase in expression of tumor suppressor P53 and pro apoptotic factor BAX genes.

Conclusion: These findings showed that NEAT1 as an oncogene has important role in tumorigenesis and its knocking-down leads to reduction of the cancer cells survival rate and migration capacity and also increase their apoptosis. Up-regulation and down-regulation of genes associated with NEAT1, suggest that this lncRNA has a pivotal role in controlling cancer related genes. Therefore, using CRISPR-Cas9 system as a simple, high specific and low cost technology in systemic deletion of NEAT1 can be effective approach in cancer treatment. However, functional studies in animal models and also targeted drug delivery for CRISPR-Cas9 technology are needed to pave the way in reaching such a goal.

Keywords: NEAT1, AGS, ACHN, PC-3.

(18760)

Plant virus nanoparticles as an In Situ Vaccine for Boosting Anticancer Immunity in cancer

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Background: Oncoimmunotherapy is now an established and growing cancer therapy strategy. The mostly widely used approach, systemic injection of T cell checkpoint blockade antibodies, is effective in a minority of patients with the most responsive tumors and usage is generally limited by autoimmune side effects. Preclinical and clinical studies show that local and systemic antitumor efficacy is achievable by *in situ* vaccination (ISV) in which immunostimulatory reagents are directly administered into the tumor rather than systemically. One type of reagent with value for *in situ* vaccination is plant virus nanoparticles (PVNPs).
Methods: Here, we investigate a minimally-studied plant virus nanoparticle, alfalfa mosaic virus (AMV), for *in situ* vaccination treatment of 4T1, the very aggressive and metastatic murine triple-negative breast cancer model. **Results:** AMV used as ISV significantly slows down tumor progression and prolongs survival through immune mechanisms ($p < 0.001$).
Conclusion: Mechanistic studies show that *in situ* vaccination with AMV increases co-stimulatory molecules, inflammatory cytokines, and immune effector cell infiltration and downregulates immune suppressive molecules.

Keywords: Alfalfa mosaic virus (AMV), *in situ* vaccination (ISV), plant virus nanoparticle (PVNP), tumor microenvironment (TME)

(18777)

Oncolytic effect of Newcastle disease virus on different cancer cell lines

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Background:
Cancer is one of the leading causes of death in worldwide. Resistance to therapy is a major obstacle to cancer treatment. Oncolytic virus (OV) therapies of cancer are based on the use of replication competent, tumor selective viruses with limited toxicity. Newcastle disease virus (NDV), an avian paramyxovirus, is a promising OV and is inherently tumor selective and cytotoxic only to tumor cells. Here, we demonstrate the oncolytic activity of NDV vaccine strain in tumor cells compared to normal (non-malignant) cells.
Methods:
In the current study, the oncolytic NDV (B1 and lasota) was used to infect the mammalian tumor cell lines (HEKT293, Hela, LNCaP, Du145, PC3) and normal cell line (BHK). NDV-induced cytotoxicity and expression of pro inflammatory cytokines (IFN-β and IFN-γ) were analyzed using MTT assay and enzyme-linked immunosorbent assay (ELISA) kit, respectively.
Results:
Tumor cells (HEKT293, Hela, LNCaP, Du145, PC3) showed less viability than normal cell line at 72 hours post-infection. ELISA experiments showed that NDV mainly induced the secretion of IFN-γ in both normal and tumor cells. In addition, NDV infection induced the production of IFN-β only in cancerous cell lines.
Conclusion:
Our findings indicate that wild-type NDV strains selectively kill tumor cells with no effect on normal cells. Therefore, our results confirmed that the B1 and lasota NDV could be introduced as a powerful candidate for the therapy of cancer.

Keywords: Oncolytic virus, Cancer Immunotherapy, Newcastle disease virus

(18797)

Evaluation of PD-1 Checkpoint on the NK Cells surface in Recurrent ALL Patients

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Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy in the world. Recurrent ALL disease do not respond to routine chemotherapy and bone marrow transplantation and they are still associated with a poor prognosis. Inhibitory checkpoints play an important role in the exhaustion of cytotoxicity function of Natural Killer (NK) cells against leukemic blasts (Pre-B and T lineage). The aim of this study was to evaluate the expression of inhibitory checkpoint expression of Programmed Death protein-1 (PD-1) on the NK cell surface in recurrent ALL patients. in-1 (PD-1) on the NK cell surface in recurrent ALL patients.

Methods: We obtained 5 peripheral whole blood samples from relapsed ALL patients (4 patients B-type and 1 patient T-type ALL, ranging from 5-13 years) and 5 samples from normal peoples (ranging from 3-16 years). Samples centrifuged gradient over Ficoll at 800 × g for 20 min at 4 °. NK cells ($CD3^{-}CD56^{+}CD16$ was isolated with positive selection using FACS methods. NK cells was characterize phenotypically by flow cytometry. Then, the expression level of PD-1 on the NK cell surfaces of each group was measured using BD caliber. The analyses of data were done by FlowJo (7.6.1) software.

Results: Assessment of NK cells purity showed 90% purity. Recurrent patients demonstrated higher PD-1 expression on $CD3^{-}CD56^{+}CD16^{+}$ NK cells (median, 21.633%; SD: 2.919) compared with controls (median, 5.000%; SD: 2.031; $P = 0.05$). Statistical analysis showed a significant increase in PD-1 expression between recurrent ALL patients with the control group.

Conclusion: Expression of PD-1 inhibitory checkpoint on the NK cell surface in patients (both of B and T types) increased compared with control group. This study has revealed that patients with recurrent ALL could express PD-1 to allow cancer cells to evade the immune system. Elevated PD-1 expression causes exhaustion of NK cells. Thus, the cytotoxicity function of NK cells decrease. It is suggested that by PD-1 blocking, can be increase the cytotoxicity function of NK cells; Therefore, PD-1 marker can be considered as a good marker for the treatment of ALL in the future.

Keywords: NK cells, Inhibitor checkpoint, PD-1, ALL, Flow cytometry

Congress Abstracts

COVID-19 Immunology & Immunopathology

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(16586)

Apoptosis and immunophenotyping of peripheral blood lymphocytes in Iranian COVID-19 patients; clinical and laboratory characteristics

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Background: A novel member of human coronavirus, named SARS-CoV-2, has been recently recognized in China and rapidly spread worldwide. Studies showed the decreasing of peripheral blood lymphocytes in a majority of patients. In this study, we have reported the clinical features, laboratory characteristic, the frequency of peripheral blood lymphocyte subpopulations and their apoptosis pattern in Iranian COVID-19 patients.

Methods: Demographic and clinical data of 61 confirmed cases with COVID-19 on admission at Imam Khomeini Hospital from March 2020 to April 2020 were collected and analyzed. Peripheral blood mononuclear cells were isolated from all samples and the apoptosis pattern was evaluated using Annexin V/propidium iodide method. The frequency of lymphocyte subsets including T-CD4$^+$, T-CD8$^+$, NK cells, B cells, and monocytes was measured in all patients and 31 normal controls by flowcytometry.

Results: Our findings demonstrated that the percentage of lymphocytes, CD4$^+$ T cells, and CD8$^+$ T cells were decreased in COVID-19 patients compared to control group. Regarding the clinical severity, the number of lymphocytes, CD4$^+$ T cells, CD8$^+$ T cells, and NK cells were also decreased in severe cases when compared to mild cases. Finally, our data have also indicated the increasing in apoptosis of mononuclear cells from COVID-19 patients which was more remarkable in severe cases.

Conclusion: The frequency of immune cells is a useful indicator for prediction of severity and prognosis of COVID-19 patients. These results could help to explain the immunopathogenesis of SARS-CoV-2 and introducing of novel biomarkers, therapeutic strategies and also vaccine development for this infection.

Keywords: COVID-19, Iran, lymphopenia, lymphocyte subsets, apoptosis

(16618)

Exhaustion Markers in CD8 T Cells of COVID-19 Patients: TIM-3 and CD39, but not PD-1

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Background: During viral infection, inhibitory receptors playa key role in regulating CD8 T-cell activity. The objective of this research was to investigate programmed cell death protein 1 (PD-1), mucin domain-containing protein-3 (TIM-3), and CD39 exhaustion markers in CD8 T cells of new coronavirus disease-2019 (COVID-19) patients.

Methods: A total of 44 patients with COVID-19 (17 subjects in a critical group and 27 patients in a non-critical group) and 14 healthy controls, who were admitted to Hospitals in Babol, were recruited to the study. After isolating of the peripheral blood mononuclear cells (PBMCs), we compared the phenotype of CD8 T lymphocytes expressing PD-1, TIM-3, or CD39, both alone and in various combinations.

Results: The findings showed that the percentage of $CD8^+$ cell counts was significantly lower in non-critical patients**.** Critical and non-critical patients were more likely than healthy controls to have an escalated frequency of $CD8^+$ $TIM\text{-}3^+$**,** $CD8^+$ $CD39^+$, and $CD8^+$ $TIM\text{-}3^+$ $CD39^+$ cells. No significant differences were observed between all groups in the $CD8^+$ $PD\text{-}1^+$ cell counts**.** There was also no difference between three groups regarding the counts of $CD8^+$ $TIM\text{-}3^+$ $PD\text{-}1^+$, $CD8^+$ $PD\text{-}1^+$ $CD39^+$, and $CD8^+$ $TIM\text{-}3^+$ $PD\text{-}1^+$ $CD39^+$ cells**.** The counts of non-exhausted cells were significantly lower in critical and non-critical individuals compared to the healthy individuals' value**.**

Conclusion: In summary, our study suggested the appearance of TIM-3 and CD39 as exhaustion markers in CD8 lymphocytes of SARS-CoV-2 patients. Critical patients have more frequency of CD8+ $TIM\text{-}3^+$ and $CD8^+$ $TIM\text{-}3^+$ $CD39^+$ lymphocytes than non-critical patients, implying that immunological dysfunction (T cell exhaustion) may exacerbate the patients' status. Thus, preventing T cell exhaustion may contribute to better function of the immune system against COVID-19 patients.

Keywords: COVID-19, Exhausted Cell, TIM-3, CD39, PD-1

(16776)

Reduced frequency of T helper 17 and T helper 1 cells and their association with critical coronavirus disease-2019

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Background: There is very little knowledge about the immune responses, particularly cellular immunity to coronavirus disease-2019 (COVID-19). The main objective of this study was to evaluate the frequency of T helper (Th) cell subtypes, including Th1, Th17, and Treg cells, in moderate-to-severe and critical COVID-19 patients compared to healthy controls.

Methods: Twenty-nine moderate-to-severe and 13 critical patients confirmed for COVID-19, and 15 healthy subjects were included in this study. Interferon-γ-producing (Th1) and Interleukine-17A-producing (Th17) and Treg cells in peripheral blood were measured with flowcytometry.

Results: The frequency of Th1 and Th17 was significantly decreased in critical patients compared to healthy subjects (aMD: -2.76 and -2.34) and moderate-to-severe patients (aMD: -1.89 and -1.89), respectively ($p < 0.05$). Differences were not significant between moderate-to-severe patients and healthy subjects for both Th1 ($p = 0.358$) and Th17 ($p = 0.535$), respectively. In contrast, significant difference was not observed between study subjects regarding the frequency of Treg cells. Patients with critical COVID-19 had a markedly lower Th1/Treg and Th17/Treg ratios compared with the controls and moderate-to-severe cases.

Conclusion: Our study showed a dysregulated balance of Th1 and Th17 cells and its relation to the severity of COVID-19.

Keywords: Coronavirus disease-2019, T helper 1, T helper 17, Treg

(18207)

Association between allergic diseases and COVID-19 in 400 Iranian patients

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Background: Coronavirus disease 2019 (COVID-19) is spreading rapidly in the world. Respiratory allergic diseases may role as a predisposing factor for the severity of the disease. The aim of this study was to investigate the clinical characteristic and allergy comorbidity and its association of the patients with COVID-19.

Methods: Demographic data, clinical symptoms and signs of the patients and having underlying diseases were registered. Allergic diseases identified by using the standard GA²LEN questionnaire. The severity of COVID-19 was assessed by visual analog scale (VAS) and ICU admission. Lab and radiologic findings were obtained from the electronic medical record system of the hospital.

Results: Of 400 patients identified with COVID-19, 158 (39.5%) had allergic diseases as comorbidity. And, it was reverse associated between having allergy and the severity of COVID-19 as needed for admission in ICU (P= 0.005, relative risk, 0.96; 95% CI, 0.77-1.19). The frequency of asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, chronic urticaria, and food allergy were 7.3%, 16%, 1.8%, 5%, 10% and 13.3%, respectively. Only, allergic rhinitis was reverse associated with the severity of COVID-19 (P= 0.02, relative risk, 0.96; 95% CI, 0.77-1.19). In addition, the data showed that 23.5% of the patients with COVID-19 had both allergic and other underlying diseases. And, these comorbidities were not associated with the severity of COVID-19 status (P> 0.05). Additionally, this findings revealed that 43% of the total patients present hypoxemia, and 93.5% had chest CT scan involvement. Interestingly, the patients with allergic diseases were significantly lower present hypoxemia and chest CT involvement (P= 0.002 and P= 0.003, respectively).

Conclusion: This study showed that allergic diseases were not found to be a predisposing factor for SARS-CoV-2 infection. Interestingly, the patients with AR developed better symptoms of COVID-19 and these patients admitted in ICU significantly lower than non-AR patients. Moreover, comorbidities of allergic and other underlying diseases in the patients with COVID-19 were not associated with the severity of the disease.

Keywords: SARS-CoV-2, COVID-19, allergic diseases, underlying diseases

(18218)

Patients with Covid 19 have significantly reduced CH 50 activity compared with healthy individuals

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Background: SARS Coronavirus 2 (Covid19-) a new virus that started in China and then spread around the world has caused the severe acute respiratory syndrome. Documented evidence has shown that the immune system is involved in the pathogenesis of this disease, markedly in causing inflammation. One of the key components of the immune system is the complement system, which has been shown to increase its activity in inflammatory diseases and as a result of damage caused by the activity of its components.

Methods: In the present study, the activity of the complement system in the classical pathway was measured by CH50 test in patients with Covid19- and healthy individuals. Fifty three patients whit real-time PCR test positive for SARS Covid-2 and hospitalized were included in the study. The mean age of these patients was 42.06 (18.7±) and 39.6% and 60.4% respectively were women and men. 53 healthy individuals were added to the study as a control group. ELISA kits were used to measure CH50 activity .The results were analyzed using SPSS 26 software and Graph pad prism 8.4.3.

Results: Statistical tests showed a significant relationship between CH50 activity and Lymphocyte (P = 0.007). In the covid-19 patients with lymphopenia the mean of CH50 was higher than the other covid-19 patients. Also, a significant relationship was seen between CRP serum level and CH50 activity (P = 0.0002) while the mean activity of CH50 in patients with third plus CRP (CRP= 3+) was higher than other groups. Comparison between patient and control groups show that the mean activity of CH50 in-patient group significantly decreased (113.58 vs 171.7) (p = <0.0001).

Conclusion: Decreased CH50 activity in patients with Covid 19 compared with healthy individuals. Moreover, a group of patients with lymphopenia and CRP positive had increased levels of CH50 activity than other patients groups.

Keywords: Complement system, Covid ,19-CH50

(18757)

Evaluation of the frequency of HLA- A*02 and - A*30 alleles in moderate and severe COVID-19 patients in Khuzestan province, Iran

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new strain of betacoronavirus, is affected a huge of human populations. Little is known about the HLA variation role in the immune response to this highly pathogenic virus.
Materials and Methods: Between 20 May to 1Augest 2020, genomic DNAs from blood samples of 109 COVID-19 patients were genotyped for the HLA- A*02 and - A*30 alleles of using Single-strand conformation polymorphism PCR (SSCP-PCR).
Results: There was no association between the HLA- A*02 and - A*30 alleles and the susceptibility to COVID-19 infection. Our results revealed the HLA –A*30 allele is conversely associated with the severity of COVID-19. As this allele may decrease the severity of COVID-19 in COVID-19 patients with moderate status. While, the same status was observed for HLA- A*02 (but this difference isn't significant in patients studied). Additionally, current study suggests that the HLA-A*02 and/or - A*30 coincidence (P-value < 0.05, odds ratio: 0.41, 95% confidence interval) will attenuate the severity of COVID-19 in cases.
Conclusions: Our findings revealed that HLA-A02, -A30 coincidence may impact positively, and indicate moderate forms of COVID-19 infection.

KEYWORDS: HLA, allele, COVID-2019, Iranian population, susceptibility, severity

(18627)

Differential antibody response to SARS-CoV2 antigens in convalescent and deceased Iranian COVID 19 patients

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Background: SARS-CoV-2 virus causing COVID-19 infection has imposed critical challenge to global public health. Kinetics of SARS-CoV-2-specific IgM and IgG responses in COVID-19 patients is a major subject to understand the importance of virus specific humoral immunity. We investigated IgM and IgG responses against SARS-CoV-2 nucleocapsid (NP) and receptor binding domain (RBD) of spike protein in two groups of convalescent and deceased patients.

Methods: Blood samples from 101 COVID-19 patients were collected. The levels of IgM and IgG specific to NP and RBD proteins were detected by ELISA.

Results: NP- and RBD-specific IgM was higher in deceased patients in comparison to convalescent patients, while there was no significant difference in NP- and RBD-specific IgG between the two groups. A significant correlation was observed between IgG and IgM titers against RBD and NP, in both groups of patients.

Conclusion: These results argue against impaired virus specific antibody response in deceased patients and in accordance with other studies which showed reducing germinal center, suggest inefficient antibody class-switching in these patients.

Keywords: SARS-CoV-2, Nucleocapsid, Receptor-binding domain, Antibody

(15507)

Intubation Rate in COVID-19 Patients: a brief review

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Background: Tracheal intubation is the placement of a flexible plastic tube into the trachea to maintain or keep an open airway. COVID-19 includes a wide range of symptoms such as fever, cough, and tiredness. Also, some complications of COVID-19 like respiratory failure and respiratory distress are life-threatening, therefore; they need conservation and supportive treatment strategies.

Methods: This review study aimed to investigate the rate of intubation in COVID-19 patients. Studies with inclusion criteria from 2020 were included in this study.

Results: 15 studies were included in this review. Studies were conducted in the USA, Spain, Italy, China, and Iran. Most patients were intubated in the intensive care unit. Rapid sequence induction was mostly used for intubation. According to the previous studies the intubation rate reported 5 to 88 %.

Conclusion: The most important reasons that require endotracheal intubation were hypoxia, respiratory distress, loss of consciousness, and cardiopulmonary arrest. Studies showed that during a pandemic, due to overcrowding in the intensive care unit, tracheostomy might be a suitable solution for patients to get off the mechanical ventilation, reducing the respiratory effort in patients with limited pulmonary reserves, shortening the dead space, and enabling the suctioning of accumulated mucous. The discrepancy in statistics may be due to the variety of study population, study environment, or intubation criteria. There were a few shreds of evidence regarding extubation. Due to the lack of definitive treatment for COVID-19, and the empirical treatments based on research, it seems that a comprehensive intubation algorithm in covid-19 patients is extensively required.

Keywords: Intubation, COVID-19, Intensive care unit, pulmonary disease, infectious disease

(15510)

Asthma and COVID-19: Asthma as Risk Factor for COVID-19 infection? A systematic review

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Background: Asthma is an inflammatory pulmonary disease. Cellular immune responses are the most frequent immunological response in asthma. Concerns about risk factors for infection have increased with the COVID-19 pandemic. Primary studies indicated that children with accompanying comorbidities such as asthma may be at greater risk of COVID-19 comparable to adults with similar comorbidities.

Methods: This review study aimed to investigate the association between asthma COVID-19 infections. Google scholar database on October1st, 2020 was used to identify eligible articles. The Keywords used to find papers: (Asthma*) and (COVID-19*), (Asthma*) and (COVID-19*) and (risk factor*). The publication time was limited to 2020 onward. A total of 6780 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full-texts. Reports on the topic of asthma as risk factor for COVID-19 infection were included in this review.

Results: 29 studies were included in this review. Given that overexpression of ACE2 in rhinovirus infections, and activation of ACE2 regulates many antiviral responses to cytokines. This may lead to cytokines exacerbation which is COVID-19 pathological response. These results suggest that viral infections that cause worsening of asthma show synergistic bio molecular interactions due to COVID infection. Besides, people with asthma have a delayed or deficiency in the antiviral immune response, with deficiency and delay in lung cell interferon (IFN)-α,5 IFN-β6 and IFN-λ7 responses reported in many studies, and deficiency of the latter IFN clearly related to increased asthma exacerbation.

Conclusion: Clinical studies in different countries showed that, asthmatic patients with COVID-19 infection are small fraction of all infected patients. Although patients with asthma are vulnerable to respiratory infections such as rhinoviruses, there is no conclusive evidence to support an association between asthma and COVID-19 infection. Various studies suggested that asthmatic patients continue medications particularly inhaled corticosteroids and avoid allergens.

Keywords: COVID-19, asthma, risk factor, ACE, infectious disease, pulmonary disease

(16574)

Red cell distribution width (RDW): a prognostic indicator of severe COVID-19; inexpensive but valuable indicator

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Background: Novel Coronavirus outbreak has posed a global threat. While the infection appears to be mild in most patients, considering its high rate of transmission, a large number of people are at risk of developing severe to critical illness in total which makes prognosis studies a priority.
Methods: A total number of 204 inpatients diagnosed with COVID-19 including 122 men and 82 women (Mean age: 58.83±15.93 years old) treated at Imam Reza Hospital, Mashhad, Iran were included in the study. Patients were divided into severe and moderate groups according to their clinical signs and examinations and pulmonary imaging features. Demographic Data, laboratory test results, treatments, patients' complications and outcome were recorded. Mann-Whitney U test and spearman correlation coefficient (r) were performed to assess RDW correlation with severity and serious complications in patients including intensive care unit (ICU) admission, shock, secondary infections, intubation, length of hospitalization and death. Receiver operating characteristics (ROC) curves analysis was carried out to define the reliability of RDW as a predictive indicator in severe COVID-19.
Results: The results showed statistical significant correlations between high levels of RDW and developing secondary infections and longer hospitalization (P values ≤0.001). The optimal cutoff for RDW to predict the length of hospitalization (≤ 7 days or more than 7 days) was estimated to be 14.65% with 94% sensitivity and 71.3% specificity. The area under curve was calculated to be 0.895 through Roc curve analysis.
Conclusion: High predictive value of RDW, a routine blood test parameter, could be used in diagnosing COVID-19 patients at higher risk for developing secondary infections and longer hospital stay which in turn helps with better management of the disease.
Keywords: red blood cell distribution width; coronavirus disease-19; prognosis; secondary infection.

(16700)

Evaluation of death rate of children under 5 years of age with Covid 19 in the country since the outbreak of the disease

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Background: Covid 19 is an acute respiratory infectious disease caused by a new coronavirus. The World Health Organization (WHO) has declared the infection a pandemic. The incidence, severity and prognosis of this disease in children are different compared to adults. The aim of this study was to investigate the mortality rate of children under 5 years of age with Covid 19 in the country since the outbreak of the disease.

Method: In this cross-sectional study, all information of children under 5 years of age who reported coronary death was analyzed.

Results: According to the results, 40 cases, ie 5.77 per thousand of children with Covid, 19 died, of which 57% were girls and 43% were boys. 99% were mechanically ventilated, 71% had Wellers fever, 75.3% irritability, 62.44% dizziness, 72.72% cough, 55% conjunctival redness, 55% abdominal pain, 62.34% diarrhea, 62.34% nausea and vomiting, and 88% underlying disease.

Conclusion: Coronary mortality is higher in children with underlying disease, so educating families about health protocols and community sensitization to Covid 19 infection and death in children under 5 will have a better effect on reducing morbidity and mortality.

Keywords: Covid 19, children under 5, country

(16733)

Understanding the Clinical and Demographic Characteristics of Second Coronavirus Spike in 192 Patients in Tehran, Iran: A Retrospective Study

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Background: During the last months of coronavirus pandemic, with all those public restrictions and health interventions, the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears now to have been raised in some countries around the world. Iran was one of those first countries facing the second wave of coronavirus, due to the lack of appropriate public restrictions because of economic problems the country is facing. This study aimed to investigate the clinical and demographic characteristics of severe cases and non-severe cases of Coronavirus Disease (COVID-19) in 192 patients in Tehran, Iran, between June 16 and July 11, 2020.

Methods: This retrospective study included 192 patients with COVID-19. The diagnosis was confirmed using a real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2. The patients were divided into severe cases (n = 82) and non-severe cases (n=110). Demographic and clinical characteristics were compared between the two study clusters.

Results: The mean age of the 192 patients diagnosed with COVID-19 was 54.6 ± 17.2 years and the most common presenting symptoms were a persistent cough (81.8%) and Fever (79.7%). The logistic regression model revealed that age, BMI, and affected family members were statistically associated with severity. Patients with complicated conditions of disorders faced more hospitalization days and medical care than the average statistical data.

Conclusion: There were demographic and clinical differences between severe and non-severe clusters. As the coronavirus spike in the case and death reports from June 2020, we observed the rise in the incidence of severe cases, where 42.7% (82/192) of cases resulted in severe conditions.

Keywords: Cluster Analysis, Human Characteristics, Viral, COVID-19

(16752)

Corona virus from virology to diagnosis and treatment

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Background: Virological information: from 2002 until now, corona virus changed from a common cold responsible, to a serious pandemic. *Coronaviridae* family classified in α, β, γ and δ. SARS-CoV-2 is a βcoronavirus with envelop (bilayer phospholipid, spike, envelop and hemagglutinin-esterase proteins), phosphorylated nucleocapsid proteins, large positive sense SS RNA. Viral infection mechanisms and its outcomes: trimeric spike protein that bind to ACEII there on several organ cells, after binding, humanTMPRSS2 protease cleave and activate spike then virus enter to the host cell, released its RNA and subsequently translation and replication result in virion formation and exocytosis. This virus affects immune system and result in, lymphopenia, TCD4 and CD8 over activation and reduction, cytokine storm that cause organ failure and ARDS.

Diagnosis: by nucleic acid tests, based on RT-PCR and NGS, nucleic acid detection kits and nucleic acid test papers can detect SARS-COV2 RNA but have false negative problem. More than serological diagnosis tests, CRISPR/Cas13 System and imaging technology like chest radiography and CT scan can help in detection.

Treatment: therapeutic strategies targeted 1) entrance and replication of virus like Remdesivir, Lopinavir/Ritonavir, Hydroxychloroquine, IFNα, IFNβ and 2) limitation of inflammatory response by corticosteroids, Tocilizumab.

Conclusion: in this article we disgust about some virological information, diagnostic tests and therapeutic strategies in COVID-19 pandemic. Understanding virological features, infection pathway, and viral pathology can affect diagnostic tests and therapeutic strategies that determine globally fate of this pandemic disease.

Keywords: covid-19, coronavirus, diagnosis, treatment.

(16791)

A review of the relationship between COVID-19 and Leukemia

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Background: The coronavirus disease 2019 (COVID-19) infection was first identified in December 2019 in Wuhan, China and it is an evolving pandemic with high morbidity and mortality. Leukemia is a group of cancers that usually start in the bone marrow and cause a large number of abnormal white blood cells to form. In this study, the relationship between leukemia and COVID-19 was investigated.
Methods: In this study, the method of library collection, search of different texts and valid scientific articles was used.
Results: Coronaviruses are positive single-stranded RNA viruses widely distributed in humans and animals. Leukemia is a type of Blood cancer. Studies have shown that patients with leukemia have a significantly higher risk of death, especially if they have recently received chemotherapy. In a study, more than 36 percent of the 224 people diagnosed with leukemia who were hospitalized with the coronavirus died. In Oxford University studies, older people with leukemia show more severe symptoms of COVID-19 than other cancer patients. In a study, when researchers ruled out patients' age, gender and other personal characteristics, people with leukemia were twice as likely to die after being infected with the coronavirus as a normal person with cancer. This information can help physician choose the best way to treat each person's cancer during the outbreak of COVID-19.
Conclusion: Recent studies by physicians show that patients with leukemia are at higher risk of death than other patients with COVID-19. Recurrent infections, bleeding, bruising, fever, chills, sudden fatigue, and weight loss are some of the most important symptoms of this disease, which weakens the immune system against the virus. Therefore, People with leukemia have to try hard to protect themselves because their immune systems are compromised by the spread of during the outbreak of COVID-19 and the lack of definitive treatment.
Keywords: COVID-19, Leukemia, relationship, Risk

(16890)

Construction of a SARS-CoV-2 RNA/miRNA/mRNA network to explore potential pathogenesis of SARS-CoV-2 through the RNA network disruption in Human cells

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Background: SARS-CoV-2 is a positive-single stranded RNA (+ssRNA) virus which caused COVID19 pandemic. MicroRNAs (miRNAs) are small, noncoding RNAs that play role in the regulation of gene expression in various organisms. In this paper, I presented the results of a predictive analysis to identify miRNAs that may bind the SARS-CoV-2 RNA. Then, I used the experimentally validated miRNA interactions with endogenous mRNAs to identify the host's miRNA/mRNA regulatory network affected by SARS-CoV-2 infection, considered SARS-CoV-2 RNA as a competing RNA. Finally, I evaluated the impact of such interactions on the signaling pathways profile of cells infected with SARS-CoV-2.

Methods: The whole sequence of SARS-CoV-2 RNA was extracted from NCBI Reference Sequence ID: NC_045512 as the reference sequence of SARS-CoV-2. MiRDB/target mining was used to search miRNAs with the ability to target SARS-CoV-2 RNA. According to the result a list of 900 predicted miRNAs targeting the submitted 29903 nt SARS-CoV-2 RNA sequence was achieved. Then experimentally validated mRNAs targets of these miRNAs gained from miRTarBase/Functional MTI. Finally signaling pathways of these the mRNAs achieved by SPEED.

Results: At result it seems that SARS-CoV-2 through RNA/RNA interactions can affect different kind of signaling pathways included; TNFa, MAPK, TGFβ, TLR, IL-1, JAK-STAT, PI3K, Wnt, H2O2, and VEGF. Notably the most significant affected pathway was TNFa (P-Value =2.81e-34, and FDR= 9.78e-34) which is critically linked to the inflammation. Therefore SARS-CoV-2 RNA/miRNA/mRNA interaction possibly could activate inflammation related signaling pathway.

Conclusion: The presented results indicate that dysregulation of RNA network during SARS-CoV-2 infection may contribute to uncontrolled inflammation in COVID19. More insilico and experimentally investigations for the RNA networks could shed light on virus-host interaction molecular mechanisms. The wide spectrum actions of miRNAs and their possible roles during SARS-CoV-2 infections showed new opportunities for the development and improvement of COVID19 diagnosis and therapy.

Keywords: SARS-CoV-2, COVID19, MicroRNAs, RNA network

(17953)

Correlation between clinical manifestations of Covid 19 patient's and antibody response

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Background: Sars-cov2 was identified in 2019 as a member of the beta-corona family of viruses. The structure of this virus includes structural proteins such as spike (s), E (envelope), M (membrane), N (nucleocapsid), and non-structural (nsp 1-16). Research has shown that IgM and IgG antibodies are made against each of the structural proteins in patients' bodies, which have been identified by various methods such as Chemiluminescence (CLIA), ELISA, Lateral flow immunoassay (LFIAs).
Since patients with Covid 19 have different clinical manifestations, including Mild, Moderate, and Severe, various studies have examined the differences in antibody responses to Covid19 antigens in groups with different clinical manifestations, such as the study indicated that in both severe and mild groups between 13 to 21 days after the onset of symptoms have seroconversion and all 3 patients have antibodies against D, S1, RBD.
In the Convalescent patients, 94.6% of the mild group had specific anti-SARS COV2 S1-IgG and also 100% of the severe group have it. The Baoqing Sun, et all Study also showed that in non-ICU patients there is a strong correlation between S-IgG and S-IgM levels, but in ICU patients there is no correlation between these antibodies, although between S-IgG and N-IgG levels has been strongly correlated in non-ICU patients. In this study, the seropositive rate in the first week in non-ICU patients, they found that 41.7% N-IgM, N-IgG, S-IgG, and 58.3% S-IgG, so both are needed for a more accurate diagnosis. Studies until now have shown that many variables can affect the antibody response in patients, including clinical manifestations, type of antigen, and the time to the onset of symptoms. The purpose of this review study was to investigate the role and effect of these variables on the level of antibodies in patients and in the timely diagnosis of the disease stage.
Keywords: Covid19, antibody, antigen, clinical manifestation

(18000)

Immune-Inflammatory and other laboratory parameters in detection of COVID-19 in hospitalized cases: with positive RT-PCR

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Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), known as the cause of the pandemic in 2019, originated from China. The Symptoms vary in range from mild to severe, from a dry cough to shortness of breath. Among laboratory findings of this disease Lymphopenia, Neutrophilia, and elevated level of Lactate dehydrogenase (LDH), Ferritin, etc. were reported. This study aims to find a significant correlation between the laboratory findings and the data retrieved from hospitalized patients diagnosed with COVID-19.

Methods: An epidemiological study on a group of hundred patients (n=100) from Imam Reza hospital in Mashhad showed the correlation between the inflammation factors and SARS-CoV-2. The COVID-19 in patients was diagnosed by Real Time Polymerase Chain Reaction (RT-PCR) method, utilizing the nasopharyngeal swab specimen. The inflammatory factors evaluated in this study were Erythrocyte Sedimentation Rate (ESR) and C - reactive protein (CRP) in the blood samples of patients. Besides, the Complete Blood Count (CBC) of these samples were examined, and the results were recorded.

Results: Obtained data of this study were analyzed using IBM-SPSS26. As a result of this analysis, the leukocyte count in the CBC panel showed a mean of 9.101± 4.13 WBCs per microliter. Also, the differential count of Neutrophils and Lymphocytes were 82.887±8.28 and 12.506±6.87 percent, respectively. Likewise, analysis of the CRP illustrated the mean of 116.860±65.19 mg/L, and the mean of ESR was 51.93±32.47 mm/h.

Conclusion: The analysis of a hundred cases indicated an increase in both ESR and CRP and revealed a significant positive correlation between the rises of these factors in patients with COVID-19. Also, more investigations on CBC results showed a decrease in the differential count of Lymphocytes and an increase in the differential count of Neutrophils. All things considered; this study evidence the inflammation factors notably correlate with each other in COVID-19 cases.

Keywords: SARS-CoV-2, COVID-19, CRP, ESR, CBC, Neutrophils, Lymphocytes, leukocytes

(18062)

A Review of the Effects of Covid-19 Based on Immunological Indices

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Introduction: With the worldwide spread of the novel Severe Acute Respiratory Syndrome Coronavirus-2 resulting in declaration of a pandemic by the World Health Organization on March 11, 2020, the SARS-CoV-2-induced Coronavirus disease-19has become one of the main challenges of our times. Transmission of SARS-CoV-2 is mediated mainly via respiratory droplets from an infected person. If people get this disease. The average incubation time until the onset of COVID-19 is 4-11days.Typical symptoms of COVID-19 include dry cough, fever, myalgia, headache, anosmia, and ageusia. Innate immune sensing serves as the first line of antiviral defense and is essential for immunity to viruses.
Methods: In this study, which was conducted in 1399, articles indexed in the databases of PubMed and Google Scholar. The obtained articles were reviewed.
Discussion: Coronaviruses belong to two subfamilies, Coronavirinae and Torovirinae, in the family of Coronaviridae. Currently, there are seven strains of coronaviruses that are known to infect humans, including the recently identified SARS-CoV-2.Belonging to the β-coronavirus genus, SARS-CoV-2 is the pathogen that causes the new infectious respiratory disease. Coronavirus binds to the ACE2 molecule and enters cells where it triggers a series of signaling pathways.ACE2 is expressed in almost all organs in the body. The recognition of pathogen associated molecular patterns results in subsequent cytolytic immune responses, mainly through the type IFN and natural killer cells. Expression of T1IFN and down-stream signals modulate cell responses and reprogram cells into an “anti-viral state”, subsequently promoting infection control and pathogen clearance.
Conclusion : binding of SARS-CoV-2 to ACE2 downregulates its expression and impacts thereby on its main function, the regulation of the renin-angiotensin system. This innate immune activation and resultant expression of pro-inflammatory cytokines, adaptive immune cells become involved in the host’s defense against viral infections. The anti-viral immune response is crucial to eliminate the invading virus, but a robust and persistent anti-viral immune response might also cause massive production of inflammatory cytokines and damage to host tissues.
Keywords: Immunology, Covid-19

(18078)

Risk factors for mortality of 557 adult patients with COVID 19 in Babol, Northern Iran: a retrospective cohort study

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Background: This study aimed to investigate the risk factors for mortality in patients with COVID-19.

Methods: We included 121 deceased and 436 discharged cases with COVID-19 in Babol, Northern Iran, for this retrospective cohort study. The cases were between March 1 and April 1, 2020.

Results: Multivariate Poisson regression analysis revealed that older age (aRR: 1.03, 95% CI: 1.01, 1.05, p< 0.001), hospital length of stay (aRR: 0.94, 95% CI: 0.90, 0.97, p= 0.003), ICU admission (aRR: 4.34, 95% CI: 2.95, 6.37, p< 0.001), cerebrovascular disease (aRR: 1.96, 95% CI: 1.20, 3.19, p= 0.007), ventilator-associated pneumonia (VAP) (aRR: 2.09, 95% CI: 1.22, 3.55, p= 0.006), septic shock (aRR: 2.98, 95% CI: 1.44, 6.19, p= 0.003), acute respiratory distress syndrome (ARDS) (aRR: 3.80, 95% CI: 2.28, 6.31, p< 0.001), acute kidney failure (AKF) (aRR: 1.45, 95% CI: 1.12, 3.76, p= 0.021), acute heart failure (AHF) (aRR: 1.63, 95% CI: 1.01, 2.62, p= 0.043) and lymphocyte count (aRR: 3.01, 95% CI: 1.99, 4.57, p< 0.001) were associated with mortality.

Conclusion: Findings show that the elderly with comorbidities such as cerebrovascular diseases had an increased risk of death. Some complications, such as pneumonia, septic shock, ARDS, AHF, and AKF, played critical roles in death.

Keywords: COVID-19, mortality, clinical characteristics, laboratory findings

(18080)

Prognostic value of C-reactive protein in COVID-19 patients

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Background: Although some biomolecules have been explored for possible biomarkers for the prognosis of COVID-19, there are not reliable prognostic indicators for disease progression and severity. We aimed to evaluate the ability of C-reactive protein (CRP) as a predictor of COVID-19 infection.
Methods: This retrospective study included 429 patients diagnosed with COVID-19 from March 30, 2020, and April 30, 2020. The study population was divided into severe cases (n=175) and non-severe cases (n=254). Data on demographic characteristics, clinical features, and laboratory findings on admission were collected.
Results: The proportion of patients with increased CRP levels was significantly higher in severe cases than in non-severe patients. The ROC curve analysis revealed that CRP could be used as an independent factor to predict the severity of COVID-19 infection. Also, patients with CRP > 64.75 mg/L were more likely to have severe complications.
Conclusion: The serum levels of CRP can predict disease severity and progression in COVID-19 patients.

(18124)

Immune and bioinformatics identification of T cell and B cell epitopes in the protein structure of SARS-CoV-2: A systematic review

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Abstract: The beginning of 2020 was marked as the emergence of a COVID-19 outbreak caused by a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently, there is no vaccine or approved treatment for this infectious virus so the invention of an efficient vaccine is certainly a high priority. Some studies have employed several techniques to facilitate the combination of the immunoinformatics approach and comparative genomic approach in order to determine the potential peptides for designing the T-cell epitope-based peptide vaccine using the 2019-nCoV envelope protein as a target. Via screening the bioimmunoinformatic SARS-CoV2 derived B-cell and T-cell epitopes within the basic immunogenic of SARS-CoV2 proteins, we presented a set of inferred B-cell and T-cell epitopes from the spike (S) and nucleocapsid (N) proteins with high antigenicity and without allergenic property or toxic effects. Our findings provide a screened set of epitopes that can be introduced as potential targets for developing peptide vaccines against the SARS-CoV-2 virus.

(18160)

COVID-19 Cytokine Storm Complications in Asthmatic Patients

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Abstract: The pandemic COVID-19, inflicted millions of people in more than 200 countries. Overall, COVID-19, causes severe complications in immunocompromised individuals. The immunopathogenesis of COVID-19 is different from that of SARS and MERS. Some evidences suggest that severe COVID-19 complications are associated with the cytokine storm syndrome, which along with ARDS, contribute to the high mortality rate of the disease. Significantly high levels of cytokines and chemokines including IL-1β, IL-1RA, IL-2, IL-7, IL-8, IL-9, IL-10, FGF2, G-CSF, GM-CSF, IFN-γ, IP10, MCP1, MIP1α and β, PDGFB, TNF-α, CCL3, CCL5, CCL2, CXCL10 and VEGFA have been noted in COVID-19 patients. Explaining the immunopathology of the cytokine storm syndrome, apoptosis of epithelial and endothelial cells leads to vascular leakage and inflammatory cells infiltration, resulting in hypoxia and ARDS. Patients with severe COVID-19 pneumonia should be evaluated for hyper-inflammation. However, Asthma is a complicated disease and bronchial inflammation is the most prominent pathological feature in asthma. Therefore, COVID-19 symptoms can be worse in asthmatic patients than others because of already existing breathing problems in these patients. Corticosteroids with anti-inflammatory functions which are used in asthmatic patients may have adverse outcomes in coronavirus infection. Thus, asthmatic patients who use corticosteroids and have vulnerable airways may suffer from complex sequel in the case of concomitant COVID-19 infection. Furthermore, asthmatic patients have a suppressed immune system in the lung, which increases their susceptibility to COVID-19 infection.

Keywords: COVID-19, Asthmatic, Cytokine, Corticosteroids

(18192)

The sufficient vitamin D and Albumin level have a protective effect on COVID-19 infection

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Background: COVID-19 disease caused by SARS-CoV-2 characterized by a wide spectrum of clinical manifestations, from asymptomatic to severe multi-organ involvement. The information regarding the protective agents of SARS-CoV-2 infection are not well known. So, the identification of protective factors that are able to control the risks, severity, and progression of disease are urgently needed. The current study evaluated the role of vitamin D and albumin in the severity, progression, or possible prevention of COVID-19 infection.

Methods: In present study, 191 patients were registered, who visited the emergency room at Imam Khomeini Hospital and checked for COVID-19 with RT- PCR. The control group were healthy volunteer in which were matched in age and sex with the case group. Blood samples were used to asses Albumin and vitamin D levels.

Results: According to our result it was a direct association of vitamin D deficiency with the COVID-19 disease and severity. We found that 81.8% of patients with COVID19 shows vitamin D deficiency. In addition, patients with covid-19 that had respiratory symptoms, the average level of albumin was significantly decreased.

Conclusion: Our study has been showed a significant negative correlation between the amount of vitamin D levels ad COVID-19 infection and severity.

Keywords: COVID-19; vitamin D; Albumin; coronavirus

(18208)

Cytotoxic T Lymphocyte Evaluation in Sars-Cov2 patients

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Background: In this research, the ratio and expression of CD4 and CD8 markers in COVID-19 patients were evaluated.

Methods: Peripheral blood samples of 25 COVID-19 patients and 25 normal individuals with similar age and sex as the control group were collected. White blood cells, platelets, and lymphocytes were counted and CD4 and CD8 T lymphocytes were evaluated by flowcytometry.

Results: The number of white blood cells, lymphocytes, and platelets were reduced significantly in COVID-19 patients ($P < 0.05$). The difference in CD4:CD8 ratio, CD4 T-cell frequency, CD8 T-cell frequency, and CD4 mean fluorescence intensity (MFI) was not significant between COVID-19 patients and healthy individuals ($P > 0.05$); however, the CD8 MFI increased significantly in COVID-19 infected patients ($P < 0.05$).

Conclusion: Although, there is no significant difference in the ratio of CD4 to CD8 between two groups, the expression level of CD8 in COVID-19 patients was significantly higher than the normal individuals. This result suggested that the cellular immune responses triggered by COVID-19 infection were developed through overexpression of CD8 and hyperactivation of cytotoxic T lymphocytes.

Keywords: Coronavirus, COVID-19, 2019-nCov, CD4 lymphocyte, CD8 lymphocyte

(18219)

Significantly decreased serum levels of vitamin D3 in Covid-19 patients

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Background: SARS Corona virus-2 is a new viral infection that appeared in Wuhan, China in December 2019 and led to a global epidemic. Severe acute respiratory syndrome is a hallmark of the new virus. Recent research has confirmed the important supportive role of vitamin D in immune cell function, particularly in modulating inflammatory responses in viral infections. In general, the underlying evidence indirectly supports the link between vitamin D deficiency and the severity of Covid 19 disease.

Methods: Fifty three patients whit real-time PCR test positive for SARS Covid-2 and hospitalized were included in the study. The mean age of these patients was 42.06 (18.7 ±) and 39.6% and 60.4% respectively were women and men. 53 healthy individuals were added to the study as control group. Vitamin D3 levels were measured by the ELISA technique in all participants. According to the range in the kit, the amount of vitamin D up to 20 mg/ml was considered sufficient. The results were analyzed using SPSS 26 software and Graph pad prism 8.4.3

Results: Serum vitamin D3 levels were measured in all patients. 27 patients (50.9%) were deficient for vitamin D3. Comparison of mean serum vitamin D between healthy individuals and patients showed that a significantly decrease in the covid-19 patients (21.47 vs 26.79, p=0.0084).

Conclusion: In the present study, a significant decrease in serum vitamin D levels was observed in patients compared to the control group.

Keywords: Covid-19, vitamin D

(18401)

Evaluation of the COVID-19 transmission and specific IgM and IgG antibodies among health care workers in Birjand city

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Background: COVID-19 pandemic has caused more than 60 million documented infections and over 1.6 million deaths. Among different groups, healthcare workers (HCWs) are at high-risk of infection because of close and frequent contacts with COVID-19 patients. The data regarding the adherence of HCWs to protective measures and their serology surveillance is scarce. The aim of this study was to evaluate the adherence HCWs to safety protocols and personal protective equipment (PPE) usage as well as the seroprevalence of COVID-19 specific antibodies among the HCWs who work in COVID-19 referral hospitals of Birjand city.

Methods: Demographic data as well as Information about frequency and duration of exposure to COVID-19 patients, the usage and type of personal protective equipment and their compliance with safety protocol were collected by means or questionnaire which was distributed among health care workers in different departments of COVID-19 referral hospitals at Birjand city. After collecting the questionnaires, five milliliters of venous blood was taken from participants and serum was separated and kept at -20 ^{oC} until analysis. Sera were checked for presence of COVID-19 specific IgM and IgG by using commercial ELISA kits.

Results: In total 137 (65.8% female, 34.2% male) health care workers participated in this study. About 84% reported close and frequent contact to COVID-19 patients and 94.6% of responders used PPE when visiting COVID-19 patients. Among participants, 4.3% had history of COVID-19 confirmed by PCR test. None of the tested sera were positive for IgM but 3.7% (5 cases) were positive for IgG antibody and two had borderline level of IgG antibody.

Conclusion: The result of this study confirmed that in spite of high level of exposure to COVID19, the rate of transmission was very low possibly because of strict compliance with safety protocol.

Keywords: COVID-19, antibody, Health care worker

(18566)

The benefits of Vitamin D in the COVID-19 pandemic: biochemical and immunological mechanisms.

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Abstract: In December 2019, a new infectious complication called CoronaVirus Infectious Disease-19, briefly COVID-19, caused by SARS-COV-2, is identified in Wuhan, China. It spread all over the world and became a pandemic. In many individuals who had suffered SARS-COV-2 infection, cytokine storm starts through cytokine overproduction and leads to Acute Respiratory Syndrome (ARS), organ failure, and death. According to the obtained evidence, Vitamin D (VitD) enhances the ACE2/Ang (1–7)/MasR pathway activity, and it also reduces cytokine storms and the ARS risk. Therefore, VitD intake may be beneficial for patients with SARS-COV-2 infection exposed to cytokine storm but do not suffer hypotension. In the present review, we have explained the effects of VitD on the renin-angiotensin system (RAS) function and angiotensin-converting enzyme2 (ACE2) expression. Furthermore, we have reviewed the biochemical and immunological effects of VitD on immune function in the underlying diseases and its role in the COVID-19 pandemic

Keywords: Vitamin D; ACE2; cytokine storm; SARS-COV-2

(18623)

Clinical characteristics, laboratory and radiological findings of hospitalized COVID-19 patients with allergy

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Background: Sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19) can infect a wide range of people, especially those with underlying disease, and spreads quickly. It's clinical and laboratory characteristics in patients with allergy are known little. Hence, we described the epidemiological and clinical characteristics along with outcomes of COVID-19 patients with allergy.

Methods: We retrospectively investigated demographic data, clinical characteristics, laboratory and radiological findings of 80 confirmed COVID-19 patients with allergy admitted to Baqiyatallah Hospital in Tehran, Iran from March 24, 2020 to April 24, 2020.

Results: From among 80 patients, the mean age ± standard deviation was 52.85±13.28 years, 46 patients (57.5%) were male and mean body mass index was 28.54±4.21 Kg/m^2. The most frequent symptoms were fever (42 [52.5%]), cough (59 [73.8%]), dyspnea (56 [70.0%]), myalgia (51 [63.7%]), chill (48 [60.0%]) and weakness (46 [57.5%]). As for laboratory findings (value ± SD [normal range]), neutrophil count (70.42±11.33% of leukocytes [50-70]), erythrocyte sedimentation rate (40.40±21.66 mm/hour [up to 15]), aspartate transaminase (37.19±14.08 U/L [<35]), lactate dehydrogenase (688.56±208.36 U/L [207-414]) and C-reactive protein (24.57±22.93 U/L [up to 5]) were above the normal range. On admission, ground-glass opacity (50%) and bilateral pneumonia (48.8%) were the most common radiological findings. The length of hospital stay was 5.49±3.53 days, and 2 patients (2.5%) died.

Conclusion: Findings highlight the allergy as an underlying disease in hospitalized COVID-19 patients and emphasize the importance of identifying effective therapies for these patients.

Keywords: COVID-19, Allergy, Underlying disease, Clinical characteristics

(18632)

Molecular docking studies to inhibit the interleukin 6 receptor and prevent the progression of COVID-19

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Background: SARS-CoV-2 is a virus from the beta corona virus family causing the COVID-19 pandemic. The main target of this virus in humans is the respiratory system. SARS-CoV-2 causes inflammation and tissue damage by inducing cytokine storm. Interleukin 6 is a member of the cytokine family which increased expression is associated with the progression of COVID-19. The aim of this study was to find suitable inhibitors to prevent the interleukin 6 receptor to prevent inflammation caused by COVID-19.

Methods: First, the names of active herbal ingredients were collected from various articles and information, 3-D structures and codes of these ingredients were collected from Pubchem database. Preparation of 3-D structures of active ingredients and interleukin 6 receptor was performed using Chimera software. Then molecular docking studies were performed using Autodock vina software. Finally, among all the active ingredients, the ingredients that had the highest affinity were selected.

Results: Among the studied substances on which molecular docking was performed, five substances named Isosaponarin, Adian-5-ene, Protohypericin, Protopseudohypericin, Hipericin had more binding affinity than LMT-28 which was previously used to inhibit this receptor.

Conclusion: These five active substances can prevent inflammation caused by SARS-CoV-2 by inhibiting the interleukin 6 receptor. Further studies can confirm the accuracy of these results and be an effective approach in controlling the symptoms and death of patients with this disease.

Keywords: IL6R, SARS-CoV-2, IL6, Herbal active ingredients

(18648)

Epidemiological and immunological features of COVID-19 patients: a retrospective, single center study

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the pathogen of coronavirus disease 2019 (COVID-19), is infecting more people across the world. Investigating the changings in levels of blood immune system cells can help to better diagnosis and management of COVID-19 patients. In this study we aimed to evaluate demographic and immunological features of COVID-19 patients.

Methods: A total of 272 COVID-19-confirmed patients admitted to Baqiyatallah hospital, Tehran, Iran, from May 26, 2020 to June 26, 2020 enrolled in this retrospective study. Data were collected and the impact of COVID-19 on levels of blood immune system cells and C-reactive protein (CRP) was investigated. Continuous and categorical variables were expressed as mean ± standard deviation and percentage, respectively, and independent sample t-test was used to compare continuous variables.

Results: Among 272 patients, mean age and mean body mass index were 54.95±13.62 years and 28.27±4.23 Kg/m2, respectively. 65.8% were male and 47.8% of patients had fever (temperature ≥ 37.3 °C). CRP was 34.73±30.60 mg/L (88.6% above normal range (NR) [up to 5]), white blood cell count was 6.25±2.35 ×109/L (8.1% below NR, 8.8% above NR [3.7–9.5]), platelet count was 192.168±83.11 ×109/L (31.3% below NR, 2.2 above NR [145-420]), neutrophil count was 72.68±11.12% of leukocytes (3.3% below NR, 64.3% above NR [50-70]) and lymphocyte count was 21.32±9.52% of leukocytes (11.4% below NR, 0.4% above NR [11-49]). 5.9% of patients died and lymphocyte count in them was significantly low compared to that of in survivors (16.41±8.05 vs. 21.63±9.53; P=0.033);

Conclusion: Low levels of lymphocyte can be used as marker of poor prognosis in patients with COVID-19.

Keywords: SARS-CoV-2, COVID-19, Epidemiological characteristics, Immune system cells

(18659)

Design and production of semi-automatic gene extraction device based on negative pressure

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Background: The current COVID-19 pandemic is the defining global health crisis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reverse transcription polymerase chain reaction (RT-PCR) is the gold standard recommended test for detection SARS-CoV-2 that require RNA extraction, followed by amplification and detection. Tests should be performed on a large fraction of the population to the prevention of disease transmission, especially by asymptomatic cases. Increases demand for laboratory testing could be managed by quick nucleic acid extraction.

Methods: In this study, we designed and manufactured a semi-automatic gene extraction device, which is used vacuum pressure to remove multiple centrifuge steps. Device components included: vacuum pomp, vacuum manifold, one-way valve, connecting system, waste bottles and vacuum gauge. One- way valve is applied for transition liquid from column to vacuum manifold to prevent risks of carryover contamination.

Results: In the clinical laboratory, nucleic acid extraction relies on the manual procedure, which the workload is large, and problems such as several centrifugation steps and replacement of microtube increase the test time and cross-contamination, respectively. Semi-automatic gene extraction device overcome the above problems and can be used for wide range of samples. Semi-automatic gene extraction device showed equal performance regarding extraction amount and quality compared to centrifuge -based method.

Conclusion: A semi-automatic gene extraction system support all nucleic acid extraction kit and its low cost make it possible to equip all laboratories.

Keywords: Negative pressure, nucleic acid extraction, vacuum device

(18706)

MicroRNA-1246 and COVID-19: Killing two birds with one stone?

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Background: Up to December2020 there were more than 74,000,000 confirmed cases of coronavirus disease 2019 (COVID-19) worldwide caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Among the therapeutic strategies to treat SARSCoV2 infection, inhibition of viral entry into target cells and viral replication are more interesting. Recently, studies have focused on miRNA-based therapies for the treatment of viral diseases. Accordingly, the aim of this review was to introduce a microRNA that has special ability in targeting both host cellular mRNA and viral mRNA and consequently in altering the risk of SARS-CoV-2 infection.

Methods: We searched the PubMed database and Google scholar engine (2019-2020) using the “COVID-19”, “SARS-CoV-2”, " MicroRNA" and” angiotensin converting enzyme 2 (ACE2)” as keywords.

Results: Based on recent bioinformatics analysis and experimental evidence, we find out microRNA-1246 could inhibit both SARS-CoV-2 entry and replication by targeting ACE2 and ORF3a, respectively (Figure1). *In vitro* and *in vivo* studies indicated that microRNA-1246 could directly target the 3′-UTR of ACE2 and downregulates expression of ACE2 receptor. On the other hand, based on our computational analysis, among the predicted SARS-CoV-2 mRNA targets by human miRNAs, microRNA-1246 could target ORF3a that involved in viral replication. Since SARS-CoV-2 enters cells by binding its spike (S) protein to ACE2 receptor, microRNA-1246 not only could inhibit viral entry by targeting host-cellular ACE2 mRNA, but also could block viral replication by targeting viral ORF3a mRNA. Hence, it could alter the risk of SARS-CoV-2 infection, especially in at-risk patients or patients with comorbidities.

Conclusion: The significant potential of RNA-based drugs such as ASOs, siRNAs and miRNAs promise to be effective in a broad spectrum of disorders such as infectious diseases. Further studies will be required to validate the capacity of microRNA-1246 as a therapeutic agent or prognostic biomarker in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, MicroRNA-1246, angiotensin converting enzyme 2 (ACE2)

(18736)

SARS-COV-2 specific IgG responses in ICU and non-ICU patients with COVID-19

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Background: Covid-19 is an emerging disease that has spread all over the world. The long-term humoral response as one of the immune responses and the study of IgG antibody levels in ICU and non-ICU patients can be useful for controlling the infection caused by SARS-CoV-2. In this study, we intend to measure IgG antibody levels in ICU and non-ICU patients with ELISA kit. This study showed that two weeks after appearing first symptoms, specific IgM was converted to IgG antibody. SARS-CoV-2 contains four major proteins, most often IgG antibodies specific for spike proteins and nucleocapsid proteins.

Methods: Data of this systematic review was collected by searching valid databases such as PubMed, Google Scholar, Scopus and Web of sciencedatabases. About 100 articles were found that 10 articles among them were the most relevant.

Results: In ICU patients, plasma IgG levels decreased significantly between days 12 and 40 after appearing first symptoms, however in non-ICU patients, IgG levels persisted steadily from day 19 to 57 after the onset of the first symptoms. The mechanisms involved in the rapid decrease in IgG levels observed in our ICU patients remain to be elucidated. One explanation for this outcome could be reduced B cell count in severe cases. Decreasing the number of CD4 +T cells can interfere with the production of B memory cells.

Conclusion: Based on these results, over time, the immunity of ICU patients to SARS-CoV-2 may rapidly decline, leading to the possibility of re-infection.

Keywords: Covid19, IgG, IgM, Humoral immunity.

(18174)

Analyses of Cardiac Biomarkers in COVID-19 Patients

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Background: COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is often associated with respiratory symptoms. Various studies have shown that SARS-CoV-2 correlated with cardiovascular disease (CVD). In this study, we aimed to measure changes in lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), and creatine phosphokinase (CPK) in patients with COVID19 to provide an opportunity to improve the diagnosis and monitoring of the disease.
Methods: We extracted laboratory data related to 159 patients with confirmed COVID-19 and evaluated LDH, CK-MB, and CPK as important cardiac biomarkers.
Results: The age range of the patients was almost 62 years old. The average blood urea nitrogen (BUN) value was 58.61 mg/dL. Also, the average values of CPK, LDH, and CK-MB were 268.24, 758.69, and 39.87 U/L in COVID-19 patients, respectively. The average LDH value in dead patients was 1012.22 U/L, while in recovered patients was 545.20 U/L (P-value < 0.0001). Also, the average CK-MB level in dead patients was 60.84 U/L, while in recovered patients was 35.17 U/L (P-value = 0.0026).
Conclusion: Elevated LDH and CK-MB following heart injury in COVID-19 patients are correlated with increased mortality. Monitoring these biomarkers in COVID-19 patients may help to reduce the mortality rate of the disease.

Keywords: SARS-CoV-2, COVID-19, CVD, cardiac biomarkers, LDH, CK-MB

(18173)

Evaluation of Renal Biomarkers in Patients with SARS-CoV-2

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Background: The COVID-19 disease, first reported in late 2019 in China and spread rapidly around the world. Since the outbreak of the disease, acute kidney injury (AKI) has been reported as a complication of COVID-19 in various studies. In this study, we investigated the correlation between changes in renal biomarkers in patients with COVID-19 and mortality rate, to help the diagnosis and treatment of the suffered patients.
Methods: We analyzed laboratory data from 206 patients with SARS-CoV-2 and evaluated the renal biomarkers, blood urea nitrogen (BUN), and Creatinine (Cr).
Results: The age range of the patients was almost 62 years old. The average LDH, BUN, Creatinine, and lymphocyte values in COVID-19 patients were 755 U/L, 59.1 U/L, 1.5 U/L, and 16.8 % respectively. The average BUN value in dead patients was 85 mg/dL, while in recovered patients was 40.5 mg/dL (P-value < 0.0001). Also, the average creatinine level in dead patients was 1.86 mg/dL, while in recovered patients was 1.24 mg/dL (P-value = 0.0004).
Conclusion: AKI in patients with COVID-19 increases BUN and creatinine, which in turn correlated with increased mortality in these patients. Thus, monitoring these biomarkers may help in the decrease of the mortality rate of COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, Renal Biomarkers, Kidney Injury Blood Urea Nitrogen, Creatinine

(17973)

Importance of hematological findings in patients with Covid-19

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing Coronavirus disease 2019 (COVID-19) that was detected in Wuhan of China. The outbreak of COVID-19 pandemic has had a massive global impact that was leading to considerable morbidity and mortality worldwide. During this outbreak, there is an instant need for laboratory predictor documentation to distinguish between mild and severe forms of disease. In addition COVID-19 diagnosis, the hematology laboratory provides critical information to clinicians regarding prognosis, disease course, and response to therapy. Systemic infection of COVID-19 has a significant effect on the hematopoietic system and homeostasis. We provide a summary of the changes of hematologic parameters and evaluate whether these changes may assist clinicians in diagnosing and predicting disease progression of COVID-19.

Methods: Our study was based on PUBMED and GOOGLE SCHOLAR databases by related key words such as: "COVID-19 ", "Hematology", "Hematologic Impact", "Hematological Parameters" from December 2019 to after.

Results: Based on the studies, a summary of the major important hematological features in patients infected with COVID-19 is as follows: Lymphopenia, Thrombocytopenia, Leukopenia and sometimes Neutrophilia, elevation of D-Dimer, prolongation of Prothrombin Time (PT), and Partial Thromboplastin Time (PTT), and also increased level of Fibrin Degradation Products (FDP) could occur. Moreover, elevation of Erythrocyte Sedimentation Rate (ESR), C - reactive protein (CRP), Procalcitonin, Ferritin, Lactate Dehydrogenase (LDH), and Interleukin-6 (IL-6) are other laboratory features. ICU admission was associated with higher levels of Neutrophils, D-Dimers, prolonged PT and degree of lymphopenia. Patients with high IL-6, CRP, D-dimer, and neutrophil-to-lymphocyte ratio (NLR) had the highest likelihood of mortality.

Conclusion: Elevated D-Dimer levels increase during disease course is associated with disease worsening. Other coagulation abnormalities such as PT and aPTT prolongation, FDP increase, with severe thrombocytopenia lead to life-threatening disseminated intravascular coagulation (DIC). Also venous and arterial thrombosis causing Cardiovascular-brain failure that directly linked to high mortality from COVID-19. So the involvement of elements of the hematopoietic system is prominent in severe cases and associated with poor prognosis and mortality. Better comprehension of the pathophysiology mechanisms of COVID-19 induced hematological abnormalities may finally result in better ways to treat them and reduction the associated morbidity and mortality.

Keywords: COVID-19, Hematology, Hematologic Impact, Hematological Parameters

(18605)

The association between genes and their related pathways in COVID-19 pathogenesis in order to proposing treatment strategies

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Background: To date, many genes have been found to be associated with severity and susceptibility to SARS-CoV-2 infection. Due to the high prevalence of COVID-19, the aim of this study was to investigate some of important genes in COVID-19 pathogenesis and its subsequent cytokine storm to suggest appropriate treatment options.

Methods: A systematic search was performed to identify studies published in multiple databases (Cochrane, Embase, Pubmed and google Scholar) up to 2020, and recently published abstracts were also reviewed. Using the key words SARS-coronavirus 2, Host genetics, COVID-19 GWAS, Cytokine storm and Interferon.

Results: Based on literature review, we found various factors including NLR family pyrin domain containing 1 (NLRP1), NLRP3, NLR Family CARD domain containing 4 (NLRC4), leucine-rich repeat (LRR), and nucleotide-binding domain oligomerization (NOD) that are involved in activation of inflammation and cytokine storm in severe COVID-19. It has been also shown that over-activation of Interleukin-18 (IL-18) due to a functional mutation can also increase the severity of COVID-19. Mutations in MDA5 gene, which is responsible for detecting dsRNA have been shown to increase respiratory tract viral infections. Moreover, Corona virus is able to escape the MDA5 sensor using EndoU endoribonuclease, which is highly conserved in various corona viruses. Thus, inhibition of EndoU in SARS-CoV-2 may be a potential therapeutic target in COVID-19 patients. Furthermore, Genome-wide association study (GWAS) study of the COVID-19 patients showed significant signals in the 3p21.21 region containing the SLC6A20 gene (interacting with Angiotensin-converting enzyme 2), C- CXCR6 (regulating the location of CD8 T memory cells in the lung to counteract respiratory pathogens), CCR9 (A key regulator of the early stages of allergic inflammation of the respiratory tract) and CCR1 (a gene associated with inflammatory cascade and airway overreaction).

Conclusion: According to the above description, inhibition of CCR1, CCR9, IL-18 and EndoU (SARS-CoV-2 protein) can be therapeutic targets in COVID-19 patients, which certainly needs further research in this area.

Keywords: SARS-coronavirus 2, Host genetics, COVID-19 GWAS, Cytokine storm

(18547)

Immune profiling of SARS-CoV2; what we know and what we don't know

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Background: COVID-19, described as a world war 3, is the current worldwide challenge and nearly all the countries have faced this disaster until now.
Methods: In this review, we tried to gather different articles which analysis immune cells in patients with COVID-19 and then discuss the immune profile differences with healthy controls and also between the mild and severe cases.
Results: Patients with COVID19 have higher neutrophil count, higher neutrophil to lymphocyte ratio (N/L), high serum levels of C5a and C5b-9, lower number of NK cells and lymphocytes. Frequency of plasmablast increased while memory B cells decreased in peripheral blood. Among helper T cells, the percentages of Th1 and Th1Th17 cells increased. The frequencies of Treg and Tfh cells were within a normal range. Patients with severe disease compared with milder cases, have higher neutrophil count and N/L ratio, lower percentages of monocytes, eosinophil, basophil, and lower number of NK cells. They also have lower lymphocyte count, lower number of T and B cells, $CD4^+$ T cells, and $CD8^+$ T cells. In contrast to severe types, patients with mild disease have a larger population of total T and $CD8^+$ T cells with highly specific expanded clones and also more TCR clones. Patients with ARDS have the most proportion of plasmablast. In cases who died of COVID-19, IgM was higher compared to recovered cases or both antibodies were undetectable during the disease course
Conclusion: By different unknown mechanisms and in several pathways virus deviates the immune system from its programmed route. Therefore, cross talk between innate and adaptive immunity does not take place properly and the disease appears by different severity in genetically susceptible individuals.
Keywords: COVID19, immunity, innate, adaptive

(16912)

Immunopharmacological perspective on IL-1 in COVID-19

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Abstract: The newfound coronavirus disease 2019 (COVID-19) initiated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an international public health concern threatening life of millions of people worldwide. The virus seems to have a propensity to infect older males especially those with underlying diseases. The cytokine storm following hyperactivated immune responses due to SARS-CoV-2 infection is probably the crucial source of severe pneumonia that leads to acute lung injury, systemic inflammatory response syndrome, or acute respiratory distress syndrome, and finally multiple organ dysfunction syndrome and death in many cases. Several studies revealed that interleukin 1β (IL-1β) levels were elevated during COVID-19 infection. Additionally, IL-1 cytokine family has a pivotal role in the induction of cytokine storm due to uncontrolled immune responses in 18COVID-19 infection. This article reviews the utilization of IL-1 inhibitor agents in controlling the inflammatory outcomes initiated by SARS-CoV-2 infection.

Congress Abstracts

Immunodeficency

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18530)

CTLA-4 Expression in Stimulated Lymphocyte from Common Variable Immunodeficiency Patients with Enteropathy and with No Known Monogenic Disease

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Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency disease with various clinical symptoms and a heterogeneous genetic background. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have essential roles in the modulation of the immune responses. Here, we have investigated the expression of CTLA-4 proteins in CVID patients with enteropathy.
Methods: In this study, the expression of CTLA-4 proteins was assessed by flow cytometry in 10 diagnosed CVID patients with enteropathy and 10 healthy donors. Human peripheral blood mononuclear cells (PBMCs) were extracted from whole blood and were cultured in a complete RPMI-1640 medium. The cells were stimulated with an anti-CD3 monoclonal antibody (mAb) and anti-CD28 mAb for 72 hours at 37 °C and 5% CO_2 to monitor Mobilized CTLA-4. The cells were then re-stimulated with 20 ng/mL phorbol 12-myristate 13-acetate (PMA) and one µM Ionomycin for 40 minutes at 37 °C and 5% CO2 in the complete RPMI-1640 medium. In the final step, PE anti-CTLA-4 was utilized before analysis by flow cytometry.
Results: CTLA-4 expressions were significantly lower in patients with enteropathy than in CVID without enteropathy and healthy donors. There was a correlation between the expressions of CTLA-4 in CVID patients with enteropathy and without enteropathy.
Conclusion: The presence of enteropathy in CVID patients could indicate a lack of expression in CTLA-4 proteins. This can be helpful in the early diagnosis and initiation of appropriate treatment in these patients.
Keywords: CVID; immunodeficiency; Enteropathy; CTLA-4

(18742)

Evaluation of effective factors on IL-10 signaling in B cells in selective IgA deficient patients

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Background: Selective IgA deficiency (SIgAD) is the most prevalent form of primary immunodeficiencies. The pathogenesis of the disease is still unknown. Several studies suggested a defect in B cell responses to IL-10, however, the main reason for this defect has not been reported. Elucidating IL-10 signaling defect and its correlation with clinical manifestations could be helpful for better understanding and treatment of the disease.

Methods: In this study, 15 SIgAD patients and 15 age and sex-matched healthy controls were included. Surface expression of TGF-bRII, IL-10R and IgA were assessed by flow cytometry in human purified B cells before and after stimulation by IL-10. Protein expression of STAT3, p-STAT3 and SOCS3 were measured by Western blot. TGF-β and IgA secretion were evaluated by ELISA. Finally, the measurement of B cell apoptosis was performed by flow cytometry.

Results: TGF-bRII expression level was decreased after stimulation with IL-10 in patients compared with controls. Notably, TGF-b level was higher after stimulation with mCD40L and IL-10 in the control group than those stimulated by mCD40L alone. The IgA^+ B cell percentage and IgA secretion level were significantly increased in controls compared with SIgAD patients. The relative concentration of the total of STAT3 was decreased compared with controls.

Conclusion: Defect in IgA production in SIgAD patients could be due to defective B cell responses to IL-10 stimulation that probably originates from defective regulation of TGF-βresponse by IL-10. Furthermore, it is suggested that defect in STAT3 protein baseline expression could impair cytokines signaling such as IL-10 and IL-21.

Keywords: Selective IgA deficiency, B cell, IL-10, STAT3, TGF-β, Apoptosis

(18495)

The Effects of Mesenchymal Stem Cells Conditioned Media and Exosomes on the function of neutrophils from chronic granulomatous disease patients

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Background: In chronic granulomatous disease (CGD) patients, reactive oxygen species (ROS) production by neutrophils is impaired. So, they are susceptible to infections. Studies showed that, mesenchymal stem cells (MSCs) have protective effects on the function of neutrophils, and an approach that MSCs use to apply their effects is secreting soluble factors and exosomes. So, we investigated the effects of MSC-exosomes and MSC-conditioned media (MSC-CM) on the function and apoptosis of neutrophils in CGD patients.

Methodology: In this study, neutrophils were isolated from healthy donors and CGD patients and then incubated with exosomes or CM that were prepared from MSCs. Then, neutrophil respiratory burst, apoptosis and phagocytosis capacity were evaluated by NBT assay, Annexin V-PI method and Giemsa staining.

Results: It was demonstrated that both MSC-exosomes and CM could improve the phagocytosis capacity and ROS production of neutrophils in CGD patients and healthy donors. In contrast to the healthy group, in CGD patients, exosomes significantly reduced the percentage of viable neutrophils.

Conclusions: This report indicated that MSC exosomes and CM could increase the function of the neutrophils isolated from CGD patients. But decreasing the number of the living cells is one of the limitations of them.

Keywords: Mesenchymal Stem Cell, Chronic Granulomatous Disease, Exosome, Conditioned Media

(18717)

Evaluation of Radiation Sensitivity in Patients with Hyper IgM Syndrome

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Background: HIGM syndrome is a rare form of primary immunodeficiencies characterized by normal/increased amounts of serum IgM and decreased serum levels of other switched immunoglobulins classes. Since the affected patients are continuously infected with various types of pathogens and are susceptible for cancers, diagnostic and therapeutic tests including imaging techniques are recommended for the diagnosis and treatment of these patients, which predispose them to higher accumulated doses of radiation. Given the evidence of class switching recombination machinery defect and its association with ab increased rate of DNA repair, we aimed to evaluate radiation sensitivity among a group of patients diagnosed with HIGM syndrome.

Methods: 19 HIGM patients (14 CD40 L and 3 AID deficiencies and 2 unsolved cases without known genetic defects) and 17 control subjects (10 healthy subjects as negative control group, 7 ataxia telangiectasia patients as positive control group) were enrolled. G2 assay was carried out for the determination of radiosensitivity.

Results: Based on radiation-induced chromosomal changes among the studied HIGM patients and their comparison with the controls, almost all (95%) the patients had degrees of radiosensitivity: 6 patients with low to moderate, 1 patient with moderate, 11 patients with severe and 1 patient without radiation sensitivity.

Conclusion: Today, X-ray radiation plays a very important role in diagnostic and therapeutic procedures; while increased exposure has devastating effects especially in radiosensitive patients. Considering higher sensitivity in HIGM patients, utilizing radiation-free techniques could partly avoid unnecessary and high-level exposure to radiation, thus preventing or reducing its harmful effects on the affected patients.

Keywords: Primary immunodeficiency; hyper immunoglobulin M syndrome; G2 assay; radiation sensitivity (radiosensitivity); chromosomal aberration

(18245)

Increased expression of B lymphocyte induced maturation protein 1 (BLIMP1) in patients with common variable immunodeficiency (CVID)

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Background: Common variable immunodeficiency (CVID) is a primary immune deficiency disorder characterized by hypogammaglobulinemia and defect in response to vaccines. B cell maturation and differentiation is defective in this disorder, and CVID patients demonstrate commonly reduced numbers of memory B cell and antibody-secreting plasma cells. Since the B-cell lymphoma 6 protein (BCL6) and B lymphocyte induced maturation protein 1 (BLIMP1) molecules are two important transcription factors in the maturation of B cells to plasma cells, we evaluated the expression levels of BCL6 and BLIMP1 in B lymphocytes from peripheral blood in patients with CVID.

Methods: Blood samples were collected from 12 patients with CVID and 12 healthy donors. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll density gradient separation. Subsequently, $CD19^+$ B cells were purified using MACS. The expression protein and transcriptional level of BCL6 and BLIMP1 were assessed using flow cytometry and Real-time PCR, respectively.

Results: Our results showed that the expression levels of BLIMP1 were significantly higher in patients compared to control subjects.

Conclusion: Our findings suggest that increased expression levels of BLIMP1 could be involved in defective maturation of B cells in CVID patients and provide mechanistic insights into the pathogenesis of this disorder.

Keywords: CVID; Plasma cell; BCL6; BLIMP1

(18744)

The Characteristics of DOCK8 in Immune Cells

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Dedicator of Cytokinesis 8 (DOCK8) is belonging to the DOCK-C subfamily of the DOCK protein family. These family members act as guanine nucleotide exchange factors (GEFs) that mediate the function of Rho GTPases. Thus, the DOCK family would regulate various signaling pathways. In the physiologic state, DOCK8 modulates both innate and adaptive immunity responses. Adjusting the formation of immunological synapses in B cells and developing the memory $CD8^+$ T cells are facilitated by DOCK8. Recent studies have revealed that the bi-allelic DOCK8 mutations would be a causative role of primary immune-deficiency syndromes in humans. Based on documents, some abnormalities in morphology and functions of leukocytes have been seen in DOCK8-deficient patients. However, DOCK8-deficient patients are able to produce normal immune-cell types and lymphocytes. The alterations in the immune system of these patients would be as follows; the reduction in peripheral T cells, increased turnover of $CD4^+$ and $CD8^+$, and decreased memory response of the immune cells. These changes may be a reason for recurrent infectious diseases, malignancies, and auto-immune problems in DOCK8-deficient patients. This study was proposed to identify the characteristics of DOCK8 in the immune system.

Keywords:
DOCK8, Immune Cells, Primary Immuno-deficiency Syndrome, $CD4^+$ cells, $CD8^+$ cells.

(18284)

A rare case of CARD9 deficiency associated with a history of recurrent fungal infections and controllable abdominal mass

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Background: CARD9 deficiency is a genetic disorder characterized by susceptibility to fungal infections. Patients with CARD9, which is also associated with invasive fungal infection (such as meningitis) and deep dermatophytosis. The manifestations related to CARD9 deficiency usually start at the first ages of childhood and it is critical to detection and treat the disease appropriately to minimize infections and prevent mortality.

Methods: We present a case with recurrent fungal infections and abdominal mass and the result of his gene sequence indicates a CARD9 deficiency. Additionally, we checked the genes interacted to CARD9 using the STRING software.

Results: We are exploring how CARD9 mutation that cause susceptibility to fungal infections impact the function of immune cells by studying a patient with genetic disorders such as CARD9 deficiency associated with abdominal mass. Additionally the importance of CARD9 in immune system was found using STRING software. According to this part of research CARD9 can interact to MALT1, Syk, PIPK2, NOD1, NOD2, PRKCD, BCL10, and some of MAPKs.

Conclusion: The patient studied had no serious complications until the age of 14, although the CARD9 deficiency was a hereditary disorder and this item is the key roles in immune system. Surprisingly, the size of abdominal mass in patient studied was controlled by antifungal treatment.

Keywords: caspase activation and recruitment domain, immunologic deficiency syndromes, abdominal mass**.**

(16633)

RFXANK mutation and Reduced Circulating B cells in a rare case with Bare Lymphocyte Syndrome type II

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Background: Bare lymphocyte syndrome type 2 is a primary immune deficiency disorder appeared by recurrent microbial infections and genetic mutations of MHC-II associated transcription factors. Absence of MHC-II glycoproteins on the surface of immune cells causes immune system dysfunction. Here, we report a rare case with reduced number of circulating B cells probably due to the reported frame shift mutation in RFXANK gene locus.

Methods: Sanger sequencing and flowcytometry analysis were performed to analysis the probable genetic mutations and immune cells count in this case.

Results: The frame shift mutation in RFXANK gene caused by a guanine deletion was detected by whole exome sequencing. Also, the homozygosity and heterozygosity of mutation in patient and his parents were confirmed by Sanger sequencing. Furthermore, flow cytometry data demonstrated significantly low percent of HLA-DR expression on peripheral blood mononuclear cells.

Conclusion: The reported mutation in RFXANK gene not only affected HLA-DR expression by B cells, but also impaired the proper expression of CD19 and CD20. Consequently, a significant reduction in circulating B cells were seen in this patient. Although the exact mechanism must be clarified by further studies, it could be concluded that RFXANK protein is involved in CD19/CD20 transcriptional regulation in B cells. Such unexpected findings are important to be considered by the clinicians for a correct diagnosis when they are examining the suspected cases of CID.

Keywords: MHC class II deficiency; RFXANK; Primary immunodeficiency disorder

16917

Common Variable Immunodeficiency (CVID) and Autoimmunity

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Autoimmunity is observed by almost one-third of patients with CVID. Different mechanisms including genetic defects and dysregulation of innate and adaptive immunity leads to autoimmunity in these patients CVID. The clinical phenotypes of autoimmunity in CVID patients comprise fall in a wide spectrum, from organ-specific autoimmunity to systemic complications. The most common autoimmunity is autoimmune cytopenia in CVID patients. In this article, we have provided a collection of the most significant and recent information about prevalence, genetics, pathogenesis and clinical manifestations of autoimmunity in CVID patients, and provided an overview on its management and future perspective.

Keywords: common variable immunodeficiency, autoimmunity, autoimmune cytopenia, adaptive immunity

(18281)

Is it possible that Ataxia Telangiectasia is simultaneously occurred with Idiopathic thrombocytopenic purpura: A Case Report Study?

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Background: Ataxia telangiectasia (*AT*) is an autosomal recessive disorder and combined immunodeficiency syndromes, characterized by progressive neurodegenerative telangiectasia and some laboratory abnormalities. Regarding the fact that autoimmune disorders; such as *ITP* (Idiopathic thrombocytopenic purpura), are not generally expected in the course of *AT*, here, we present a patient with a sophisticate presentation of these two conditions.

Methods: In this study, we examined a patient who had referred to our Center due to fever, shortness of breath, cough, and pneumonia. So, *WES* (Whole Exome Sequencing) was done to confirm his disease.

Results: Due to antibiotic resistance during treatment, progressive ocular telangiectasia and ataxic gate, *AT* was diagnosed. Confirmedly, a novel mutation in *ATM* gene (*NM_000051: exon7: c.C664T: p.Q22*) was found in DNA sequence. Furthermore, he had a history of several hospitalizations due to frequent *ITP*.

Conclusion: Given the existence of a novel mutation of *AT*, it can justify the association of *AT* with autoimmunity disorder, such as *ITP*. The other difference between these two case report studies is related to the type of mutations detected. Our data showed that novel mutation (NM_000051: exon7: c.C664T: p.Q22) was found in patient studied that leads to 11 hom stop–gain mutation which gene ATM in, and it can cause protein dysfunction.

Keywords: Ataxia telangiectasia, combined immunodeficiency syndromes, idiopathic thrombocytopenic purpura, antibiotic resistance, autoimmunity disorder

(18194)

Norovirus was the most frequent virus in chronic diarrhea of patients with Primary Immunodeficiency

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Primary immunodeficiencies (PID) are a group of scarce immunologic disorders presenting with immune dysregulation and a wide range of infections. Chronic diarrhea is a frequent complication that is observed in 20% of PID patients. Since numerous reasons for the diarrhea can be described and encompass various microbes such as viruses; therefore, we aimed to evaluate the virus composition in the chronic diarrhea of the patients with PID who referred to the Department of Allergy and Clinical Immunology, Rasoul Akram Hospital with PCR method. We investigated 54 patients with PID and no virus was detected in 42 (77%) patients and among 12 residual patients (23%) *Norovirus* was the most frequent virus in 4 patients7.4%)) and there was a patient with concomitant *Norovirus and Cytomegalovirus*. In conclusion, we found a number of viruses causing chronic diarrhea in PID patients; therefore, appropriate treatment is applicable to reduce the long-term complications of these patients.
Keywords: Primary immunodeficiency, chronic diarrhea, Norovirus, Cytomegalovirus,

(18372)

An infant with mutation in EPCAM gene

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Background:
Epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein with diverse biological functions including regulation of cell proliferation and cancer stemness. This protein is found in epithelial cells and helps cells stick to one another. Mutations in the EPCAM gene have been identified in two hereditary syndromes.1- Congenital tufting enteropathy (CTE), a rare autosomal recessive form of intractable diarrhea of infancy and 2- Lynch Syndrome (HNPCC).
On the other hands, very early-onset intestinal inflammation can be due to the absence of EPCAM, which results in tufting enteropathy [TE].
Case presentation: Here, we report a 19-month-old girl, admitted with severe dehydration due to watery diarrhea and repeated hospitalization. According to her past medical history, she comes from irrelevant parents with positive history of chronic diarrhea in her sister and grandfather. Because of nonspecific pathology in colonoscopy with normal laboratory analysis and immunological workup, she was nominated for genetic examination in order to identify the underlying causes of her disease. Genetic evaluation by Whole Exome Sequencing (WES) revealed a homozygous pathogenic mutation in ClinVar (NM_002354.2 (EPCAM): c.556-14A>G). Sanger sequencing confirmed that patient and her affected sister are homozygous and parents (father, mother and grandfather) are carrier heterozygous for this mutation.
Unfortunately, she died She died at the age of 22 months.
Conclusion:
Excluding or confirming known VEOIBD genotypes should be considered early in the disease course in all cases of therapy-refractory VEOIBD, as it can have a direct impact on patient management.
Key words:
VEOIBD, EPCAM disease, monogenic disorders, Children

(18282)

A case report of the asynchrony in The Onset of Clinical Manifestations in Identical Twin with STK4 deficient disorder

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Background: Primary immunodeficiency diseases (PIDs), a rare group of gene defects with different disorders characterized by various kinds of gene mutations. Defects in human serine-threonine kinase 4 (STK4), has a role in the regulation of apoptosis and proliferation, affects the immune system with recurrent infections. In the current paper, we report twin brothers with a novel STK4 mutation, whilst one of whom showed clinical manifestations associated with this mutation with a delay of two years.
Materials and methods: In this study, the mutation in the STK4 gene was assessed for family studied by Whole Exome Sequencing (WES). Additionally, we describe the probable reasons for this delay. Additionally, we checked the genes interacted to STK4 using the STRING software.
Results: We observed the Incidence of recessive alleles of the STK4 gene among the members of this family. Additionally the importance of STK4 in immune system was found using STRING software. According to this part of research STK4 can interact to SAV1, YAP1, and CASP3, essential in immune responses and apoptosis.
Conclusion: We identified the STK4 genetic defect effect on twin brothers that showed almost the same clinical symptoms associated with immune deficiency, while, the severity of the disease was higher in one of the twins, which may be due to another genetic defect, LRBA defect, and likely differences in the percent of B lymphocyte population and CD4+/ CD8+ state.
Keywords: Primary immunodeficiency diseases (PIDs), STK4, delay, severity, LRBA defect

(18778)

Study Iran's position in the treatment of immunodeficiency diseases with emphasis on the need for screening patients

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Introduction: Immune deficiency is a disease in which the body's immune system is weak and the body is prone to a variety of infections. The cause of most immunodeficiency diseases is genetic and is more common in infancy. Immune deficiency is divided into two categories of primary and secondary immunodeficiency; Primary immunodeficiency is inherited and its symptoms appear from childhood, but secondary immunodeficiency occurs in the case of diseases such as AIDS. Until a decade ago, immunodeficiency diseases were considered a rare disease, but now, due to its prevalence, it is no longer so, and according to studies, about 70 to 90% of immunodeficiency patients are not recognized worldwide. And necessary measures should be taken to fully identify patients. It should be noted that science has advanced in various fields of medicine and many immunodeficiency diseases can be treated with timely diagnosis.

Methods : In this study, by examining articles and data based on the scientific database, while examining Iran's position in the development of research and treatment of immunodeficiency patients, we specifically address Iran's achievements in screening immunodeficiency patients and the importance of this issue in promoting Iran's position in the field. we examine the development of health services in the world.

Results: Due to the increase in Iran's research rank in the field of treatment of immunodeficiency diseases, which in the last decade we have seen Iran's rank rise from 22nd to 18th in the world, it is necessary to increase public awareness about immune system diseases. Also, based on screenings conducted by the Immunodeficiency Research Center of Tehran University of Medical Sciences, it is estimated that one person in every 2,000 people has this disease, which is a very worrying statistic. But the latest studies show that Iran is the most active in the field of patient identification among the countries in the region, but is ranked second among Asian countries after Japan. Iran, along with European countries, is one of the pioneers in launching a database of immunodeficiency systems 20 years ago, and so far, the information of 2,200 patients has been registered.

Conclusion: Due to the high capacity of Iranian researchers and physicians in conducting research and development of treatment of immunodeficiency patients and also due to the efforts of centers active in this field to screen patients should still be based on accurate statistics of immunodeficiency diseases and the number of patients in the country need to increase public awareness of immunodeficiency diseases through mass media and education. It should be noted that timely diagnosis and appropriate treatment is the way to get rid of diseases of the immune system. Therefore, screening through awareness, education and development of diagnostic and treatment centers should continue to be emphasized in the field of immunodeficiency diseases by policy-making and executive bodies.

Keywords: immunodeficiency patients, Iran

(18420)

Evaluation of Alpha1 antitrypsin in serum of children with idiopathic Bronchiectasis

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Background: Bronchiectasis is a clinical syndrome associated with a chronic cough, sputum production, recurrent respiratory infections, and permanent bronchial dilation. The association between alpha-1-antitrypsin (AAT) level and bronchiectasis is controversial and there is a lot of debate about this issue. We aimed to investigate this association in children with idiopathic bronchiectasis.

Methods: The study was conducted on 19 patients with idiopathic bronchiectasis as a case group (mean age 15.9±2.1) and 20 healthy individuals as a control group (mean age 14.9±2.6). Serum AAT level was measured using nephelometric analysis (mg/dl). Other criteria including age, sex, parent consanguinity, number of hospitalization, age of the first symptom were evaluated in both groups related to AAT level.

Results: The mean serum level of AAT in the case and control group were (1.3±0.29; 1.5 ±0.59), respectively with statistical significance (P=0.001). The case group had a more positive attitude toward consanguinity than control group (66.7% versus 33.3%; P<0.001). No significant correlation was found between age and AAT level in both case and control groups (p>0.05). There was no significant difference between the case and control groups regarding sex and mean age. The results showed that 80% of patients had first symptom of disease under 1-y-o, 6.6% 1-to 5-y-o, 6.6% 5 to 10 y-o, and 6.6% in more than 10-y-o. In the case group, 53.3% had a history of medical hospitalization for one time, 26.7% two times while 20% of patients had no medical hospitalization.

Conclusion: Decreased AAT serum level and high consanguinity rates may be considered as two risk factors for idiopathic bronchiectasis occurrence.

Keywords: Apha-1-antitrypsin level, Idiopathic bronchiectasis, Nephelometry

(18718)

Genetic Mutations and Immunological Features of Patients with Hyper-Immunoglobulin M Syndrome in Iran

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Background: Hyper-immunoglobulin M (HIGM) syndrome is a rare heterogeneous group of primary immunodeficiency disorders characterized by low or absent serum levels of IgG and IgA along with normal or elevated serum levels of IgM.

Methods: Clinical and immunological data were collected from the 75 patients' medical records diagnosed in Children's Medical Center affiliated to Tehran University Medical Sciences and other Universities of Medical Sciences in Iran. Among 75 selected patients, 48 patients (64%) were analyzed genetically using targeted and whole-exome sequencing

Results: The ratio of male to female was 2.9: 1. The median age at the onset of the disease, time of diagnosis, and diagnostic delay were 10.5, 50, and 24 months, respectively. Pneumonia and lower respiratory tract infections (61.3%) were the most common complications. Responsible genes were identified in 35 patients (72.9%) out 48 genetically analyzed patients. Cluster of differentiation 40 ligand gene was the most mutated gene observed in 24 patients (68.5%) followed by activation-induced cytidine deaminase gene in 7 patients, lipopolysaccharide- responsive and beige-like anchor (1 patient), nuclear factor-kappa-B essential modulator (1 patient), phosphoinositide-3-kinase regulatory subunit 1 (1 patient), and nuclear factor kappa B subunit 1 (1 patient) genes. Nineteen (25.3%) patients died during the study period, and pneumonia was the major cause of death occurred in 6 (31.6%) patients.

Conclusion: Physicians in our country should carefully pay attention to respiratory tract infections and pneumonia, particularly in patients with a positive family history. Further investigations are required for detection of new genes and pathways resulting in HIGM phenotype.

Keywords: Primary immunodeficiency; hyper immunoglobulin M syndrome; G2 assay; radiation sensitivity (radiosensitivity); chromosomal aberration

Congress Abstracts

Immunogenetics & Bioinformatics

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18658)

Killer cell immunoglobulin-like receptors (KIRs) gene diversity in Iranian patients with breast Cancer

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Background: Killer cell immunoglobulin-like receptors (KIRs) gene family consists of various activating and inhibitory genes, which are essential for NK cell development, education and activation. The gene content of KIR haplotypes is different in centromeric and telomeric (Cen/Tel) regions of KIR haplotypes. Therefore, in the present study we aimed to investigate the association of KIR Cen/Tel gene motifs with the various clinicopathological characteristics of breast cancer patients.
Methods: KIR genotyping of 16 *KIR* genes were performed in 226 Breast cancer patients and 226 age-sex matched healthy controls by sequence-specific primers-polymerase chain reaction (SSP-PCR) method. We appraised distribution of clinicopathological characteristics of breast cancer patients for analyzing the impact of KIR gene motifs on occurrence of these clinical features.
Results: Possessing Bx-Bx, Cen-Bx and Tel-Bx were associated with increased risk of lymph node metastasis (LNM), while AA-AA, Cen-AA, Tel-AA showed protective role against LNM. Higher frequency of lymphatic invasion was seen in carriers of Cen-Bx specially Cen-BB, although lower frequency of AA-AA, Cen-AA was observed in patients with lymphatic invasion. AA-AA and Cen-AA were negatively associated with tumor necrosis; however, Cen-Bx was associated with increased risk of tumor necrosis. Also, AA-AA was more frequent in cases with clinical stage II, and Bx-Bx was more common in cases with clinical stage III. Furthermore, AA-AA and Cen-AA confer resistance to ER+, PR+, HER2+ and triple-positive cases. Higher frequency of Bx-Bx and Cen-Bx was found in ER+, triple-positive and ER+, PR+, HER2+, triple-positive respectively.
Conclusion: Possessing AA-AA, especially centromeric region, confers resistance to LNM, lymphatic invasion and tumor necrosis. However, Bx-Bx and Cen-Bx are positively associated with increased susceptibility to more aggressive breast cancer.
Keywords: NK cell, Killer immunoglobulin like receptors (KIRs), Breast cancer (BC), Lymph Node Metastasis (LNM), Invasion

(18492)

HLA class II alleles may predict the severity of COVID-19 disease

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Background: HLA genes with extreme diversity can make a contribution for individual variations to the immune response against SARS-COV-2 infection. This study aimed to explore the distributions of HLA class II alleles frequencies as well as their relation with the severity of disease in a group of Iranian COVID-19 patients.

Methods: This prospective and case-control study was conducted on 144 confirmed COVID-19 patients including 46 cases with moderate or mild form, 54 cases with severe and 44 cases with critical disease. HLA-DRB1 and –DQB1 alleles were determined by PCR-SSP method and compared between three groups of the patients and in comparison to a group of ethnically matched healthy controls (n=153).

Results: HLA-DRB1*15 was the only marginally significant alleles that showed lower frequency in the patients compared with healthy controls (P=0.06). Patients with moderate COVID-19 had higher frequencies of HLA-DRB1*04 (P=0.03) and HLA-DRB1*10 (P=0.05) alleles versus severe and critical patients. We found a higher significantly frequency of HLA-DRB1*03 allele in the critical subgroup of the patients than healthy controls (P=0.01). Moreover, we observed a significantly higher Neutrophil/Lymphocyte ratio in critical cases versus moderate to severe patients (P=0.002).

Conclusion: Our results indicate a possible contribution of some HLA class II alleles in disease severity and clinical features of COVID-19 disease.

Keywords: HLA class II, Alleles, COVID-19

(18448)

Relevance of autoantibody profile with HLA-DRB1 and -DQB1 alleles in a group of Iranian systemic lupus erythematosus patients

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Background: One of the most relevant genetic components in systemic lupus erythematosus (SLE) is human leukocyte antigen (HLA) gene complex which plays a central role in autoimmune responses. This study aimed to explore the associations of HLA-DRB1/-DQB1 alleles and haplotypes with SLE risk and the appearance of autoantibodies in SLE disease.

Methods: A total of 127 SLE patients and 153 ethnically matched healthy controls were enrolled. HLA-DRB1 and HLA-DQB1 alleles were determined by PCR-SSP method and then HLA alleles and haplotypes frequencies were compared between two groups and among the patients in terms of autoantibodies spectrum.

Results: We found that HLA-DRB1*03 and HLA-DRB1*16 alleles were significantly associated with increased risk (P=0.008 and P=0.002 respectively) and DRB1*01 conferred a decreased risk for SLE (P=0.03). Similar associations were observed at haplotype level; DRB1*03~DQB1*02 (OR1.91,P=0.01), DRB1*16~DQB1*05 (OR3.65,P=0.004) and DRB1*01~DQB1*05 (OR0.36, P=0.04). Remarkably, we observed significantly associations of DRB1*03 with the appearance of anti-SSA/Ro (P=0.005), anti-SSB/La (P=0.001) and anticoagulant (P=0.007), DRB1*15 with anti-SSA/Ro (P=0.02), DRB1*16 with anti-Sm (P=0.02), DRB1*04 with anti-β2gpI ($P=1\times10^{-5}$), anti-cardiolipin (P=0.002) and rheumatoid factor (P=0.004) and DRB1*13 with anti-Sm (P=0.02) and anti-β2gpI (P=0.01) antibodies. Also, negative associations of DRB1*04 with anti-Sm, anti-SSA/Ro, DQB1*03 with anti-Sm and DRB1*11 with anti-Sm and anti-β2gpI were observed.

Conclusions: We identified DRB1*03 and DRB1*16 as risk alleles and DRB1*01 allele with a decreased risk for SLE disease. More importantly, we found a close link between genetic susceptibility for SLE and status of autoantibodies that was more evident for DRB1*03 allele.

Keywords: Systemic lupus erythematosus; HLA-DRB1; HLA-DQB1; Autoantibody

(18362)

Association of IL-10 genetic polymorphisms (592 A/C and 819T/C) with the susceptibility to Acute Lymphocytic Leukemia in Children of Southwestern Iran

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Abstract: Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children. Various genetic and environmental factors are contributing to the development of this disease. One of these effective factors is cytokine polymorphism. One of the most important cytokines is Interleukin 10 (IL-10). In this study, we investigated the relationship between IL-10 polymorphisms (819T / C, 592A / C) and acute lymphocytic leukemia in children in Ahvaz. In addition, its association with age, sex, stage of the disease,and the immunophenotypes of the patients were analyzed.

A blood sample from 185 age-matched children (92 ALL and 93 healthy controls) was collected. Genomic DNA was extracted by salting out method and genotyped for rs1800871 and rs1800872 *IL10* genes were identified using Real-Time allelic discrimination Taq-Man assay. Leukemia risk associated with the genotypes was estimated by SPSS software (odds ratio and unconditional logistic regression).

Using wild type 819-T as a reference group, No association between individual homozygotes (CC) and heterozygotes (TC) for the C allele819T/C was found. However, the combination of homozygotes and heterozygotes (TC + CC) for this allele conferred a significant increase in the risk of ALL with an odds ratio of 2.05 and 95% confidence interval of 1.05-4.02 ($P<0.034$). On the other hand, using the wild type 592-A as reference genotype, no significant association between ALL and healthy subjects in terms for individual or the combination of the alleles (AC, CC, or AC+CC). No significant relationship between age and sex of the patients and IL-10 polymorphisms ($P>0.05$). The relationship between genotypes IL-10 (rs1800871, rs1800872) and the stage of the disease and were significant ($P=0.046$) and with immunophenotypes of the patients ($P>0.05$)

Key words: polymorphism, acute lymphoblastic leukemia, Interleukin 10

(18180)

The impact of interleukin (IL)-33 gene polymorphisms on asthma incidence in the Iranian population

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Background: IL-33 is a member of the IL-1 superfamily that is secreted in response to tissue damage, allergens, and microorganisms by epithelial cells in the lungs. There are several single nucleotide polymorphisms (SNPs) in intron 1 and the promoter region of *IL-33* gene that are reported to have associations with susceptibility to asthma and allergic diseases.

Method and materials: We investigated SNPs of IL-33 (rs1342326 and rs3939286) in 126 asthmatics patients and 300 age/sex-matched controls. Different molecular experiments, including TaqMan Real-Time PCR assay, total serum IgE level, eosinophil count, and skin prick test were performed to achieve the project objectives. We evaluated several phenotypes associated with asthma, such as Rhinitis, Sinusitis, Nasal polyps, food allergy, skin allergy, and their histories among asthmatic patients through a questionnaire.

Results: The frequencies of mutant genotypes in both SNPs were significantly higher in asthmatics patients compared with controls. The C/C genotype of rs1342326 was associated with atopic, mild, and late-onset asthma, which enhanced the level of eosinophils in peripheral blood. Nevertheless, the A/A genotype of rs3939286 showed a significant association with severe, non-atopic, and childhood-onset asthma. The rs3939286 in the IL-33 gene was significantly associated with an increased risk of asthma in women (OR: 1.57, CI: 1.07-2.30, p-value: 0.020) in the sex-stratification analysis. We investigated the impact of these SNPs on aeroallergens, but we could not demonstrate any significantassociation.

Conclusion: We conducted the study in Iran and showed that SNPs of IL-33 are one of the most influential genes in asthma among the Iranian population. It is important to identify possible genetic risk factors, epigenetic mechanisms, and changes in environmental factors to provide effective individualized therapy and control this multifactorial disease.

Keywords: Asthma; Interleukin-33; single nucleotide polymorphism; environmental factors

(17952)

Increased frequency of KIR2DS4 del/del among *AA* genotype carriers with B cell acute lymphoblastic leukemia in southwestern Iranian population

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Background: Acute lymphoblastic leukemia (ALL) is known to be the most common malignancy among children. The early onset of ALL suggests a key role of genetic factors in its development. Killer cell immunoglobulin-like receptor (KIR) gene complex that encodes a group of key receptors expressed at the surface of natural killer cells has been of great interest as a possible genetic factor affecting the susceptibility to ALL. In this case-control study, we aimed to verify whether the inheritance of specific KIR genes or genotypes were associated with susceptibility to childhood B-ALL in southwestern Iranian population.

Methods: To this end, KIR genotyping was carried out for 120 patients with childhood B-ALL and 120 sex-matched healthy controls using PCR-SSP method. The frequencies of 11 KIR genes and KIR2DS4 variants were investigated among patients and healthy controls.

Results: We found no association between KIR genes, KIR *AA*, *Bx*, centromeric, and telomeric genotypes and susceptibility to childhood B-ALL. Moreover, no association between childhood B-ALL and KIR B-content scores was detected. However, *AA* genotype carriers homozygous for KIR2DS4 deleted variant were found to be at a higher risk of developing childhood B-ALL compared with those who inherited at least one KIR2DS4 full-length variant.

Conclusion: It seems that the inheritance of different KIR genes does not affect the risk of childhood B-ALL in southwestern Iranian population. However, among individuals with *AA* genotype, homozygosity of KIR2DS4 deleted allele seems to increase the risk of childhood B-ALL.

Keywords: Acute lymphoblastic leukemia, killer cell immunoglobulin-like receptor

(18561)

Clinical, epidemiological and genetic findings in patients with polyautoimmunity

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Background: In recent decades, the emergence of new molecular diagnostic modalities has unraveled the underlying genetic defects of inborn errors of immunity (IEIs) with predominant autoimmune manifestations. The identification of new mutant genes responsible for autoimmunity may help the diagnosis of affected individuals at the early stages of the disease, better prognosis, and prevention of similar birth defects in a family. In this regard, we aimed to evaluate the genetic profile and pattern of autoimmune disorders among Iranian patients with polyautoimmunity.

Methods: Forty-five patients with early-onset polyautoimmunity were included in the study. Polyautoimmunity was defined as the presence of two or more autoimmune disorders in one patient. The clinical data were collected via a questionnaire from hospital records or direct interviews with relatives. The DNA extraction from serum samples and genotyping by next-generation sequencing (NGS) were performed for all patients.

Results: The study population included 15 [33.3%] male and 30 [66.7%] female. The most prevalent ethnic groups were Persians (51.2%) and Azeris (39.0%). The median age at the time of evaluation and the onset of autoimmune symptoms were 12.0 and 6.0 years, respectively. Most patients (58.5%) were born to non-consanguineous parents. In 23 (54.8%) patients a positive family history of autoimmune disorder was reported. The autoimmune disorders mostly included insulin-dependent diabetes mellitus (IDDM) in 39 (86.7%) patients, celiac disease in 29 (64.4%) patients, and autoimmune thyroiditis in 20 (44.4%) patients. The most frequent overlap in autoimmune disorders was present between IDDM and celiac (n=25, 55.6%) and then IDDM and autoimmune thyroiditis (n=15, 33.3%).

Conclusion: The prevalence of monogenic IEIs in patients with early-onset polyautoimmunity is higher than in the general population. In these patients, immunologic workup and genetic evaluation may lead to early diagnosis of IEIs, which can positively impact the evolution of complications and even management of autoimmune disorders.

Keywords: Autoimmune polyendocrinopathy, inborn errors of immunity, insulin-dependent diabetes mellitus, autoimmune thyroiditis

(18514)

Relationship between HLA-DRB1 and -DQB1 alleles and history of H. pylori infection in Iranian multiple sclerosis patients

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Background: Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS) in humans. Although the etiology of MS is unknown, pathogenesis involves a complex interaction between genetic and enviromental factors. Helicobacter pylori (H. pylori) is a one of environmental factors involved in autoimmune diseases. This study aimed to explore the associations of HLA-DRB1/-DQB1 alleles, haplotypes and genotypes with MS risk and history of H. Pylori infection in MS disease.

Methods: We studied 125 MS patients and 153 healthy controls. HLA typing was performed by a polymerase chain reaction (PCR) amplification with sequence-specific primers (PCR-SSP) method. HLA alleles, haplotypes and genotypes frequencies were compared between two groups and among the patients in terms of history of H. pylori infection.

Results: We observed that HLA-DRB1*15 (P=0.03) and HLA-DQB1*06 (P= 0.02) were significantly associated with increased risk of disease whereas, DRB1*14 (P= 0.004) showed a significantly negative association with MS. Analysis of the HLA-DRB1-DQB1 haplotypes and genotypes frequencies in both groups of the study showed that DRB1*15-DQB1*06 (P=0.01) haplotype and DQB1*06/*06 (P=0.01,OR3.73) genotype were positively associated with MS disease and only DRB1*14-DQB1*05 (P=0.004) haplotype (P=0.04) was negatively associated with the disease. Also, Among the HLA-DRB1 and -DQB1 alleles, only HLA-DQB1*02 (P=0.02) showed a significant association with history of H. pylori infection in MS patients.

Conclusions: We identified DRB1*15 as risk allele and DRB1*14 allele as protective allele for MS disease. Also, we found relationship between HLA-DQB1*02 allele with history of H. pylori infection. Also, we found that the risk of disease is reduced in people with susceptible alleles (DR2, DR3, DQ2 and DQ6) who had a history of H. pylori infections.

Keywords: Multiple Sclerosis; H. pylori; HLA-DRB1; HLA-DQB1

(18508)

Relationship between Serum Complement (C3 and C4) Levels and HLA-DRB1 and -DQB1 in Patients with Systemic Lupus Erythematosus

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Background: Systemic lupus erythematosus is a chronic autoimmune disorder that has different serological and clinical manifestations**.** One of the most relevant genetic factors in systemic lupus erythematosus (SLE) is human leukocyte antigen (HLA) gene complex which plays a central role in autoimmune responses. Furthermore, various serological biomarkers such as complement C3, C2, C4 and Anti-ds-DNA have been identified in this disease. This study aimed to explore the associations of HLA-DRB1 and -DQB1 alleles and haplotypes with SLE risk and their relationship with Serum complement level (C3 and C4) in SLE disease.

Methods: In this cross-sectional study 127 patients with systemic lupus erythematosus were studied. In this study, serum levels of serum C3 and C4 of patients were measured by nephelometric method. In addition, HLA-DRB1 and HLA-DQB1 alleles were determined by PCR-SSP method and then HLA-DRB1 and –DQB allele's frequencies were compared with serum complement level among SLE patients.

Results: We found that HLA-DRB1*03 and HLA-DRB1*16 alleles were significantly associated with increased risk (P=0.008 and P=0.002 respectively) and DRB1*01 conferred a decreased risk for SLE (P=0.03). Similar associations were observed at haplotype level; DRB1*03~DQB1*02 (P=0.01), DRB1*16~DQB1*05 (P=0.004) and DRB1*01~DQB1*05 (P=0.04). Moreover, we observed significantly association of DRB1*15 (P=0.03) allele with decrease serum levels complement. Conversely, negative association observed between DQB1*03 (P=0.02) allele with decrease serum levels complement.

Conclusions: We identified DRB1*03 and DRB1*16 as risk alleles and DRB1*01 allele with a decreased risk for SLE disease. Also, we found a close link between HLA-DRB1*15 with decrease serum complement levels that one of the most susceptible alleles and negative association between with HLA-DQB1*03 with decrease serum complement levels that one of the most protective alleles in SLE pathogenesis. Therefore, we found that the decrease in the serum level of complement is significantly related to HLA alleles.

Keywords: Systemic lupus erythematosus; HLA-DRB1; HLA-DQB1; complement

(18450)

Clinical relevance of HLA-DRB1 and DQB1 genes in systemic lupus erythematosus patients

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Background: Given to the potential link between genetic risk factors and clinical features of systemic lupus erythematosus (SLE), this study aimed to explore the relationship between HLA-DRB1/DQB1 alleles and haplotypes and clinical subphenotypes of the disease in a group of Iranian SLE patients.

Method: HLA-DRB1 and HLA-DQB1 alleles were determined by PCR-SSP in 127 SLE patients and 153 ethnic-matched healthy controls. The relationships between various clinical manifestations and HLA alleles/haplotypes were analyzed in the patients.

Results: We found that HLA-DRB1*03 and HLA-DRB1*16 alleles were significantly associated with increased risk (P=0.008 and P=0.002 respectively) and DRB1*01 conferred a decreased risk for SLE (P=0.03). Similar associations were observed at haplotype level; DRB1*03~DQB1*02 (OR1.91,P=0.01), DRB1*16~DQB1*05 (OR3.65,P=0.004) and DRB1*01~DQB1*05 (OR0.36, P=0.04). We observed the positive associations of DRB1*07 and DRB1*07-DQB1*02 haplotype with arthritis and pulmonary involvement (P=0.006 and P<0.001 respectively), DRB1*03 and DQB1*02 alleles and DRB1*03-DQB1*02 haplotype with cutaneous (P=0.03, P=0.004 and P=0.02 respectively) and renal involvement, and DRB1*13 as well as DRB1*13-DQB1*06 haplotype with renal involvement. Conversely, negative associations of DRB1*13 with cutaneous and gastrointestinal disorders (P=0.004 and P=0.02 respectively) and DRB1*01 with renal involvement (P=0.03) were found in our patients. Patients carrying susceptible HLA-DR alleles had higher risk for expression of cutaneous involvement (P=0.03), anti-coagulant antibody development (P=0.01) and lower risk for pulmonary disorders compared to patients negatives for susceptible alleles (P=0.04).

Conclusion: Our findings on associations between HLA risk allele (DR3) as well as non-risk alleles with particular clinical manifestations and between the protective allele (DRB1*01) and protection against renal involvement indicate the important role of HLA class II genes in predisposing of specific clinical features of SLE disease which could be implicative for therapeutic applications and better management of SLE patients.

Keywords: Systemic lupus erythematosus; HLA-DRB1; HLA-DQB1; Clinical manifestations

(18297)

Overexpression of miRNA-34a-5p in gastric cancer associated fibroblast cells contribute to PDL1 reduction in these cells

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Background: Cancer-associated fibroblast cells are the most important component in the tumor microenvironment which play a key role in tumor progression. Several studies have shown that microRNA dysregulation in these cells contributes to the tumor progression ability of CAFs. The purpose of this study was to explore understanding the role of miRNA-34a overexpression in CAFS from gastric cancer patients on PDL1 expression in these cells. **Method:** the primary CAF cells were isolated from patients with gastric cancer. miRNA-34a-5p was transfected to these cells with lipofectamine 2000 according to the manufactures instruction. We evaluated the effect of miR-34a-5p on PDL1 expression in CAFs by real-time PCR.
Result: our results have shown that PDL1 expression was decreased in the transfected CAF cells.
Conclusion: This study showed that microRNA34a in CAFs perhaps can improve immune response via PDL1 downregulation in these cells. We suggested that miRNA34a in CAFs has a potential role in therapeutic approaches to cancer immunotherapy.
Keywords: Cancer associated fibroblast cell, miRNA34a, PDL1

(18259)

Association of interleukin-1β polymorphisms in patients with Chronic Hepatitis C Virus in Tehran Province of Iran

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Background: Host genetic factors play a major role in determining the outcome of hepatitis C infection. Interleukin-1β (*IL-1*β) promoter polymorphism will affect susceptibility to inflammatory diseases. This study aimed at determining the association between polymorphisms of *IL-1*β and response to treatment in patients with hepatitis c virus (HCV) in province Tehran.

Methods: In this cross-sectional study, 80 patients with HCV that 40 responders to treatment and 40 non- responders to treatment as well as 40 healthy individuals were randomly selected. Genomic DNA was extracted from blood samples. Genotypes IL-*1*β −511 (C / T) and *IL-1*β −31 (C / T) were determined by amplification refractory mutation system–polymerase chain reaction (ARMS-PCR) technique.

Results: : In the group of patients who were responders to treatment, genotype *IL-1*β −511 (C / T) was seen more than other genotypes , whereas in non- responder patients to treatment, all three genotypes CC, CT, TT were observed . In both groups of responder and non- responder patients, genotype *IL-1*β -31-TT was more than other genotypes. There was no significant difference between the two groups (P = 1.00)

Conclusion: There was no significant difference in genotype *IL-1*β-31-TT between responders and non-responders to treatment groups, on the other hand, In the group of patients who were responders , the genotype *IL-1*β −511 (C / T) was more observed, **it seems the possible beneficial effects of this mutation in these patients.**

Keywords: Interleukin-1β, Polymorphism, Hepatitis C, ARMS-PCR

(18228)

Knockdown of SOX12 expression by Antisense LNA GapmeRs induced apoptosis factors and correlate with CTNNB1 gene expression in acute myeloid leukemia cell line (M07e)

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Background: Recent improvements in molecular medicine and gene therapy are led to discovering novel cancer treatments. Usage of antisense LNA GapmeRs is one of the molecular research fields for the diagnosis and treatment of cancers. Acute myeloid leukemia (AML) is a heterogeneous hematopoietic malignancy characterized by the rapid accumulation and malignant proliferation of immature myeloid progenitors. SOX12 is a novel potential target for acute myeloid leukemia however; the role of SOX12 in leukemia remains unknown.

Methods: In this study, SOX12 was blocked by antisense LNA GapmeRs (ALG) in human Acute Myeloid Leukemia cell line (M07e). Cells were transected with Gapmer anti-Sox12 at 24, 48, and 72 h post-transfection. Transfection efficiency was assessed by a fluorescent microscope. Furthermore, a quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) was accomplished to evaluate the SOX12, CTNNB1, CASP3, and, CASP9 expression. Cell viability was evaluated by MTT assay.

Results: Our results showed that SOX12 expression was decreased remarkably in the ALG group, moreover SOX12 knockdown was associated with a decrease in CTNNB1 expression. Besides, downregulation of SOX12 in M07e cell line could induce apoptosis, probably through the upregulation of CASP3 and CASP9.

Conclusion: The findings declare that inhibition of SOX12 could be a new target in the treatment of AML and approach treatment based on antisense therapy.

Keywords: Acute myeloblastic leukemia, Antisense LNA GapmeRs, SOX12, CTNNB1, Apoptosis

(18121)

Interleukin -17 polymorphisms in acute kidney injury patients

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Background: Cardiopulmonary bypass (CPB) has been demonstrated to provoke a systemic inflammatory response believed to be responsible for some of the serious postoperative complications such as renal dysfunction. Therefore, we tested the hypothesis suggesting that the gene variants of IL- 17A (IL-17), as an inflammatory cytokine, are associated with acute kidney injury after CPB (AKI-CPB).
Methods: A total of 135 Iranian patients undergoing cardiopulmonary bypass were included in this study, of whom 65 (48.1%) developed AKI. Blood specimens were collected preoperatively and at 12 hours postoperatively. The IL-17 gene polymorphisms (rs2275913 and rs3819024) were determined using sequence-specific primers (PCR-SSP).
Results: There were no associations between gene polymorphisms (rs2275913and rs3819024) and incidence of AKI- CPB. There was an association between thers2275913 SNP and the severity of AKI.
Conclusion: Although we did not find any significant association between gene polymorphisms (rs2275913and rs3819024) and incidence of AKI-CPB, our results showed that there is an association between rs2275913 and the severity of AKI- CPB.

(17948)

Association between Chronic Hepatitis B Virus infection and polymorphisms of *rs9277535* in HLA-DP in the southern khorasan population (East of Iran)

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Background: Chronic hepatitis B virus (HBV) infection is a major global health concern. Because the result of HBV infection depends mainly on host immune responses, and HLA, as an important component of the immune response, plays a critical role in immunologic reactions to HBV infection. HLA genes are located in chromosome 6p21.31, and molecules are glycoproteins that deliver foreign peptides to the surface of the cell, presenting the peptides to CD4+ T helper cells, and enhancing the adaptive host immune responses to eliminate pathogens such as HBV. Many studies have reported that the HLA-DP locus is also associated with HBV clearance. **Aim of study**: we aimed to explore the association of the *HLA-DP* polymorphisms rs9277535 with HBV susceptibility in the Southern Khorasan population.

Methods: In the study, people were divided into two groups, which were control (who have previously recovered from HBV infection, spontaneously, HBc-positive antibody / HBsAg negative) and other were patients with chronic HBV infections, HBsAg positive test results for At least 6 months. The detection of the hepatitis B core antibody (anti-HBc) and HBsAg in the serum samples were done using a commercially ELISA kit and Genomic DNA was extracted from peripheral blood mononuclear cells by using the salting-out method. The HLA-DP rs9277535 were evaluated by PCR and, the purified PCR products were sequenced using the Applied Biosystems 3730/3730XL DNA analyzer sequencing.

Results: In the present study, The result manifested a statistically significant difference between case and control individuals and we found SNP, rs9277535 of HLA-DP, did associate with the HBV susceptibility and the G allele of the SNP Was a potential protective allele in HBV in the Southern Khorasan population, On the other hand, according to our data, only rs9277535 A allele significantly increased the risk of persistent HBV infection.

Conclusion: In conclusion, this study demonstrated that HLA-DP rs9277535 polymorphisms are strongly associated with HBV susceptibility in the Southern Khorasan population (East of Iran).

Keywords: Chronic hepatitis B, Immune response, Polymorphism, Human leukocyte antigens DP (HLA-DP)

(16879)

Genetic diagnosis of immunodeficiency using Whole Exome Sequencing

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Background: Immunodeficiencies (IDs) are a group of clinically, immunologically, and genetically heterogeneous of errors of immune system. There are more than 200 different forms of immune deficiency diseases. Genetic molecular diagnosis could help to characterize these diseases, subsequently improve IDs diagnoses and therapies. The genetic causes of these diseases can be identified using whole exome sequencing (WES).

Methods: Herein, we applied WES in 8 patients with a clinical presentation of ID from Southwest of Iran. In-silico analyses using various tools were done to find out pathogenic ID causing variants from WES data. Then Sanger sequencing was done for the variants validation and allele segregation in the probands and their families.

Results: At result the molecular diagnosis was achieved in 5 of 8 cases with different types of ID. We found one reported and four novel variants including; c.514_518delCAAGC (rs767481076) and c.513_514insGCTTG in *RAB27A,* c.446_447insTTT in *RAG2*, c.6917C>G in *LRBA*, and c.545C>A in *PTPRC* genes with homozygous genotype in the patient and heterozygous genotype in their unaffected parents. We didn't find any pathogenic variants for 3 cases. Bioinformatics analysis using Mutation taster, PredictSNP, PolyPhen, and ACMG classification from VarSome showed these variation are highly possibly diseases causing. Notably these variants except *PTPRC:* c.545C>A, were absent in the public databases including ExAC and GnomAD. *PTPRC:* c.545C>A had allele frequency=0.000112 and 0 homozygotes in GnomAD database. Also none of the variants were not found in our homemade database made of more than 1000 WES file data.

Conclusion: Our findings support the utility of WES as an important diagnostic tool for the patients with ID. Genetic profiling of these disorders could improve clinical diagnosis and management. We conclude that all the presented variants should be considered in ID molecular profiling in southwest Iran.

Keywords: Immunodeficiency, Whole exome sequencing, genes, pathogenic variants

Congress Abstracts

Immunohematology & Transplant

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

18346

The new approach for stabilization the reactivity of coombs control cells by fixation of RBC membrane

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Background: Coombs control cells are used in blood banks as a control of the human antiglobulin test to detect false negative results. The availability of this reagent in laboratory due to short shelf-life of RBC is limited. In this study, the protocol for preparation of coombs control cells was developed based on fixative components.

Methods: To select best media for storage RBC, known O^+ phenotype from healthy blood donors were divided into three groups RIS, fixative agent (glutaraldehyde and paraformaldehyde in various concentrations), and *Alsever's* solution. For this purpose, the reactivity of sensitized RBC (sRBC), morphology and lysis marker evaluated in supernatant during storage time.

Results: The results were shown the fixation process affects the antigenicity of RBCs, but it depends on the concentration of the fixative. So, the high concentration of fixative components was rule out. Although Alsever's provides ideal conditions for the storage of sRBC in terms of metabolic changes, it's not desirable media for the stability of morphology and agglutination reaction. The result of our study showed that fixation sRBC in glutaraldehyde 0.001% in RIS is the best media for preparation coombs control cells.

Conclusion: Treatment sRBC with glutaraldehyde is an appropriate approach for preparation coombs control cells that can overcome the limitation of *Alsever's* solution and be cost-effective to available for transfusion service.

Keywords: Coombs control, Fixation, Sensitized RBC

14400

Transitional immature regulatory B cells and regulatory cytokines can discriminate chronic antibody-mediated rejection from stable graft function

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Background: The **balance between inflammatory and anti-inflammatory responses of the immune system has been demonstrated to determine the fate of transplanted allografts.** Here we analyzed $CD19^{+}CD24^{hi}CD38^{hi}$ immature transitional regulatory B (TRB) cells, as well as the gene and protein levels of interleukin (IL)-10 and transforming growth factor (TGF)-β in the three separate groups, include of stable transplanted subjects, chronic antibody-mediated rejection (cAMR) patients, and healthy individuals.

Methods: Peripheral blood mononuclear cells (PBMCs) from stable subjects (n=36), cAMR patients (n=36) and healthy controls (n=18) were isolated. Flowcytometry was performed for CD19, CD24, and CD38 surface markers. ELISA and quantitative real-time PCR were performed for IL-10 and TGF-β cytokines.

Results: The percentages of immature TRB cells were significantly decrease in cAMR patients (0.98%) versus stable recipients (2.81%) and healthy subjects (4.03%) (P= 0.001 and P< 0.001, respectively). Total lymphocytes, circulating B cells, memory and mature subsets of B cells did not show any significant difference between the groups. TGF-*β mRNA was 3-fold* upregulated in the cAMR group compared to stable patients (P< 0.001.), but without significant alteration at the protein level. Also, long-term survival renal transplant recipients had a higher protein but not mRNA levels of IL-10 than short-term survival renal transplant recipients.

Conclusion: It seems that immature TRB cell subpopulation might be a crucial regulator of immune system response and plays an important role in determining the transplantation outcome. Furthermore, immunosuppressive IL-10 and TGF-*β* cytokines might act as a double sword and can exhibit either pathogenic or protective effects against allograft.

Keywords: Regulatory B cells, Kidney transplantation, Interleukin 10, Transforming growth factor beta, chronic antibody-mediated rejection.

15465

Evidence for a rebalanced hemostatic system in pediatric liver transplantation: A prospective cohort study

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Background: In adults with end-stage liver disease concurrent changes in pro- and antihemostatic pathways result in a rebalanced hemostasis. Children though, have a developing hemostatic system, different disease etiologies, and increased risk of thrombosis. This study aimed to assess the hemostatic state of children during and after liver transplantation.

Methods: Serial blood samples were obtained from 35 children (≤16 years) undergoing primary liver transplantation (June 2018- June 2019) in Isfahan,iran. Routine hemostasis tests, thrombomodulin-modified thrombin generation, clot lysis times, and hemostatic proteins were measured. Reference values were established using an age-matched control group of 30 children.

Results: Thrombocytopenia was present in study patients. Von Willebrand factors were doubled and ADAMTS13 levels decreased during and after transplantation up until day 30, when platelet count had normalized. Whereas prothrombin time and activated partial thromboplastin time were prolonged during transplantation, thrombin generation was within normal ranges, except during perioperative heparin administration. Fibrinogen, factor VIII levels, and clot lysis time were elevated up until day 30.

Conclusion: In conclusion, children with end-stage liver disease are in tight hemostatic balance. During transplantation a temporary heparin-dependent hypocoagulable state is present, which rapidly converts to a hemostatic balance with distinct hypercoagulable features that persist until at least day 30. This hypercoagulable state may contribute to the risk of posttransplant thrombosis.

Keywords: clinical research/practice, liver allograft function/dysfunction, liver transplantation/hepatology, pediatrics, thrombosis and thromboembolism

15506

Investigating the role of BAFF and its receptors in renal transplant recipients with chronic antibody-mediated rejection

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Background: Chronic antibody-mediated rejection (cAMR) considers as a main cause for late allograft loss, and as the lacking efficient treatment, it should detect as soon as possible. B-cells are the main cause of cAMR because of producing antibodies. Therefore, due to the important roles of B-cell activating factor (BAFF) and its receptors (BAFF-R, BCMA and TACI) in B-cell survival and antibody production, and the pivotal improtance of B-cells in cAMR, as well as, the few number of studies that have investigated BAFF and its receptors in cAMR renal transplant patients, we decided to evaluate BAFF and its receptors in renal transplanted patients.

Methods: The study included 40 kidney allograft patients with cAMR, 40 stable kidney allograft patients, and 8 healthy volunteers with normal kidney function. The serum level of BAFF was analyzed by ELISA and mRNA expressions of BAFF and BAFF receptors (BAFF-R, BCMA and TACI) were measured using quantitative Real-time PCR.

Results: BAFF serum level was increased significantly in both cAMR and stable patients compared to healthy volunteers (P= 0.038 and P= 0.018, respectively). The mRNA expression level of BAFF was upregulated in cAMR and stable patients than healthy volunteers (P= 0.004 and P= 0.002, respectively). BCMA mRNA expression was increased significantly in cAMR and stable patients compared to healthy volunteers (P= 0.002 and P= 0.022, respectively). There was an overexpression of TACI mRNA in cAMR patients compared to stable patients (P= 0.01).

Conclusion: Both soluble protein and mRNA transcript of BAFF increased in transplant recipients, as well, BAFF transcripts had a positive correlation with years post-transplantation and increased over the years after transplantation in both stable and cAMR patients. However, BAFF neither at the serum level nor at the mRNA transcript level cannot be a good biomarker for cAMR prognosis. In addition, expression of TACI, compared to other receptors of BAFF, confer a potential to be used in distinguishing cAMR and stable kidney transplanted patients.

Keywords: Renal transplantation, Chronic antibody-mediated rejection, BAFF, BAFF-R, TACI, BCMA

16727

PD-L1 overexpression protects the mesenchymal stem cell-derived cardiomyocyte-like cells against alloreactive immune responses in mice

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Background: Although the autologous transplant cells are immunologically durable, allogeneic cell transplantation is inevitable in a series of cases. Mesenchymal stem cells (MSCs) are one of the suitable candidates for cardiac tissue regeneration that has been shown to acquire immunogenicity concurrent with cardiomyogenic differentiation. The present study aimed to exploit PD-L1, as a key immunomodulatory checkpoint ligand to protect the MSCs-derived cardiomyocyte like cells (CLCs) against the detrimental alloimmunity.

Methods: Mouse bone marrow-derived MSCs were lentivirally transduced to overexpress PD-L1. MSCs were *in vitro* differentiated into CLCs and the expressions of immunologic molecules were compared between MSCs and CLCs. The *in vitro* and *in vivo* allogeneic immune responses were also examined.

Results: The differentiated CLCs had higher expressions of MHC-I and CD80. Upon *in vitro* co-culture with allogeneic splenocytes, CLCs caused more $CD4^+$ and $CD8^+$ T cell activation, lymphocyte proliferation, and IFN-γ release in comparison to MSCs. PD-L1 overexpression on CLCs decreased the activation of $CD8^+$ T cells, lymphocyte proliferation, and IFN-γ response. The PD-L1 overexpressing CLCs elicited lower *in vivo* $CD4^+$ and $CD8^+$ T cell activation and reduced anti-donor antibody response accompanied by an increased durability and reduced T cell infiltration.

Conclusion: Regarding the inevitably to use allogeneic stem cell resources for cardiac tissue regeneration, it is vital to save these therapeutic cells against the detrimental alloreaction. PD-L1 overexpression on CLCs has exhibited the potential to be exploited as a preparative strategy prior to allogeneic cardiac cell therapies in order to increase their efficacy and durability. Moreover, the establishment of clinical-grade PD-L1 overexpressing MSCs could reinforce the development of "off-the-shelf" cell therapies for cardiac regeneration.

Keywords: PD-L1, Cardiac regeneration, Tolerance induction, Immune-checkpoint

16872

Enhancing effects of PNU-74654 on the antiproliferative effects of 5-FU in breast cancer via the inhibition Wnt pathway

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Background: PNU-74654 is an inhibitor of Wnt/β-catenin pathway, which has anti-growth and anti-proliferative effects on cancer cells. And may, therefore, be a potential-therapeutic target. The purpose of this study was to investigate the effects of PNU-74654 suppresses activation of Wnt proliferative signaling in BC cells, either alone or in combination with fluorouracil (5FU).

Method: The 4T1 and MCF-7 cell were grown in DMEM containing 10% heat-inactivated FBS and 1% streptomycin/penicillin and maintained at 37°C in 5% CO2 atmosphere.

The effect of drugs on modulation of the cell cycle was evaluated in the cells treated for 24 hr with 5-FU, PNU-74654, and their combination at IC50 concentrations. Cells were stained by propidium iodide (PI) and cell cycle modulation was assessed using a FACSCalibur flow cytometer, equipped with the CELLQuest software for data analysis. The ability of 5-FU, PNU-74654, and its combination with 5-FU to induce cell death was explored by measuring sub-G1 regions during cell cycle analysis, as described previously.

Western blotting

Briefly, proteins were separated on polyacrylamide gels, then transferred to a nitrocellulose membrane, incubated with the primary (rabbit anti-CyclinD1 and anti-p-GSK3α/β, 1:1,000; diluted in the blocking solution; anti-β-actin, 1:10,000; all from Abcam, Cambridge, UK) and secondary (goat anti-rabbit, 1:10,000; Westburg, Leusden, The Netherlands) antibodies and detected followed by chemiluminescence detection.

Results:

GSK3α/β is one of the main regulators of the Wnt pathway which its downregulation could activate this pathway and its downstream targets including cyclin D1 and survivin. Cyclin D1 is involved in regulation of G1 to the S phase in the cell cycle. Our results showed that the PNU-74654 inhibited the expression of cyclin D1 and survivin at messenger RNA (mRNA) level. Moreover, it has been reported that the thrombin is overexpressed in BC patients and enhances cell proliferation in cancer cells. We have already shown the effect of thrombin on Wnt/β- catenin activation via phosphorylated level of GSK3-α/β.The stimulatory effect of thrombin on cyclin D1 upregulation was abrogated in the presence of PNU-74654. Also, we found that the high expression of cyclin D1 in thrombin-MCF-7 treated cells was mediated through Wnt activation. Also, we already observed that the PNU-74654 attenuates GSK3α/β phosphorylation and Wnt/β-catenin signaling activation in thrombin-treated cells.

Also PNU-74654, 5-FU, and their combination affected cell cycle distribution of BC cells. PNU-74654 significantly ($p < 0.05$) increased the percentages of the cells in G1 phase (e.g., from 56.6% in the control to 68.6% in the G1 phase) after 24 hr, whereas reducing the percentage of the cells in S and G2, suggesting that the PNU-74654 might favor 5-FU activity through a significant increase of cells in the G1 phase and inhibiting cells in G1 to S.

Conclusion:

Our data showed that use of combination of PNU-74654 and 5FU can consider as anticancer drug by suppressing activation of Wnt proliferative signaling in BC cells. More studies on other cancer cell line and models should be done to clarify the exact anti-cancer roles of this drug.

Keywords: Breast cancer, Wnt signaling pathway, PNU-74654, cell cycle.

16793

Reduced CD4^{+} CD25^{++} CD45RA^{-} Foxp3^{hi} Activated Regulatory T Cells and its Association with Acute Rejection in Patients with Kidney Transplantation

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Background: It was found that regulatory T cells (Tregs) importantly affect the maintenance of the kidney graft. However, Tregs are a heterogeneous population with less to more suppressive activity. The aim of this study was to determine the effects of different subsets of Tregs, as well as their ratio to effector T cells (Teff), on kidney transplantation outcomes.

Methods: A total of 58 participants were enrolled in this study and divided into four groups: (i) first kidney transplant recipients (stable 1); (ii) second kidney transplant recipients (stable 2); (iii) transplant recipients with acute rejection (AR); and (iv) healthy control subjects. By using flow cytometer, the frequencies of CD4^{+} CD25^{++} CD45RA^{-} Foxp3^{hi} activated Tregs (aTregs), CD4^{+} CD25^{+} CD45RA^{+} Foxp3^{lo} resting Tregs (rTregs), CD4^{+} CD25^{+} CD45RA^{-} Foxp3^{lo} non-suppressive T cells, CD4^{+} CD25^{+} Foxp3^{-} cells Teff, and total Tregs were analyzed in all subjects.

Results: The frequency of aTregs (as well as the ratio of aTregs/Tregs) was significantly lower in the AR patients than the other three groups. In contrast to AR patients, stables 1 and 2 had a higher aTreg/Treg ratio than those in the control group. Although patients with AR had a significantly lower total Tregs than the other three groups, the balance of total Tregs and Teff was similar between patients with and without AR.

Conclusion: Patients with AR had poorer immunoregulatory properties than those with normal graft functioning, as well as those in the control group. These reduced immunoregulatory properties in patients with AR could lead to graft rejection.

Keywords: Regulatory T cell, Activated Tregs, Effector T cell, Kidney transplantation, Acute rejection

18543

Extraction and purification of α–Defensin from leukocytes trapped on leukoreduction filters by cation exchange chromatography

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Background: The α-defensin or human neutrophil peptides (HNPs) 1 to 3 are essential arms of the innate immune system that have activity against Coronavirus as well as their antimicrobial, immune regulatory, and anticancer activities. Due to their disulfide bonds, the synthesis of α-defensin by chemical and recombinant technologies is challenging. Nonetheless, blood banks routinely use leukocyte reduction filters (LRFs) containing billions of leukocytes, a source of peptides like α-defensin, to provide sufficient leukoreduced blood products. Therefore, this study aimed to develop and optimize procedures for recovering the trapped and viable leukocytes in LRFs. Besides, we optimized approaches in order to extract and purify natural HNP 1-3 from the recovered neutrophils using cation exchange chromatography.

Methods: We used an optimized elution system to recover the trapped leukocytes in LRFs, then we sonicated the isolated granulocytes. We have also developed an original approach based on the purification of the HNP 1-3 from the recovered neutrophils by cation exchange chromatography. Afterwards, utilizing the Bradford protein assay, SDS-PAGE, and western blotting, we tested and confirmed the purified peptides.

Results: Purifications were performed on the column (a TSKgel CM-3SW 7.5 x 75 mm) and peak representing the combination of HNP 1–3. Moreover, clear blue bands on the clear background were resulted in all SDS-PAGE results. The presence of the HNP 1–3 (3.4 kDa) band was detected in western blot results. Besides, viable neutrophils recovered, and α-defensins were extracted and purified.

Conclusion: Our experience showed the use of LRFs, which used to be considered as discarded products, can be considered as an economic, attractive, and safe source for large numbers of human cells. Also, the recovered neutrophils are provided and can be extracted from LRFs for purifying natural HNP 1-3 with no cost.

Furthermore, these filters can be a valuable, novel, and readily available replacement for the traditional sources of cellular research and possible clinical purposes.

Keywords: Natural human α-defensin; Leukoreduction filters; Cation exchange chromatography; Cell recovery

18677

Association between Prognosis factors together and Response to Therapy and ABO blood groups in Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) constitute a family of genetically heterogeneous lymphoid neoplasms derived from B- and T-lymphoid progenitors. ALL affects both children and adults. Several prognostic factors have been identified for children and adults with ALL, and risk categories have been defined to guide therapy. Some of the better-defined prognostic factors include age, WBC count, and abnormalities and ABO blood group. The aim of the present study was to observation the relation between Prognosis factors by together and Response to Therapy and ABO blood groups in Acute Lymphoblastic Leukemia. 200 ALL patients and 210 sex and age-matched healthy controls were enrolled in this study. The laboratory and clinical characteristics recorded at presentation were age, wbc, platelet, EMI, CRD and overall survival. Statistical analyses were accomplished using SPSS version 23, P-values less than 0.05 were considered statistically significant. There was a significant associations between increase of WBC with age, EMI and Spleenomegaly, Hepatomegaly and high risk of ALL patient (P=<0.001). And patients with phenotype Tcell had more white blood cells than patients with phenotype Bcell. And there was relationship between decrease platelets with increasing WBC(p=0.048) and reduction age(p=0.03), hemoglobin and EMI positive and Spleenomegaly. On the relationship between marker CD10+ with Prognostic factors was seen significant associations among this marker with decreasing age, WBC, increasing hemoglobin and standard risk. Between mean WBC and Increasing the percentage EMI with peripheral blood blast was seen significant relationship(p=0.015). Also there were a significant relationship between survival duration and age, white blood cells, platelets, hemoglobin, EMI and percentage of blasts in the blood(P=<0.001). The ABO blood group distribution showed that there is significant differences between O blood group and patients with ALL (p=0.037)and age,platelet,EMI(p=0.04). The result of this study showed a significant association of Prognosis factors and response to therapy by together, ABO blood group and risk of ALL development.

Keywords: Prognosis factors, Acute lymphoblastic leukemia, ABO blood group

18713

Frequency of dendritic cell subsets and ILT3, ILT4 gene expression in two different immunosuppressive protocols in kidney transplant recipients

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Background: Dendritic cells (DCs) have a major role in the initiation of an *immune response* and Immunoglobulin-like transcript 3&4 (ILT3&ILT4) are inhibitory receptors that induce tolerance in DCs. Recent studies show that immunosuppressive agents affect frequency of DCs. Herein, we compared the effect of mycophenolate mofetil (MMF) and *sirolimus* (SRL) in tacrolimus (TAC)-based immunosuppression on DC subsets frequency and ILT3/ILT4 gene expression in kidney transplant recipients.

Methods: In this clinical trial study (IRCT2016062528620N1), we enrolled 24 adult transplant recipients who received MMF/TAC (n=14) or *SRL* /TAC (n=10). Peripheral blood samples were obtained from recipients, 24-48 hours before transplantation and 4 months after transplantation. The frequency of DC subsets was analyzed by flow cytometry and gene expression of ILT3 /ILT4 were estimated by *real-time PCR*.

Results: Our results showed *that* MMF vs. SRL treated recipient showed an increase in pDC % with increased in the expression of ILT3/ILT4 , while those receiving SRL+TAC down regulated both genes and decrease pDC frequencies.

Conclusion: MMF+TAC induces an increase in circulating pDCs and the expression of ILT3 and ILT4 with a reduction of mDC1 ,which was in favor of better allograft survival, However, for confirming the results of this preliminary study, a cohort study with larger sample size is necessary.

Keywords: Dendritic cells; Kidney Transplantation; Immunoglobulin-like transcript; ILT3; ILT4; Micofenolat Mofetil; Tacrolimus; Sirolimus

18715

Special Anti-Hepatitis Antibody Content of IVIGs Made of Iranian Plasma

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Background: Intravenous immunoglobulin (IVIG) is a biological product containing a mixture of IgGs which is needed to protect especial patients against various microbial pathogens. Worldwide the prevalence of viral hepatitis shows remarkable decrease due to the improvement of the socioeconomic condition and hygiene. There is a concern that whether these changes could diminish the protective effect of immunoglobulin's. The content of anti HAV and anti HBS antibodies were studied in IVIGs made of Iranian plasma under contract fractionation, to determine whether the antibody titers in the IVIGs are still adequate for hepatitis treatment/ prophylaxis in special cases.

Methods: 38 IVIG products which were purified from the Iranian recovered and source plasma were selected and enrolled in the study. The content of antibody against hepatitis A, hepatitis E, hepatitis D, hepatitis G and antibodies against hepatitis B surface antigen and hepatitis B core antigen in different IVIG lots' have been determined by ELISA method. Anti- HAV and Anti HBS antibody were titrated.

Results: Anti-HAV antibody in all understudied IVIGs was 38304± 17735mIU/mL and it was significantly higher in IVIGs manufactured by recovered plasma. Anti HBS antibody in all investigated IVIGs was 2487±965mIU/mL with no significant difference between two types of donors. Anti-HBC, Anti-HEV, and Anti-HGV were detected in all products but not titrated, whereas any anti-HDV was not found.

Conclusion: It was declared that both anti-HAV and anti-HBs antibody titers in IVIG products derived from Iranian plasma is suitable for replacement therapy. Secondly, antibody titers in IVIGs made of different types of plasma, either in recovered or source plasma has shown a variation which might be considered in the relevant planning for different therapeutic/ prophylactic strategies. Finally, antibodies against hepatitis B and A have been higher than those in studies in Europe and the United States.

Keywords: Intravenous immunoglobulin (IVIG), anti-HAV, Anti-HBS, plasma

16681

FAS-670A>G gene polymorphism and risk of allograft rejection after organ transplantation: Systematic review and meta-analysis

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Background: The association between the increased risk of allograft rejection after organ transplantation and FAS promoter polymorphism has been evaluated previously. However, the results were inconclusive. Therefore, we conducted a meta-analysis to obtain a more precise estimation of the association between this polymorphism and the risk of allograft rejection.

Methods: All eligible studies reporting the association between FAS-670A>G polymorphism and the risk of allograft rejection published up to December 2019 were collected by comprehensive systematic database search in web of science, Scopus, and PubMed. After that, the odds ratio (OR) and 95% confidence interval (95% CI) were calculated to assess the strength of association between the FAS gene polymorphism and the risk of allograft rejection.

Results: This meta-analysis included 6 case-control studies with 277 rejection patients and 1001 non-rejection controls after allograft transplantation. The overall results showed no significant association between the FAS-670A>G polymorphism and the risk of allograft rejection in five genetic models (dominant model: OR= 0.81, 95% CI= 0.58-1.12; recessive model: OR= 0.10, 95% CI= 0.80-1.53; allelic model: OR= 0.96, 95% CI= 0.79- 1.18; GG vs. AA: OR= 0.92, 95% CI= 0.62-1.36; and AG vs. AA: OR= 0.75, 95% CI= 0.52-1.08).

Conclusion: Our findings suggest that the FAS-670A>G polymorphism was not associated with the risk of allograft rejection after organ transplantation. Further comprehensive and well-designed studies are required to assess these associations.

Keywords: FAS, allograft rejection, polymorphism, meta-analysis

16874

The Association Between Vitamin D and Acute Rejection in Human Kidney Transplantation: A Systematic Review and Meta-analysis

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Abstract

Introduction: vitamin D (VitD) deficiency is associated with several diseases such as multiple sclerosis, rheumatoid arthritis, respiratory infection and etc. In the field of transplantation (kidney transplantation) some studies reported that patients with VitD deficiency are of increased risk of acute rejection but other study did not show such risk. On the other hand, since VitD is a modulatory factor and can reduce inflammatory response, understanding the exact role of it in transplantation may contribute to tolerance condition in this patients.

Methods: the electronic databases including PubMed, Scopus, Embase, ProQuest, Web of Science, and Google Scholar were searched for eligible studies. In general, 14 studies with a total of 4770 patients were included in the meta-analysis. Regarding the methodological heterogeneity, we selected random-effects combination model. Moreover, the odds ratio (OR) was chosen as an effect size for this study.

Results: After combination of 14 studies, we showed that Patients in the VitD deficient group had 82% increased risk of acute rejection compared to patients in the VitD insufficient/sufficient group and this effect was significant (OR 1.82; 95% confidence interval (CI) 1.29, 2.56; $I^2 = 52.3\%$). This result was significant and regarding the narrow CI, it can be a conclusive result. Study quality and gender variable were the main sources of inconsistent results in the primary studies. Moreover, by using meta-regression, we showed that VitD deficiency independent from the estimated glomerular filtration rate (eGFR) of patients increased the risk of acute rejection.

Conclusion: The normal VitD status of patients few days before and after transplantation may reduce the risk of acute rejection as it has definite modulatory effects on immune cells.

Keywords: kidney transplantation, vitamin D, 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D, acute rejection

17941

Involvement of interferon-γ + 874A/T polymorphism in the pathogenesis of and therapeutic response to immune thrombocytopenia

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Background: Immune thrombocytopenia (ITP) is an autoimmune disease characterized by symptoms of thrombocytopenia and bleeding due to production of autoantibodies against platelets. Recently, the occurrence of polymorphisms has been identified as one of the main causes of disease onset.
Methods: To conduct this study, we recruited 140 patients and control individuals with no history of platelet loss. After collection of specimens, the prevalence of interferon-γ polymorphism was evaluated using the allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR) technique and confirmed by sequencing techniques.
Results: The results showed that the frequency of the AA genotype was higher in the control group, compared with patients with ITP; however, in the acute and chronic groups, the frequency of the AT genotype was higher than that of the AA genotype. We also discovered that there was no significant correlation between platelet counts before and after treatment, nor in its related parameters with interferon (IFN)-γ polymorphism.
Conclusion: rs2430561 does not seem to have any role in ITP pathogenesis and treatment response.
Keywords: IFN-Ɣ; immune thrombocytopenic purpura; pathogenesis; platelet; polymorphism;

18581

Relationship Between ABO Blood Group and Colon Cancer in Ahvaz Hospitals During 2019-2020

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Background: Cancer as a non-communicable disease is currently the leading cause of death in the world and Colon cancer is one of the most deadly and common types of cancer in various countries, including Iran. Various studies have shown that there is a relationship between ABO blood groups and colon cancer. The study aims was to investigate to investigate the relationship between blood groups and colon cancer.

Methods: This study was performed by preparing a checklist of patients with colorectal cancer in 2019 and 2020 in Ahvaz hospitals and this information was received from the Cancer Research Center of Ahvaz University of Medical Sciences. The relevant information was entered into SPSS software and analyzed.

Results: The results show that 50% of patients had blood group O, while 30% of patients had blood group A and 15% of patients had blood group B and only 5% of patients had blood group AB, also 95% of patients had RH antigen. In this regard, 85% of the patients were men, 75% of whom were in the age group of 50 to 70 years and the age groups of 15 to 35 years and 35 to 50 years were 5 and 20% of the patients, respectively.

Conclusion: Findings show that blood group O^+ is most associated with colon cancer. In fact, men with blood group O^+ in the age group of 50 to 70 years have the highest susceptibility to colon cancer. Therefore, blood type can be used as a marker in identifying people at high risk for colon cancer

Keywords: Colon cancer, Blood group, RH antigen

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(18348)

The characteristics of red blood cell alloantibodies in thalassemic patients

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Background: Alloimmunization can lead to serious clinical complications in transfusion-dependent patients. Demographic characterization of main blood group antigens can be helpful to find antigen-matched products. Knowing the most common alloantibodies in transfusion-dependent thalassemia patients make it possible to prevent alloimmunization.

Methods: A total of 62 alloimunized thalassemia patients who were referred to Adult Thalassemia Clinics in Mazandaran from all provinces in 2019 were included in this study. The antibody screening and identification were performed with using a panel of recognized blood group antigens. Also, RBC phenotyping for Rh system was performed by standard tube techniques with commercially available typing sera.

Results: A total of 62 thalassemia patients (27 males and 35 females) were included in the study. Thirty-four patients (54.8%) had beta thalassemia major and twenty-eight (45.2%) had thalassemia intermedia. The median age of patients was 35 years (range: 14–57 years). The most frequent blood group was O (35.5%). Anti-K (26.9%), anti-E (21.79%) and anti-D (12.8%) were the most commonly isolated antibodies. Also, the frequency of rare alloantibody anti-Kpa was 5%. Fifty patients had a single alloantibody (80.6%) and twelve patients (19.4%) had multiple antibodies. The incidence of multiple antibodies in intermediate thalassemia is higher than major.

Conclusion: Phenotype determination of RBCs indicated a low prevalence of E antigen (24%) in thalassemia patients. Also, anti-E was the second most common alloantibody in this study. It seems that a policy antigen E and Kell negative blood transfusion can have a significant effect on reducing the incidence of alloimmunization.

Keywords: Alloimmunization, thalassemia, phenotyping, multitransfused

15th Virtual International Congress of
Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

Congress Abstracts

Immunology of Exercise, Aging, and Nutrition

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

15505

Fasting and the Immune System: A Systematic Review

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Background: Observing the principles of proper nutrition has an important effect on strengthening the immune system to fight infections. Fasting is one of the acts of worship that God has commanded in which man must abstain from eating and drinking during certain. Also in terms of medical science and nutrition, given that the pattern and diet during this month is very different from other months of the year, so this month can be studied as a unique model in the impact of changing dietary patterns on human health. Therefore, this study intends to investigate the effects of fasting on the immune system.
Methods: In this study, which is a systematic review, by reviewing valid books, topics and concepts related to the topic, searched in selected scientific databases, including Iran medex, Pubmed, SID with the keyword nutrition, Immune system, fasting were used and 100 articles were obtained. Among these articles, the full-text articles that were available and published in the last 5 years.
Results: Fasting has a great effect on the immune system by reducing the amount of food intake and the resulting hunger, and starvation or reducing the amount of food intake at specific intervals affects cellular and humoral immunity and reduces inflammatory responses and regulation the immune system. During fasting, hematopoietic stem cells are stimulated by the shock of starvation and their proliferation rate increases, resulting in more new cells being produced. Fasting can increase the total leukocyte population at all ages.
Conclusion: The results showed that combining fasting with daily lifestyle increases health and reduces the risk of many diseases for individuals and many results show the spiritual and material impact of fasting on improving the level of the immune system. According to the mentioned points, the risk of viral and infectious diseases can be reduced.
Keywords: fasting, nutrition, immune system

16848

The intrinsic and extrinsic elements regulating inflammation

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Abstract:
Inflammation is a sophisticated biological tissue response to both extrinsic and intrinsic stimuli. Although the pathological aspects of inflammation are well appreciated, there are still rooms for understanding the physiological functions of the inflammation. Recent studies have focused on mechanisms, context and the role of physiological inflammation. Besides, there have been progress in the comprehension of commensal microbiota, immunometabolism, cancer and intracellular signaling events' roles that impact on the regulation of inflammation.
Despite the fact that inflammatory responses are vital through tissue damage, understanding the mechanisms to turn off the finished or unnecessary inflammation is crucial for restoring homeostasis. Inflammation seems to be a smart process that acts like two edges of a sword, meaning that it has both protective and deleterious consequences. Knowing both edges and the regulation processes will help the future understanding and therapy for various diseases.

Keywords: Inflammation, Obesity, Nutrition, Microbiome, NF-KB, NLRP3 inflammasome

(16699)

The amount of interleukin-6 in the serum of strength athletes and endurance athletes compared to non-athlete people

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Abstract:

Background: The purpose of this study is to compare the IL-6 level of serum in young strength athletes with the endurance athletes and non-athletes. This research is functional and the data were collected by using field study.

Material and Method: For this, among the healthy candidates for attending in the research, 20 people (weight: 78 kg ± 4.1; height: 179 ± 3.59; age: 26 ± 4.38; and body mass index of 24± 1.51) were selected for endurance athletes group, and 10 people (weight: 79 kg ± 4.62; height: 181 ± 2.51; age: 25 ± 4.32; and body mass index of 24± 1.63) were selected for and 12 people (weight: 79 kg ± 4.62; height: 181 ± 2.51; age: 25 ± 4.32; and body mass index of 24± 1.63) were selected for non-athletes group (control group). The endurance athletes group are athletes who has done at least six months of regular aerobic practices and the strength athletes group has done at least six months strength training and the control group consists of people who have no athletic background. Blood samples were taken from all the 3 groups when they were relaxed to evaluate the above factors in ELISA method. Noting that the data were normal, these data were analyzed by individual t-student test in a significant level (P≤ 0/005).

Result(s): By comparing the amount of IL-6 in the serum of all the 3 groups, IL-6 level in endurance athletes showed a significant reduction compared to other two groups (P≤ 0/05).

Conclusion(s): The results of this research showed that aerobic exercises is the cause of reduction in IL-6 level. This change is probably due to the reduction of inflammation in skeletal muscles, which is in turn due to the low intensity of exercises.

Key Words: interleukin-6, strength and endurance athletes

18041

The effect of docosahexaenoic acid (DHA) on the cellular and exosomal expression of mammalian target of rapamycin (*mTOR*) and related microRNAs in breast cancer cell lines

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Background: The omega-3 long chain polyunsaturated fatty acid, docosahexaenoic acid (DHA), shows anti-proliferative effects in cancer cell lines and in animal models. mTOR is the one of the regulators for proliferation and survival of cancer cells. The present study investigated the effects of DHA on cellular and exosomal expression of mTOR and related tumor-suppressor microRNAs (miRs) in triple positive (BT-474) and triple negative (MDA-MB-231) breast cancer cell lines. **Methods:** BT-474 and MDA-MB-231 cell lines were treated for 24 hours with 100 **µM** DHA under normoxic and hypoxic conditions. The exosomes were isolated by ultracentrifuge and determined by electron microscopy and CD9, CD63, CD81 immunoblotting. cDNAs from cellular and exosomal total RNAs were used for evaluation the expression of mTOR and related tumor-suppressor miRs, miR-101 and miR-214, by quantitative Real-time PCR.
Results: We demonstrated that DHA significantly decreased cellular and exosomal expression of mTOR in both normoxic and hypoxic conditions for both cell lines. Consistently, DHA caused significant increased expression of miR-214 in all treated groups but altered expression of miR-101 showed different patterns in cells and exosomes.
Conclusion: According to the beneficial effect of DHA in decreasing the expression of a master regulator for proliferation of cancer cells, mTOR, in part by increased expression of miR-214, it could be used as supplementary therapy in breast cancer cases. Also, miRNA replacement therapy would be useful by suppressing the expression of mTOR in breast cancer treatment.
Keywords: DHA, breast cancer, exosome, mTOR, miRNA

18373

Anti-inflammatory and antioxidant effects of synbiotics in type-2 diabetes mellitus patients with periodontal disease under nonsurgical-periodontal-therapy. A double-blind, placebo-controlled trial

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Background: The aims of this study was to investigate the effects of supplementation synbiotic with nonsurgical-periodontal-therapy (NSPT) on the inflammatory and antioxidant parameters in type 2 diabetes mellitus (T2DM) patients with chronic periodontitis (CP).

Materials and Methods: In this randomized double-blind placebo controlled clinical trial, 50 patients suffering from DM and periodontal disease were recruited and randomly assigned to two groups: intervention group (n= 25), received one capsule of synbiotic supplement (500 mg in each capsule) per day after lunch and control group (n=25) received placebo capsule containing 500 mg wheat flour for 8 weeks. All patients were treated with NSPT during the intervention period. Serum levels of interleukin-1b (IL-1b), Malondialdehyde (MDA), total antioxidant capacity (TAC), superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and periodontal indices including pocket depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP) and plaque were measured before and after the intervention.

Results: The results showed that synbiotic supplementation with NSPT significantly decreased the mean levels of IL-1b, MDA, TNF-α, IL-6, and mean of periodontal status indexes including PD and CAL and also decreased plaque index in the intervention group in compare to the baseline ($p < 0.05$). Also, there were significant differences in the mean changes of IL-1b, IL-6, and MDA between intervention and control groups after the intervention ($p < 0.05$). Serum levels of TAC, SOD, and GPx significantly increased in intervention group ($p < 0.05$). Furthermore, there were significant differences in the mean changes of TAC and GPx in intervention group in compare to control group ($p < 0.05$).

Conclusions: Synbiotic supplementation with NSPT may be beneficial in improving inflammatory and antioxidant Parameters in T2DM Patients with CP.

Keywords: Type 2 Diabetes Mellitus; Inflammation; Periodontal disease; Synbiotic; Antioxidant

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: AJUMS. REC.1395.452 and registration code of Iran clinical trials: IRCT2016110430694N1

18428

Combined All-Extremity High-Intensity Interval Training Regulates Immunometabolic Responses through Toll-Like Receptor 4 Adaptors and A20 Downregulation in Obese Young Females

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Metainflammation and malfunctions of toll-like receptor 4 (TLR4) are related to obesity-induced immunometabolic morbidities. There are almost no studies relating exercise training to the TLR4 pathway and its adaptors and negative regulators. Thirty young women with obesity (exercise group and control group) were included in a 10-week all-extremity combined high-intensity interval training program. The immunomodulatory impacts of exercise on TLR4, its related adaptors (TIR domain-containing adaptor-inducing IFN-β [TRIF], myeloid differentiation factor 88 [MyD88], and tumor receptor-associated factor 6 [TRAF6]), transcriptional factors (nuclear factor [NF]-κB and interferon regulatory factor 3 [IRF3]), and negative regulator (A20) mRNA levels were assessed by real-time PCR. Also, the serum concentration of TLR4 final products (tumor necrosis factor α [TNFα] and interferon γ [IFNγ]) was measured by ELISA. Cardiorespiratory and body composition parameters were tested, as well. There was a significant improvement in body composition and cardiorespiratory fitness. This intervention downregulated TLR4 (from 2.25 ± 1.07 to 0.84 ± 1.01), MyD88 (from 4.53 ± 5.15 to 1.27 ± 0.88), NF-κB (from 1.61 ± 2.03 to 0.23 ± 0.39), IRF3 (from 1.22 ± 0.77 to 0.25 ± 0.36), and A20 (from 0.88 ± 0.59 to 0.22 ± 0.33) levels and reduced the TNFα concentrations (from 22.39 ± 11.43 to 6.26 ± 5.31) significantly in the exercise group, while no statistically significant change was found in TRIF and TRAF6 expression and IFNγ circulating levels. It is concluded that long-term exercise modifies the inflammatory pathways and modulates the immune function at the early stages of inflammation initiation in circulating immune cells. Accordingly, we suggest time-efficient exercise protocols as a possible therapy approach for the prevention of M1 polarization.

Keywords: Exercise therapy; Immunoregulatory effects ; Toll-like receptor 4 ; Obesity; Metainflammation

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran
ICIA 2021 AHVAZ IRAN

18754

Study on the effects of vitamin D on the gene expression and DNA methylation of *FOXP3* gene in the splenocytes of C57BL/6 mice

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Background: Vitamin D plays a variety of physiological functions, such as regulating mineral homeostasis. It has been reported that calcitriol, the active form of vitamin D, exerts some immunomedulatory effects through affecting several types of immune cells, such as regulatory T (Treg) cells. In this study, the impacts of calcitriol on the gene expression and methylation of the conserved non-coding sequence 2 (CNS2) region of the forkhead box P3 (*FOXP3*) gene promoter in $CD4^+$ T cells of mice, were evaluated.

Methods: Fourteen C57BL/6 mice were recruited in this study and divided into two intervention and control groups. In the vitamin D treatment group, each mouse received 100 ng calcitriol through intraperitoneal injection every other day. After 21 days, mice were sacrificed and $CD4^+$ T cells were isolated from splenocytes, and RNA and DNA of the cells were extracted. The expression of *FOXP3* were relatively quantified by real-time PCR, and the DNA methylation percentage of every CpG site in the CNS2 region was measured individually by bisulfite-sequencing PCR.

Results: Vitamin D intervention could significantly increase the expression of *FOXP3* gene in the $CD4^+$ T cells of mice comparing with the control group. Meanwhile, methylation of the CNS2 region of *FOXP3* promoter was significantly decreased in three of ten CpG sites in the vitamin D group compared to the control group. For the first time, we showed that calcitriol treatment led to DNA hypomethylation in the CNS2 region of the FOXP3 gene promoter of healthy mice.

Conclusion: The results of this study showed that vitamin D can engage the methylation process to induce *FOXP3* gene expression. Hypomethylation could be a potential mechanism for increasing *FOXP3* gene expression by facilitate the access of transcription factors to bind to this region. This study suggests that the epigenetic modification of *FOXP3* gene could be an important therapeutic strategy in autoimmune conditions like Multiple Sclerosis.

Keywords: Vitamin D, *FOXP3*, Methylation

18784

Effect of Vitamin A, Vitamin D and their combination on gene expression of CD4+ T cells cytokines and transcription factors in experimental model of Multiple Sclerosis in C57-BL/6 mouse

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Background: Multiple sclerosis (MS) as an autoimmune disease is one of the world's most common neurologic disorders. Recent studies have shown that vitamin A and D have important roles in immune system function. The present study investigates the effects of ATRA, calcitriol and combination treatment of calcitriol and ATRA in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS).

Methods: Inbred female C57Bl/6 mice, 9–10 weeks old, were allocated to four preventive groups, each consisting of eight animals, ATRA (250µg/mouse), calcitriol (100 ng/mouse), combination of ATRA and calcitriol (125 µg/mouse and 50 ng/mouse) and vehicle groups. EAE was induced by MOG35-55 peptide and pertussis toxin. Splenocytes were isolated from EAE-induced mice and the expression of retinoic acid receptor-related orphan receptor gamma t (ROR-γt), Interleukin-17 (IL-17), transforming growth factor beta (TGF-β), and forkhead box P3 (FOXP3), GATA binding protein 3 (GATA3), Interleukin-4 (IL-4), T-cell-specific T-box transcription factor (T-bet), interferon gamma (IFN- γ) genes were measured using real time polymerase chain reaction. Data analyzed by the SPSS 22.0 software. Differences between groups were considered statistically significant when P values were less than 0.05.

Results: The expression of ROR-γt and IL-17, T-bet, IFN- γ genes in the splenocytes of ATRA, calcitriol and combination- treated mice was significantly reduced compared to those of vehicle- treated mice ($P < 0.05$). The expression of GATA3 and IL-4 genes in the splenocytes of ATRA, calcitriol and combination- treated mice was significantly increased compared to those of vehicle- treated mice ($P < 0.05$).

Conclusion: This study demonstrated in vivo inhibitory effects of combination treatment of ATRA and calcitriol on the mRNA expression of IL-17, ROR-γt, T-bet, IFN- γ and stimulatory effects on the mRNA expression of GATA3, IL-4, TGF-β and FOXP3 in splenocytes from EAE female mice. Thus, this nutraceutical approach may be promising for the treatment and/or prevention of MS.

Keywords: Calcitriol, ATRA, Experimental autoimmune encephalomyelitis, Gene Expression

18809

Is inflammatory and metabolic response to an acute session of resistance training different among trained and untrained individuals?

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Background: An acute session of resistance training (RT) may have resulted in different metabolic and inflammatory changes. The purpose of this study is to compare the metabolic and inflammatory alternation in resistance-trained and untrained men.

Methods: Twenty-eight young healthy men (14 trained and 14 untrained people) participated in this present study. Metabolic and inflammatory responses, muscle damage, blood pressure (BP) and glycemic changes following an acute RT were evaluated before, immediately and 1 hour after training. The training consisted of 3 sets of 8 upper-body exercises at 80% of 1-RM.

Results: Baseline percentage of muscle mass and creatine kinase (CK) activity were significantly greater within the resistance-trained individuals compared to the untrained group. After conducting an RT session, there was a significant reduction in insulin concentration and resistance within the two groups and in blood glucose only within the untrained group. Furthermore, CK, lactate dehydrogenase (LDH), BP and heart rate (HR) were increased in both trials following training session without any between-group differences. Unlike CK, LDH activity was reduced during 1 hour of training ($P < 0.05$). Among the different inflammatory markers, only IL-6 significantly increased in both groups. IL-6 alternation remained unchanged after 1 hour of training in the trained group, while it increased 1 hour after training session in untrained individuals ($p < 0.05$). The levels of IL-10, TNF-alpha, IL-6/IL-10 ration and TNF-alpha/IL-10 ratio did not change following both interventions. Blood glucose, insulin and HOMA-IR also remained unchanged in both trials.

Conclusions: These findings show that an acute session of RT may be resulted in some metabolic and inflammatory alternation by increasing IL-6, BP, HR, CK and LDH. The inflammatory and hypotensive response is significantly greater among untrained individuals. In terms of muscle damage markers following a RT session, there were no between-group significant differences.

Key words: Resistance training, acute, single session, inflammatory response, metabolic

15504

The effect of exercise on the immune system of athletes

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1. Department of Nursing, School of nursing University of Bandar Abbas, Islamic Azad University

Background: The type, intensity and duration of exercise determine the effect of exercise on the immune system and possibly the susceptibility of athletes to upper respiratory tract infections. In this study, the effect of a moderate-intensity exercise session on the number and activity of respiratory burst neutrophils in athletes's peripheral blood and their upper respiratory tract infections after exercise and during training seasons was investigated.

Methods: 22 male athletes entered this experimental study after obtaining informed written consent. Athletes performed an exercise session(45 minutes)of moderate intensity. Blood samples were taken before and immediately after exercise. Athletes were evaluated for upper respiratory tract infections within 24 hours of the study and were asked about a history of upper respiratory tract infections during training seasons.

Results: The resting activity of neutrophils was in the normal range at rest. Exercise significantly increased the number of neutrophils. Exercise increased the percentage of stimulated neutrophils, but this increase was not significant. Athletes showed no symptoms of upper respiratory tract infections during the 24 hours after exercise. Athletes did not report a history of increased upper respiratory tract infections during training seasons.

Conclusion: The normal state of neutrophils at rest indicates that continuous exercise has not had a negative effect on the number and function of neutrophils in athletes. The fact that athletes do not increase the risk of upper respiratory tract infections during training seasons can be a confirmation of this. The increase in neutrophils immediately after exercise is the result of an expected and natural immune response to exercise stress. Lack of respiratory tract infections on the day after exercise may be associated with an increase in neutrophils after exercise and a decrease in their activity.

Keywords: Sport, Safety system, Neutrophils, Respiratory explosion, Athlete

16552

Caffeine and anti-tumor immunity

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Background: The immune system can identify and destroy tumor cells in a process called anti-tumor immunity, using both innate and adaptive immunity including, cytotoxic CD8+ T, natural killer (NK), natural killer T (NKT), and dendritic cells. However, cancer cells evolve different strategies to avoid the tumoricidal attack. Adenosine is a crucial regulatory factor that accumulates in response to hypoxia and inflammation in the tumor microenvironment and has several roles in the tumor cells escaping from immune surveillance. Adenosine binds to specific adenosine receptors such as A2A receptors that can be antagonized by caffeine. Caffeine is a natural methylxanthine and one of the most commonly consumed food ingredients worldwide. The present study was aimed to review the mechanistic effects of caffeine on anti-tumor immunity.

Methods: Relevant studies were identified by searching MEDLINE, Scopus, and Google Scholar through November 2020.

Results: It is reported that caffeine can increase cytokine production (particularly interferon-γ), CD8+ T lymphocyte infiltration and cytotoxicity, T cell proliferation, and NK cell activity by antagonizing A2A receptors on the immune cells. Ultimately, all of the mentioned activities raise anti-tumor immunity and suppress tumor growth. Besides, caffeine is shown to reduce the inflammatory process with consequent suppression of cancer progression.

Conclusion: In conclusion, caffeine may hold therapeutic potential in the increment of anti-tumor immunity and diminishing inflammation and also the rate of cancer development. More mechanistic studies are warranted to shed light on the effects of caffeine on cancer immunosurveillance.

Keywords: Caffeine, Cancer, Tumor, Immunity

16553

Caffeine and anti-tumor immunity

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1. Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

Background: The immune system can identify and destroy tumor cells in a process called anti-tumor immunity, using both innate and adaptive immunity including, cytotoxic CD8+ T, natural killer (NK), natural killer T (NKT), and dendritic cells. However, cancer cells evolve different strategies to avoid the tumoricidal attack. Adenosine is a crucial regulatory factor that accumulates in response to hypoxia and inflammation in the tumor microenvironment and has several roles in the tumor cells escaping from immune surveillance. Adenosine binds to specific adenosine receptors such as A2A receptors that can be antagonized by caffeine. Caffeine is a natural methylxanthine and one of the most commonly consumed food ingredients worldwide. The present study was aimed to review the mechanistic effects of caffeine on anti-tumor immunity.

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Conclusion: In conclusion, caffeine may hold therapeutic potential in the increment of anti-tumor immunity and diminishing inflammation and also the rate of cancer development. Studies that are more mechanistic are warranted to shed light on the effects of caffeine on cancer immunosurveillance.

Keywords: Caffeine, Cancer, Tumor, Immunity

16555

A systematic review of the effects of garlic on multiple sclerosis

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Background: Multiple sclerosis (MS) is an autoimmune and demyelinating disease of the central nervous system with debilitating sensory and motor complications. The lack of definitive treatment for MS, and also the dissatisfaction with the currently available therapies or their side effects encourage many patients to seek herbal remedies improving their quality of life. In this regard, it is reported that many MS patients consume garlic to strengthen their immune system. Although there is some evidence supporting the immunomodulatory and anti-inflammatory effects of garlic, no previous systematic review has summarized the literature on the beneficial effects of garlic on MS. So, the present study was aimed to systematically review the available studies investigating the effects of garlic or its components on MS.

Methods: Relevant studies were identified by searching MEDLINE, Scopus, and ProQuest through November 2020, using the query "(((Multiple Sclerosis[Title/Abstract])) OR (Disseminated Sclerosis[Title/Abstract])) AND (garlic[Title/Abstract])".

Results: Out of 39 initial records, three studies met our inclusion criteria. All included studies were on the effects of S-allyl cysteine (SAC), an organosulfur compound and the main constituent of the aged garlic extract, on the animal models of MS. All three studies reported the beneficial effects of oral administration of SAC on the clinical signs, biomarkers of oxidative/nitrosative stress and inflammation in the brain and spinal cord, axonal demyelination, and mitochondrial and neurohistologic viability.

Conclusion: Present literature is limited to conclude the beneficial effects of garlic on the management of MS symptoms. However, according to the promising results of the animal studies, garlic might be an effective strategy in the improvement of MS. Human studies are warranted to obvious whether the observed effects in the animal studies can be translated to the clinical situation.

Keywords: Multiple Sclerosis, Garlic, S-allyl cysteine, Systematic review

16556

A systematic review of the effects of garlic on multiple sclerosis

Sara Shojaei-Zarghani[1]

1. Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

Background: Multiple sclerosis (MS) is an autoimmune and demyelinating disease of the central nervous system with debilitating sensory and motor complications. The lack of definitive treatment for MS, and also the dissatisfaction with the currently available therapies or their side effects encourage many patients to seek herbal remedies improving their quality of life. In this regard, it is reported that many MS patients consume garlic to strengthen their immune system. Although there is some evidence supporting the immunomodulatory and anti-inflammatory effects of garlic, no previous systematic review has summarized the literature on the beneficial effects of garlic on MS. So, the present study was aimed to systematically review the available studies investigating the effects of garlic or its components on MS.

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16557

A systematic review of the effects of ginger on rheumatoid arthritis

Sara Shojaei-Zarghani[1]

1. Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

Background: Rheumatoid arthritis (RA) is an autoimmune-inflammatory disorder characterized by swelling in multiple joints, pain, and destruction lesions in joint cartilage and bone. An imbalance between T helper17 (Th17)/Regulatory T-cell (Treg) is responsible for the development and progression of RA, in which Th17 cells are involved in inducing autoimmunity and Tregs act as immunosuppressive cells. The lack of definitive treatment for RA and the side effects of the available therapeutic strategies encourage many patients to seek herbal remedies improving their quality of life. Ginger is one of the most frequently used herbal medicine used by RA patients. However, no previous systematic review has summarized the randomized clinical studies on the effects of ginger on RA.
Methods: Relevant studies were identified by searching MEDLINE, Scopus, and Google Scholar through November 2020, using the MESH terms.
Results: Out of 318 initial records, three articles met our inclusion criteria. The included trials assessed the effects of 1500 mg ginger for 8 or 12 weeks on RA patients. These studies reported the beneficial effects of ginger on the improvement of disease activity score, serum lipid profile, and the expression of inflammatory biomarkers of high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-1β in RA patients. Moreover, ginger increased the forkhead box P3 (FoxP3) and reduced the RAR-related orphan receptor γt (RORγt) expression levels. It is worth mentioning that Tregs express the transcription factor FoxP3, and RORγt is required for the induction of IL-17 transcription.
Conclusion: Present literature is limited to conclude the effects of ginger on the management of RA. However, according to the promising results of the available studies, ginger might be an effective strategy in the improvement of RA symptoms and molecular features. More randomized clinical trials are warranted to obvious whether ginger can be prescribed in the clinical situation.
Keywords: Rheumatoid arthritis, RA, Ginger, Systematic review

16558

A systematic review of the effects of ginger on rheumatoid arthritis

Sara Shojaei-Zarghani[1]

1.Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

Background: Rheumatoid arthritis (RA) is an autoimmune-inflammatory disorder characterized by swelling in multiple joints, pain, and destruction lesions in joint cartilage and bone. An imbalance between T helper17 (Th17)/Regulatory T-cell (Treg) is responsible for the development and progression of RA, in which Th17 cells are involved in inducing autoimmunity and Tregs act as immunosuppressive cells. The lack of definitive treatment for RA and the side effects of the available therapeutic strategies encourage many patients to seek herbal remedies improving their quality of life. Ginger is one of the most frequently used herbal medicine used by RA patients. However, no previous systematic review has summarized the randomized clinical studies on the effects of ginger on RA.
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Conclusion: Present literature is limited to conclude the effects of ginger on the management of RA. However, according to the promising results of the available studies, ginger might be an effective strategy in the improvement of RA symptoms and molecular features. More randomized clinical trials are warranted to obvious whether ginger can be prescribed in the clinical situation.
Keywords: Rheumatoid arthritis, RA, Ginger, Systematic review

16567

The Molecular Mechanisms of Vitamin D in Multiple Sclerosis/EAE

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Multiple sclerosis is a chronic autoimmune inflammatory disease of the Central nervous system leading to demyelination and neurodegeneration. Several different models of MS exist,model of experimental autoimmune encephalomyelitis (EAE) commonly used that induced both active immunization with myelin-derived proteins and peptides in adjuvant or via passive transfer of activated myelin-specific CD4+ T lymphocytes. Vitamin D establish an essential fat-soluble that has potential to affect a great number of genes, because vitamin D receptor binds thousands of genomic sites in immune cell lines stimulated with 1,25(OH)2D3. In addition, vitamin D has potential effect to enhance glucocorticoid efficacy in pathway with vitamin D/glucocorticoid interaction.moreover, 1,25D inhibited mTORc1 activity in murine T cells. Treatment with a specific mTORc1 inhibitor completes therapeutic glucocorticoid efficacy in EAE and vitamin D supplementation protects from experimental autoimmune encephalomyelitis (EAE).Protective effect associates with decline proliferation of CD4+ T cells and lower frequency of T helper (Th) 17 cells that has important pathogenesis role in experimental autoimmune encephalomyelitis (EAE) and Multiple Sclerosis . metabolic pathways and several signaling critical for T-cell differentiation and activation into Th1 and Th17 subsets in vivo and in vitro are impacted by vitamin D. For example , Jak/Stat, Erk/Mapk, and Pi3K/Akt/mTor signaling pathway genes are down-regulated upon vitamin D supplementation.vitamin D can modulate risk for developing Multiple Sclerosis.

Key words: Vitamin D. Multiple sclerosis, Experimental Autoimmune Encephalomyelitis

16698

The effect of aerobic exercise and anaerobic swimming on the surface of TGF-β1 and hs-CRP and serum calcium in young women

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3. *Department of infectious diseases and tropical medicine ,Faculty of medicine , Mashhad university of medical sciences , Mashhad , Iran*

Abstract

The aim of this study was to compare the effects of aerobic exercise and anaerobic swimming on the surface of hs- CRP ,TGF-β1 (f) and serum calcium in young women was. This quasi-experimental study population consisted of 100 women who were swimming in Mashhad in the age range 25 to 30 years and are proficient in 4 main swimming. 28 patients were randomly assigned to 2 groups (two groups of 14 each aerobic and anaerobic workout swim) and 10 patients in the control group. Blood samples to measure the factors that Hagrfth and data analysis by descriptive and inferential statistics, Kolmogorov-Smirnov test and ANOVA (ANOVA) was performed and the following results were obtained:

There were no significant differences between subjects serum levels of TGF-β1.) 366/0 (p =

There were no significant differences between subjects serum hs-CRP. (048/0 (p =

There is no significant difference between the serum calcium level subjects. (145/0 p =)

Conclusion: Based on this study, aerobic exercise reduces the level of hs -CRP Web aerobic swimming in subjects that this reduction was statistically significant. But no significant changes in serum levels of TGF-β1 and calcium.

Keywords: TGF-β1, hs-CRP, calcium, aerobic and anaerobic exercise

16846

Clinical Association of Variants in TLR4 and TLR9 Loci with Immunopathology of Parkinson's Disease in an Iranian Population

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4. Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran

Background: Neuroinflammation and immunopathology in Parkinson's disease (PD) is associated with genetic and environmental factors. The current study aimed to evaluating the Toll-like receptors (TLR4 and TLR9) genes polymorphism in Parkinson's disease patients in north of Iran.

Methods: In this study, DNA extracted from peripheral blood samples of in unrelated 100 cases of Parkinson's disease and 100 healthy-matched controls with mean age of 69.98 and 71.94 years respectively. Then single-nucleotide polymorphisms (SNPs) of TLR4 and TLR9 genotyped by restriction fragment length polymorphism - polymerase chain reaction (RFLP– PCR). The outcomes confirm by Sanger sequencing and for analysis of data SNPStats software and SPSS 22 were used.

Results: Our findings indicated that the allele distribution was meaningfully different in the PD group compared with the healthy control (P = 0.02) for rs352140 belonging to TLR9 gene. Moreover, rs352140T allele carriers were observed to be correlated with PD reduced risk (TT + TC vs. CC). The dominant rs352140 model was approved as the most acceptable inheritance model for fitting the data (OR 0.041, 95% CI 0.23-0.75, P= 0.0031). Moreover, haplotype analysis showed a meaningful correlation between TLR9 polymorphisms and Parkinson's disease.

Conclusion: Results in this study indicated that rs352140T of TLR9 gene was a protective factor in Parkinson's disease. Also, this SNP can be good prognosis and may be prophylactic or therapeutic target. However, future investigations are necessary.

Keywords
Toll-like receptors 4(TLR4), Toll-like receptors 9(TLR9), Parkinson's Disease (PD), Neurodegeneration, Single-Nucleotide Polymorphisms (SNPs)

18007

Milk- extracted extracellular vesicles: a double-edged sword on the immune system

Shervin Sadafian[1], Reza Darabian Aghdas[1], Negar Valizadeh Shaeri[1], Nima Shadmehri[2], Seyedeh Negar Mousavi Firouzabadi[1], Pouya Houshmand[1]

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It has been greatly understood that maternal milk plays a vital role in developing the immune system through diverse pathways further than supplying nutrients [1]. (e.g., contributing to immune cell induction or donating antibodies) Studies on milk from varied species have revealed so much of milk composition and protein content [2][1]. On the other hand, extracellular vesicles (EVs) have been lionized through the past decade due to their important role in pathological and physiological pathways. (e.g., cancer progression, cardiovascular diseases, neurodegenerative illnesses, spermatogenesis, and ovogenesis). Also, they are found so useful in the diagnosis process and even treating methods [3][4]. EVs are nanosized vesicles secreted from nearly every kind of cell in the body and can be found in all body fluids, including milk [5]. Many investigations have been accomplished around milk-extracted extracellular vesicles, which resulted in an almost complete data bank of milk EVs proteomics, genomics, and biological functions [6][2][7]. EVs presenting in milk participate in different biological paths like activating cells or inhibiting them (like TLR cells activation or inhibiting T cells proliferation and activation.)[6][1] Some of the pathways impress an infant's immune system directly and some indirectly [8][9]. It has been cleared EVs in milk modulate immune responses by revealing immune information to the child [1]. It has been shown EVs in milk inhibited CD4+ T cells activation impermanently. Also, activated CD4+ T cells co-cultured with breast milk EVs have been temporary halted in proliferation [9]. Moreover, epithelial cell migration has been boosted in the presence of milk-extracted EVs [6]. EVs can be named double-edged sword communication agents due to different impressions of cell-derived EVs on the child's immune system. However, also, they are harmonized toward modulating the immune system and regulating developmental pathways1]].

Keywords: Extracellular vesicles, Milk, Immune system, T cell

18065

Title: Comparison of breast milk and formula in neonatal allergy prevention: A review study

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Background: Today, atopic diseases and food allergies are on the rise around the world and it is considered as one of the health problems. Food allergies are defined as an adverse immune response to food and it happens when the immune system responds to harmless proteins. Because food allergies can be life threatening and children with food allergies are more likely to develop asthma or respiratory allergies, Therefore, food allergies must be taken seriously. Breast milk is a natural baby feeder that is available from birth and formula is an artificial food that is used to feed the baby. The aim of this study was to compare breast milk and formula in allergy prevention.

Methods: This study is a review study conducted in 2020. The data of the present study were collected by searching for the keywords Allergy, Breast milk, Infants, formula in the database Google scholar, SID, SCIENCE DIRECT and related articles analyzed.

Results: Exclusive breastfeeding reduces the risk of respiratory attacks, asthma, Skin allergies and eczema in infants. Insulin in breast milk causes premature infant's intestines development and decreased permeability to macromolecules that it plays an important role in preventing allergies and the development of the infant's immune system. Breastfeeding delays IgG production. The composition of breast milk changes at different times according to the baby's age and nutritional needs, thus reducing the risk of allergies. However, changes in the composition of the formula are not specific to every baby, and due to its selectivity, the baby may be sensitive to some of the ingredients in the new formula.

Conclusion: Compared to formula, breast milk has many effects, including the prevention of allergies and the provision of non-allergenic foods that are appropriate for the baby's age.
Therefore, breastfeeding is recommended when there is no need to use formula.

Keywords: Allergy, Breast milk, Infants, Formula.

18139

Title: The role of mitokines in inflammaging

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Abstract

The age-related alterations in the immune system triggers to a progressive decrease in responses to infections and vaccinations and a vulnerability to age-related inflammatory diseases. This phenomenon, called immunosenescence. Immunosenescence has been considered as harmful for the reason that it often triggers to inflammaging. Inflammaging is occurred as a consequence of mitochondrial dysfunction, altered autophagy and changes in DNA repair mechanisms, activation of inflammasome, and senescence-associated secretory phenotype (SASP) of T cells. A mitokine, a soluble molecule secreted in response to a mitochondrial stress response. In advanced age, the mechanisms of stress response are damaged, and this situation could cause to a constant production of mitokines, in the effort of neutralizing stress. Growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21) are mitochondrial stress-related mitokines. The circulating levels of these mitokines, are increased with age and associated with many pathological conditions. Mitokines modulate acute and chronic inflammatory reactions, and possibly modulation of their expression could be as therapeutic tools and anti-aging targets. Mitokines could increase energy metabolism and protect from high fat diet harmful effects and are capable with anti-inflammatory activity. GDF15 and FGF21 are as anti-inflammatory molecules in many experimental conditions. Mitokines (especially, GDF15) could be considered as markers of biological age. Some mitokines extend average lifespan. The precise role of mitokines is less clear, and more studies are required to better clarify this topic, particularly in the immunosenescence.

Keywords: Immunosenescence, Inflammaging, Mitokines

18741

The effects of vitamin D individually and in combination with curcumin on the frequency of Treg cells and the expression of *FOXP3* gene in the PBMC of multiple sclerosis patients

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Background: Multiple sclerosis (MS) is a chronic autoinflammatory disease affecting central nervous system. Decreased frequency and functional impairment of regulatory T (Treg) cells are associated with the pathogenesis of MS. Vitamin D and curcumin, an active ingredient of turmeric, exert immunomodulatory effects on autoimmune disorders such as MS. In the present study, the immunomodulatory impacts of curcumin and vitamin D, individually and in combinations, on the peripheral blood mononuclear cells (PBMCs) of MS patients were investigated.

Methods: The PBMCs of twenty MS patients were isolated and *in vitro* exposed to 0.004 µg/mL of vitamin D and 10 µg/mL of curcumin. The cells were treated by either single or combination doses of these components to evaluate their probable additive or synergistic immunomodulatory effects. The Combined doses that used in this study included full dose (equal concentration to single dose, *i.e.,* 0.004 µg/mL of vitamin D plus 10 µg/mL of curcumin) and half dose (equal to half of single dose, contained 0.002 µg/mL of vitamin D plus 5 µg/mL of curcumin).

Results: Single doses treatment of curcumin and vitamin D could significantly increase the expression level of *FOXP3* gene and the frequency of Treg cells compared to control group (*P* .(0.05 > The combination treatment by complete and half doses showed similar effect and caused an increase in the frequency of Treg cells and *FOXP3* gene expression compared to the control. However, this increasing effect in combined treatment of half dose of these components was not significant.

Conclusion: The results of the present study revealed that curcumin and vitamin D could modulate the inflammatory process of MS disease by enhancing the frequency and function of Treg cells. Moreover, the combination treatment of curcumin and vitamin D provided better outcomes than single dose.

Keywords: Multiple sclerosis; Vitamin D; Curcumin; Regulatory T cells; *FOXP3*

18806

Effect of a single bout of treadmill running on inflammatory cytokines among athletes

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Background: Inflammation has a significant role in the pathogenesis of several chronic diseases including cardiovascular disease CVD, type 2 diabetes mellitus, Alzheimer's disease, osteoporosis, and certain cancers. Although it is believed that a single bout of exercise induces immune activation, different studies have shown different results. The present study aimed to determine the effect of a single bout of treadmill running on inflammatory cytokines immediately after the exercise and at rest in different intensities.

Methods: Twenty eligible male students (soccer players) were selected and divided randomly to two groups. The first group was 30 minutes of running at a speed of 65% of VO2max, and the second group performed six periodic repetitions with three minutes at a speed of 85% of VO2max with a 90-second rest between the repetitions. Peripheral blood were collected at baseline, immediately after the exercise and at rest and then IL-1β, TNF-α, hs-CRP, IL-6, sICAM-1, IL-10 were assessed using ELISA method.

Results: Significant changes were observed in the first protocol that was submaximal (30 minutes of running at a speed of 65% of VO_{2max}) for IL-1β and ICAM-1. Significant difference was also seen in the second protocol only for IL-6 and IL-6/ IL-10 ratio. For the other markers, there was no significant difference between different sampling time points in the two protocols.

Conclusion: Exercise with lower intensity is more effective than with higher intensity in reducing inflammation. This observation may help patients with age-related chronic disorders and may be useful for clinicians to make better choices about the type and intensity of exercise that they prescribe.

Keywords: Athletes, Inflammation, Cytokines, ELISA

Congress Abstracts

Immunology of Infectious Diseases

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18516)

Prevalence of β-lactamase producing *Acinetobacter baumannii* in Iran

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Background: *Acinetobacter baumannii* is a significant opportunistic pathogen. These bacteria have a great tendency to acquire resistance against multiple classes of antibiotics. Nowadays, increasing drug resistant rate among *A. baumannii* strains is a major concern worldwide. Resistance to broad spectrum β-lactams, aminoglycosides, fluoroquinolones, and carbapenems are observed in this bacteria. The most common mechanism of resistance is the production of *β*-lactamases,This mechanism is one of the most problematic mechanisms of antibiotic resistance. *β*-lactamase producing bacteria are increasing with the creation of new mutants.

Methods: This article is a review study. Biomedical databases (SID, Pub med, Embase, Google scholar) were searched to find relative articles. English and Persian articles were used. They were published between 2008 and 2019.

Results: The prevalence of MBL and ESBL producing *Acinetobacter baumannii* is very high in the studied samples. In most of them, the prevalence of MBLs was 99% and the highest prevalence of ESBLs was 84/2. *Acinetobacter baumannii* is highly resistant to most antibiotics. Colistin and polymyxin B are the most effective antibiotics. After polymyxins, tetracyclines are the most effective antibiotics against this bacterium.

Conclusion: According to the results of this study, *A.baumannii* not only has a very high resistance to *β*-lactams, including the third generation of cephalosporins and carbapenems, but also has a high resistance to other antibiotic groups such as fluoroquinolones and aminoglycosides. This problem requires more investments, studies, and efforts to find other antibiotic mechanisms to deal with this microorganism and progress in this area.

Keywords: *Acinetobacter*, multi-drug resistant, immunology of *A.baumannii*, β-lactamase

(16619)

Evaluation of HBx, BRCA1, and RAD51 expression in hepatitis B patients

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Background: Hepatitis B virus (HBV) virus is one of the leading causes of hepatocellular carcinoma (HCC). As one of the leading causes of cancer death, HCC poses a significant public health issue. The presence of oncoproteins (HBx) and the replacement of viral DNA in the host genome causes chronic inflammation and hepatocarcinoma. HBV causes replication in the host cell by altering the host genomic repair system, resulting in chronic inflammation. The current study set out to investigate the one of the DNA repair systems called Homologous Recombination (HR) by examining the expression of RAD51, BRCA1, and HBx genes in peripheral blood mononuclear cells (PBMCs) of hepatitis B patients. Two groups of subjects were enrolled including healthy controls (n=31) and hepatitis B patients (n=30) and. The serum levels of HBV DNA, Rad51, BRCA1, and HBx in the PBMCs were measured using real-time quantitative polymerase chain reaction (PCR.) Moreover, serum levels of liver enzymes (ALT and AST) levels were assessed by automatic biochemical analyzer technique. In HBV-infected patients, the gene expression of Rad51 and BRCA 1 were significantly upregulated compared to healthy controls ($P< 0.05$). However, There is a statistically significant correlation between Rad51($r= 0.838$; P value < 0.001) and BRCA1($r= 0.588$; P value < 0.05). genes expression and viral load., these results demonstrated that hepatitis B virus affected the homologous recombination system by increasing the expression of Rad51 and BRCA1 genes, suggesting these genes could be considered as valuable therapeutic targets for treating hepatitis B patients.

Keywords: BRCA1, HBV, Homologous Recombination, Rad51.

(16649)

Toll like receptor 3 and 9 are up-regulated in the hospitalized COV-ID-19 infected patients

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Background: It has been demonstrated that pro-inflammatory responses are the main causes of novel coronavirus (COVID-19)-related complications. The aim of this project was to explore the roles played by toll like receptors (TLRs), including TLR3, TLR7, TLR8 and TLR9, in the pathogenesis of COVID-19.

Methods: In this study 30 COVID-19 infected patients and 30 age and sex match healthy controls were evaluated. The patients were selected from the hospitalized patients in the Ali-Ibn Abi-Talib hospital, Rafsanjan, Iran, with positive real-time PCR test for COVID-19. The patients with smoking, opium consuming, autoimmunity, and allergy, infectivity with other viruses and bacteria and receiving immune suppressor drugs have excluded from the study. The sampling was performed at the starting of hospitalization and before starting the treatment. Blood samples were collected in pre-coated anti-coagulant agents tubes. mRNA levels of TLR3, TLR7, TLR8 and TLR9 were evaluated using Real-Time PCR technique..

Results: Relative expression of TLR3 and TLR9 significantly increased in the COVID-19 infected patients in comparison to healthy controls. Male patients had higher mRNA levels of TLR3 than women.

Conclusion: Based on the results, it appears that TLR3 and TLR9 are more important than TLR7 and TLR8 against COVID-19 and may participate in the pro-inflammatory-based pathogenesis of the virus.

Keywords: Toll like receptor; COVID-19; Inflammation

(16763)

Title: Evaluation of Peripheral Cytotoxic T cell percentage in relations to EBV viral Load in MS patients

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Background: Patients with multiple sclerosis (MS) have a deficiency in Epstein–Barr virus (EBV) control which can indicate a malfunction in peripheral blood CD8+ T cells. This can lead to MS by allowing EBV infected autoreactive B cells to accumulate in the CNS where they produce pathogenic autoantibodies and provide costimulatory survival signals to autoreactive T cells. In patients with MS, number of T cells progressively decline, consistent with T-cell exhaustion. An exhaustion-like phenotype of CD8+ CD3+ T cells with high expression of PD-1 was observed patients with MS compared with healthy donors.

Methods: flow cytometry was used to determine the phenotypes and frequency of $CD8^+$ cells based on the expression of CD8 and CD3 and PD-1 in 25 healthy subjects and 25 patients with MS who had not received corticosteroids or immunomodulatory treatment in previous 3 months. Additionally, Real-time PCR was used to evaluate EBV load in PBMCs.

The project received ethics committee approval from medical university of kerman Ethics Committee (reference number IR.KMU.REC.1396.2230) and patients gave their written informed consent before taking part in the study.

Results: cytotoxic CD8+ $CD3^+$ T cells are responsible for removal of EBV- infected cells in healthy donors. Our results indicated higher expression of PD-1 on circulating CD3+ CD8+ T cells in MS patients compared to healthy donors (P= .000). This phenotype is an indication of exhausted T cells. This increase in PD-1 expression correlated to higher viral load observed in MS patients.

Conclusion: Exhausted CTLs in patients suffering from MS are not able to eradicate virus infected B cells. The results suggest that inefficient immune control of EBV in patients with MS during remission may cause exacerbation of the disease. Future studies on the mechanism of T cell exhaustion may aid to better understanding of the disease and design of effective therapies.

Keywords: multiple sclerosis, exhausted T cell, Epstein-BarrVirus,PD-1.

(16773)

Exhaustion markers in CD4$^+$ T cells of COVID-19 patients: TIM-3 is more important than CD39 and PD-1

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Background: COVID-19 causes a range of clinical symptoms from mild to critical and can be life threatening. Up to now, it has led to many deaths. We aimed to evaluate exhausted markers on CD4+ T cells of COVID-19 patients.

Methods: In this study, we evaluated 44 patients with confirmed COVID-19 disease and 16 healthy individuals. Patients were divided to moderate/severe and critical groups. Peripheral blood mononuclear cells (PBMCs) were isolated and stained by anti-human CD39, PD-1, TIM-3, and anti-human CD4. The percentage of each CD4$^+$ subpopulation was calculated by flow cytometry. Furthermore, we collected clinical information and laboratory data of both control and patient groups.

Results: We detected overexpression of TIM-3 on CD4$^+$ T cells in both critical and moderate/severe patients than in healthy individuals (HI) ($p < 0.01$ and $p < 0.0001$, respectively). CD4$^+$ TIM-3$^+$ CD39$^+$ lymphocytes were significantly higher in the critical patients than in HI ($p < 0.05$). Both Patient groups showed lymphopenia in comparison with HI, but CD4$^+$ lymphocytes did not show any significant difference between study subjects. Increased amount of CRP, ESR, creatinine, BUN, and neutrophil count were observed in patients compared to HI.

Conclusion: T cell exhaustion occurs during COVID-19 disease and TIM-3 is the most important exhausted marker on CD4+ T cells.

Keywords: Exhausted T, COVID-19, TIM-3, PD-1, CD39

(16780)

Correlation between IL-28 polymorphism and spontaneous clearance in HCV patients: systematic review and meta-analysis

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Background: Hepatitis C virus (HCV) is a serious global health issue. Nearly the spontaneous clearance of patients is about 20%. While some studies have shown the association of spontaneous clearance (SC) of the virus with Interleukin (IL) 28B single nucleotide polymorphisms (SNPs), some others didn't show such a relation. Thus, the purpose of the present study was to investigate the role of IL28B polymorphisms (12979860 SNP) and SC of HCV infection. Upon initial screening of the databases, a total of 545 articles were retrieved, of which 22 studies that met predefined eligibility criteria were entered into the meta-analysis. Odds ratios (OR) with its confidence intervals (95% CI), heterogeneity, publication bias and sensitivity analysis were assessed. According to the meta-analysis results, a significant association was observed between the rs12979860 SNP and SC of HCV infection. The results indicated that the ORs of SC from hepatitis C virus infection was 2.75 times higher in those with cytokine gene polymorphisms, 95% CI (2.23 to 3.38). Our meta-analysis results suggest that IL28B rs12979860 CC is a strong predictor for SC of hepatitis C infection in pegylated interferon alpha/ribavirin (PEG IFN-a/RBV)-treated patients.

Keywords: Hepatitis C virus; IL28B gene; Polymorphisms; Spontaneous Clearance

(18246)

Optimization of hepatitis B infection in cell culture using serum and cell culture derived viral inoculums

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Background: The investigation of hepatitis B virus (HBV) infection has been hampered due to the lack of an efficient and robust in vitro cell culture system. Recently, NTCP-reconstituted HepG2 (HepG2-NTCP) cells has been used as HBV-infection susceptible model; however, viral infectivity is poor and needs optimization.
Methods: Serum-derived HBV (sHBV) and cell culture-derived HBV (ccHBV) were simultaneously used during the optimization of HBV infection in HepG2-NTCP cell line by applying different modifications.
Results: Our results showed that sHBV and ccHBV infectivity is largely similar except that adding 5% of PEG, which is commonly used to improve in vitro infection of ccHBV, significantly reduced sHBV infection. Interestingly, continuous presence of PEG during the whole course of infection (13 days) significantly reduced the virus infectivity of both ccHBV and sHBV. Our results for the first time showed that in addition to human serum, monkey serum could significantly improve ccHBV infection, while fetal and adult bovine serum as well as duck and sheep serum did not have a promotive effect. We found that adding normal serum to viral inoculum, spinoculation, and non-adherent cell conditions significantly enhanced the virus infectivity of both ccHBV and sHBV. Furthermore, combination of all these modifications significantly improved ccHBV infection compared with spinoculation and non-adherent cell condition. However, applying these parameters during sHBV infection leads to significant increase of only HBsAg and HBeAg, but not rcDNA or cccDNA compared with individual modification. Our results showed that the combination of spinoculation, trypsinization and also adding human or monkey serum to HBV inoculum is an intervention that could significantly improve permissivity of HepG2-NTCP cells to HBV infection compared with individual strategies.
Conclusion: Taken together, our study suggests different strategies for improving ccHBV and sHBV infection in HepG2-NTCP cells and researchers could exploit them as different options for improving the infection based on different objectives they pursue.
Key words: Hepatitis B virus, HepG2-NTCP cells, Serum-derived HBV, Cell culture-derived HBV

(18304)

Influence of PRR ligands on induction of innate immunity and control of HBV infection

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Background: Failure of current therapies to cure chronic hepatitis B (CHB) have led to renewed interest in therapies that stimulate the host immune system. APOBEC3 (A3) family enzymes have been shown to induce mutations in hepatitis B virus (HBV) cccDNA leading to inhibition of HBV transcription and replication. PRR agonists have been reported to suppress HBV but it is unclear whether these agonists induce A3 gene expression in hepatocytes. We therefore evaluated whether PRR signaling activates expression of A3 genes and other innate immunity genes and restricts HBV infection.
Methods: HepG2-NTCP cells were infected with HBV and treated with various PRR agonists. The level of HBV infection was subsequently assessed by measurement of HBV biomarkers, including HBV DNA, cccDNA, HBs and HBe antigens in infected hepatocytes.
Results: Amongst all tested PRR ligands, only Poly(I:C)-HMW/LyoVec and Poly(I:C)-HMW significantly inhibited HBsAg, HBeAg, HBV DNA, and cccDNA, while R848 and LPS only showed a significant inhibition on HBsAg and HBeAg, but not virus DNA. CpG and Pam3CSK4, on the other hand, had no significant inhibitory effect on any of the HBV infection parameters. Moreover, Poly(I:C)-HMW/LyoVec and Poly(I:C)-HMW were the only ligands that significantly increased IL-8 secretion. Interestingly, HBV infection reduced IL-8 secretion induced by Poly(I:C)-HMW and to a lesser extent Poly(I:C)-HMW/LyoVec. Poly(I:C)-HMW/LyoVec had a significant effect on increasing the expression level of A3F, A3G, A3H, TLR3, RIG-I, and MDA5 genes.
Conclusion: Our data suggests that PRR agonists may control HBV infection through different mechanisms. The RIG-I and MDA5 agonist, Poly(I:C)-HMW/LyoVec, seems to downregulate HBV infection through induction of A3 genes.
Key words: Hepatitis B virus, APOBEC, Pathogen recognition receptor, innate immunity

(18577)

Bioinformatics study of the most relevant signaling pathways of two human coronavirus microRNAs in cancer incidence

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Background: Due to the importance of microRNAs produced by viruses in the occurrence of secondary diseases following human coronavirus diseases (HCoVs), there is a need to investigate the signaling of these microRNAs.
Methods: The information and signal paths of the desired microRNAs were studied in the database of DAVID Bioinformatics Resources 6.8, miRWalk 2.0, KEGG pathway, and miRBase.
Results: The results of simultaneous bioinformatics data analysis of two viral microRNAs, hsa-miR-449c-5p and hsa-miR-3940–5p, which also have microRNA target sites (MTSs) in the human body, show the effect of seven important human coronavirus diseases (HCoVs), including SARS-CoV-2, SARS-CoV, and MERS-CoV and The nonpathogenic strains were HCoV-OC43, HCoV-229E, HCoV-HKU1, and HCoV-NL63 are involved in the development of cancer, especially non-small cell lung cancer (NSCLC) by affecting the metabolic pathway of the cell.
Conclusion: The coding genes, followed by the proteins produced by these genes, can have a major impact on the life cycle of cells and even adjacent cells. There are also many common genes between humans and viruses that viruses may use to replicate themselves and at the same time affect the metabolism of human cells, the pathway of which their proteins require more attention and study.
Keywords: microRNA, HCoV, SARS-CoV-2, Signaling pathways

(18460)

Immunogenicity of HspX/EsxS fusion protein of *Mycobacterium tuberculosis* along with ISCOMATRIX and PLUSCOM nano-adjuvants after subcutaneous administration in animal model

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Background: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is one of the most common and dangerous infectious diseases in the world**.** Despite vaccination with BCG, it is still considered as a major health problem. Therefore, design and production of an effective novel vaccine against TB is necessary. Our aim was to evaluate immunogenicity of HspX/EsxS fusion protein of *M. tuberculosis* along with ISCOMATRIX, PLUSCOM nano-adjuvants and MPLA through the subcutaneous route in mice model.

Methods: HspX/EsxS fused protein of *M. tuberculosis* was cloned, expressed and purified in the prokaryotic system. ISCOMATRIX and PLUSCOM nano-adjuvants were prepared by film hydration method. Subcutaneous immunization of BALB/c mice was performed by different formulations. IFN-γ, IL-4, IL-17 and TGF-β cytokines levels as well as serum IgG1, IgG2a.

Results: Our results showed that subcutaneous administration of mice with HspX/EsxS along with three adjuvants, ISCOMATRIX, PLUSCOM and MPLA increased immunogenicity of multi-stage fusion protein of *M. tuberculosis*. Additionally, HspX/EsxS protein + ISCOMATRIX or + PLUSCOM nano-adjuvants induced stronger Th1, IgG2a and IgG1 immune responses compared to MPLA adjuvant. Totally, HspX/EsxS/ISCOMATRIX/MPLA, HspX/EsxS/PLUSCOM/MPLA and two BCG booster groups could significantly induce higher Th1 and IgG2a immune responses.

Conclusion: With regard to ability of ISCOMATRIX, PLUSCOM and MPLA adjuvants to increase immunogenicity of HspX/EsxS protein through induction of IFN-γ and IgG2a immune responses, it seems that these adjuvants and especially ISCOMATRIX and PLUSCOM, could also improve BCG efficacy as a BCG booster.

Keywords: *Mycobacterium tuberculosis*, HspX/EsxS fusion protein, ISCOMATRIX, PLUSCOM, MPLA

(15404)

Title: Risk of Helicobacter pylori infection and childhood asthma in Iran: A systematic review and meta-analysis

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Background: Asthma is one of the most common chronic respiratory diseases worldwide that especially affects children. Scientific data suggesting that infectious agents, such as Helicobacter pylori infection, can influence the development of allergic reactions. Therefore, we aimed to investigate the risk of H. pylori infection in childhood asthma.

Methods: Systematic literature searching was done to retrieved articles distributed by Iranian authors in the Web of Science, PubMed, Embase, and Scopus from the beginning of databases to Jun 2019. Four studies that met our inclusion criteria were included for data collection and meta-analysis. The inclusion criteria were articles that performed among the Iranian population, the method to confirm H. pylori infection has been declared, and the
prevalence of H. pylori in both asthmatic and control groups were mentioned.

Results: The studies in the asthmatic group involved 288 participants, of which the overall occurrence of H. pylori infection was calculated at 16.6% (95% CI: 12.7–21.4). While healthy control group involved 616 cases that the overall occurrence of H. pylori infection
among them was estimated at 20.9% (95% CI: 11.9–34.0). The estimate of outcome showed that the risk of H. pylori infection was 0.75-fold (95% CI: 0.47–1.18; P = 0.21) lower in asthmatic patients than in the healthy controls, but statistically was not significant.

Conclusion: As a first country-based study, the results did not support the association between H. pylori infection and the risk of childhood asthma. However, further prospective longitudinal studies with a uniform diagnostic method of H. pylori are recommended.

Keywords: Asthma, Hypersensitivity, Child, Helicobacter pylori, Iran

(15486)

Serological examination of Brucella infection in male patients referred to “Tabriz Milad Infertility Treatment Center” by ELISA method

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Background: Men infertility is the inability of men to have children. Infertility is widespread and increasing in developing countries. Infertility can be divided into primary and secondary types. In general, the prevalence of infertility is estimated at 13-19% and secondary infertility is estimated at 5-10%. Infertility in men has various causes, one of the most important of which is infectious diseases. one of the most important infectious diseases in the world is brucellosis which is caused by different species of Brucella bacteria. The aim of this study was to investigate the relationship between infertility and brucellosis in men referred to Milad Infertility Clinic in Tabriz.

Methods: In this study, 90 person were sampled. Among them, 45 people with a history of infertility and 45 people were selected as a control sample. Spermogram test was used to examine the sperm samples of the participants and serological tests (IgG, IgM) were used to measure the surface antigens of Brucella bacteria.

Results: The results of the analysis of data obtained from serological tests showed that there is a significant relationship between brucellosis and infertility in men.

Conclusion: According to the results of this study, as well as other studies, it can be concluded that infectious diseases are as important in men as in women. Therefore, it is better to be screened for infectious diseases before pregnancy.

Keywords: Brucella, Infertility, Infection, Male

(16601)

Title: Increased Indoleamine 2, 3-Dioxygenase Expression in Humans with *Helicobacter Pylori*-Infected Gastric Mucosa

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Background: Indoleamine 2, 3-dioxygenase (IDO) plays a significant role in suppressing the immune system by inhibiting T cell responses and immune tolerance. The host response to *Helicobacter pylori* (*H. pylori*) causes the infection to persist and also has different clinical outcomes. This study aimed to determine to determine the expression of IDO protein in patients infected with *H. pylori* compared with the control group.

Methods: Antrum biopsy was obtained from *H. pylori*-negative patients (n=48) and *H. pylori*-positive subjects (n=102). IDO protein expression was evaluated by Western blotting.

Results: IDO protein expression in patients infected with *H. pylori* was significantly 2.9-fold higher than *H. pylori*-negative subjects ($P < 0.0001$).

Conclusion: The results in this research suggest that the immune responses during *H. pylori* infection may be prominently altered by IDO protein.

Keywords: *Helicobacter pylori*, Gastritis, Peptic ulcer disease, Indoleamine 2, 3 dioxygenase

(16673)

Seroepidemiology of human hydatidosis in Zanjan city, 2019

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Background: The most common indicator of the level of hydatidosis infection in human societies is the annual incidence of confirmed or operated cases of the disease, but these cases show only a small proportion of patients with the infection. But these cases show only a small part of the infected people. Studies have shown that hydatid cyst infection is one of the most important health problems in most parts of the country and therefore the study of seroepidemiology of this disease by determining the percentage of positive cases in the region can be a fundamental step to promote community health and planning. It is meant to prevent this disease.

Methods: In this descriptive-analytical study, blood samples were collected from 318 people referred to medical diagnostic laboratories in Zanjan city and evaluated for the presence of IgG antibodies against hydatid cyst by ELISA method. Demographic data of the participants were collected by a questionnaire and the results were statistically analyzed by SPSS software.

Results: The results showed that out of 318 subjects, 14 were 10 (71.4%) female and 4 (28.6%) were male who were positive by ELISA test. (57.1%) of the positive cases were rural residents and 6 people (42.9%) were urban dwellers. Also, the female population was all housewives and among men, two (14.3%) were farmers and two (14.3%). They were also ranchers. The highest percentage of infection was in the age group of 20-40 (42.1%) years and the mean age of patients in this study was 45.1. CT scan and sonography results of positive people obtained in this study: 9 patients (64.2%) had hydatid cysts in the liver, 3 patients (21.4%) had lungs and 2 patients (14.4%) had hydatid cysts. It was visible in the lungs and liver of patients. In this study, 2 patients (14.3%) had a history of hydatid cyst rupture in previous surgeries and 8 patients (57.1%) were treated with surgery.

Keywords: Hydatid cyst, ELISA, Seroepidemiology, Zanjan

(17971)

Seroepidemiological Prevalence of *Helicobacter pylori* in the last 15 years in Iran

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Background: *Helicobacter pylori* a gram-negative, microaerophilic and spiral bacterium, is the cause of most gastric ulcers and causes some gastrointestinal cancers and is the most important cause of gastric cancer and MALT lymphoma. It is estimate that about 50-25% of people in developed countries and up to 70% to 90% of people in developing countries are infected with this bacterium. Community examining with serological tests is one of the best and simplest ways to monitor the community health.

Methods: We performed a systematic review in articles published in both English (pubmed, scopus, google scholar) and Persian (sid, magiran, iran medex) from 2006 to 2020. Finally, out of about 376 articles, 18 articles have been included in our study, which their detection were based on serological tests. We divided our specimen to two categories of people, healthy individuals (children and adults) and patients who have been suffering from diseases like abdominal pain and dyspeptic symptoms.

Results: With a 95% confidence interval, the prevalence of Helicobacter pylori was calculated to be 29.7% among healthy children, 50.74% among healthy adults, and 70.79% of patients have gastrointestinal symptoms carrying bacteria.

Conclusion: The results of this study show that the prevalence of the disease among children under 10 years of age is about 20% lower than in healthy adults. However, about half of the population carries the bacterium. In addition, 30% of gastrointestinal symptoms in patients are not related to the presence of *Helicobacter pylori*.

Keywords: *Helicobacter pilory*, Iran, Seroepidemiological prevalence

(18008)

Serological prevalence human tularemia spread during the past seven years in Iran

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Introduction: Tularemia known is a common disease between human and animals caused by *francisella tularensis*, as gram negative bacteria. The bacteria are transmitted to the host through different forms of disease such as ulceroglandular, oropharyngeal, and pneumonia. The variety of transmission ways has made *francisella tularensis* a candidate for making biological weapons. Despite the rapid serological diagnosis of the disease, Unfortunately there is not a thorough and precise statistic for tularemia and limited studies have been done on it. This article investigates all studies having been done in Iran especially in high-risk areas during the past.

Method: We performed a systematic review in articles published in both English (PubMed, Scopus, google scholar) and Persian (sid, magiran, iran medex) from 2013 to 2020. Collected articles were investigated and authentic articles were included in this study.

Results: Several articles have been found on tularemia in Iran, a limited number of which have been on the human form of infection, indicating an average prevalence of 7.38% in the country. Studies have shown that among the various forms of tularemia, the ulceroglandular form of the disease is more prevalent, especially among farmers, slaughterhouse staff, butchers, hunters, and people who have eaten wild animal meat. Although the disease is also prevalent in the east of the country, the highest prevalence of the disease is seen in the western regions (Kurdistan, Marivan, Sanandaj, Sarvabad, Ilam and Lorestan).

Conclusion: Only a limited number of articles have been found on human tularemia in Iran, indicating that it has been neglected in Iranian microbiological studies, so given the importance of tularemia as a new and emerging disease, it is recommended to be informed and educated. Necessary measures should be taken against this bacterium, especially in high-risk areas, continuous monitoring and more research on this bacterium

Key words: Serological prevalence, Human tularemia, Iran

(18242)

Seroprevalence of laboratory-confirmed B.pertussis antibodies after Immunization in Iran: a systematic review and meta-analysis of healthy-population study

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Background: Pertussis (whooping cough) is one of contagious upper respiratory infection and also vaccine preventable disease with high morbidity and mortality. Based on immune response of the host, the severity of BP infection is variable and analyzing the BP seroprevalence rate in general population may improve the implementation of new strategic health management such as developed vaccination schedule. Therefore, we aimed to provide a systematic review of the seroprevalence rate of BP infection among Iranian population through estimating the prevalence of BP according to age, gender, infancy and pre and post booster vaccination.

Methods: A thorough systematic literature was performed in databases PubMed, Embase, Web of Science, Scopus, and Google Scholar and also in national Persian databases up to October 2020 to identify eligible studies evaluating seroprevalence of specific antibodies for BP in healthy individuals in Iran. Finally 28 relevant studies were included in this meta-analysis. Heterogeneity test of the selected studies was calculated using *I*2 statistic. The random effect model was used based on heterogeneity test results and pooled data expressed as the effect size (ES) with 95% confidence intervals (CIs).

Results: The overall IgG seroprevalence rate of BP infection in general population of Iran was 50% (95% CI; 43%-57%) and the overall IgA seroprevalence rate was 20% (95% CI; -2%-43%). Also, Total IgG seroprevalence rate among infants was 38% and there is no significant seroprevalence difference between females and males (39% vs 41% respectively). Furthermore, the relative rate of seropositivity is high in children (54%, 95% CI; 42%-66%) and post booster vaccinated individuals (77%, 95% CI; 59%-94%)

Conclusion: Our findings can provide a true background and assessment of BP infection in Iran and promote a schedule for cost-benefit immunization. Further consideration to disease seroprevalence is recommended by the subsequent data in order to gather effective information for clinical intervention targeted against BP.

Keywords: Bordetella Pertussis (BP), Seroprevalence, IgG, Vaccination, Immunity, Iran

(18436)

Acinetobacter baumannii.

Shadi paydarfar

Background: Serological reactions of occupied ICU staff members with designed ompA peptides of AB in comparison with non-exposed samples.

Nosocomial infections with bacterial pathogen is the most life threatening problem in world health, especially in ICU. This pathogen is an opportunistic germ that could induce infection in compromised patients. The main risk factor for these pathogens to induce infection, is the use of mechanical ventilation. The staff members in ICU are the major carrier with different devices such as catheters. The aim of this study was to investigate the antibody reaction against immunogenic peptides of ompA designed as a candidate vaccine Against acinetobacter baumannii. In the previous study, these peptides were injected subcutaneously to C57B/6 mice alongside AL(OH)3 %1 adjuvant which resulted in IgG antibody increase. If the positive reaction occurred during serological tests, it may be used these antigenic construct for preparing a diagnostic kit in crisis condition for ICU patients and also may be beneficial approach to recognition immunological status of them.

Methods: 62 serum samples obtained from exposed ICU staffs in Tehran Firoozabadi and Dezful Ganjavian hospitals and non-exposed individuals and individuals suffering with SLE. All the serums were pre-adsorbed with E-coli Lysate. In order to determine positive reaction of samples with AB lysate due to detection of existence of antibodies against AB. ELISA technique helps us to all tests.

Results: obtained results showed that from 33 samples of exposed serum, 25 of it was positive (%75.75) and 8 samples were negative. Also from 22 samples of non-exposed individuals, 6 were positive (%27.27) and 16 were negative. Strongly positive serum with lysate were reacted with only peptide 5 of ompAAB.

Conclusion: obtained results shows that not only exposed samples had a lot more Ab titre in comparison to non-exposed. But also these groups had significant high tire of Abs against peptide 5. In shows that the colonization of AB in population is growing year by year. To demonstrate the exact role of antibody against AB and immunologic peptides, there's a need for further researches.

(18480)

fungal airborne, allergen alternaria spp, on normal and dust events in Khorramabad, Iran

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Background:*Alternaria spp* is one of the most important causes of respiratory allergic diseases in the world.This study aimed to identify the airborne *Alternaria spp* as the most important fungal allergen during Middle Eastern dust (MED) events and normal days in Khorramabad, Iran

Methods: The samples were collected regularly every six days at three locations during April 2018–March 2019, with additional samplings during MED days.For phenotypic analyses,the Petri dishes were incubated at 25 °C for 72–120 h. Molecular identification of fungi was carried out using polymerase chain reaction (PCR).

Results: At least, 23,741 colonies were counted. 3,112 colonies were related to the 10 *various species* in the *genus, Alternaria*, during dust and non-dust days.The average concentration of *Alternaria spp* during dust days (1856 CFU/m3) was higher than those in normal days (1256CFU/m3).The average concentration of *Alternaria alternata*,*Alternaria terricola, Alternaria arborescens* and *Alternaria citri* during dust days, (1093 CFU/m3), (176 CFU/m3), (140 CFU/m3), (68 CFU/m3) was higher than those in normal (667 CFU/m3), (70 CFU/m3), (68 CFU/m3), (0 CFU/m3). *Alternaria citri* was only observed during MED days, not normal days. .

Conclusion: Fungal allergens such as *Alternaria* spp,were evaluated in a city affected by severe Middle Eastern dust storms during both dust and non-dust days.Dust days showed higher concentrations of fungi.

Keywords: fungal allergens, *Alternaria* alternata , dust

(18485)

Antimicrobial and Healing Effect Burdock and Nasturtium of Nettle, Extracts With Silver Sulfadiazine on Burn Infections of Staphylococcus aurous.

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Background: Staphylococcus aurous causes a wide range of diseases. Staphylococcal infection is the most common bacterial infection in humans. Antimicrobial and healing effect burdock and nasturtium of nettle, extracts with silver sulfadiazine on burn infections of Staphylococcus aurous.

Method: In this study, aqueous and ethanolic extracts of nettle, watercress and burdock root were prepared in the laboratory. Then, the MIC and MBC of the extract were determined by dilution method in the broth. In the study of the animal model, the bacteria were first inoculated with a concentration of (5×106CFU/ML) to the wound site on Syrian mice. After 24 hours, an ointment prepared with MBC concentration was prepared from extracts of the nettle, watercress and burdock root for 1 g of silver sulfadiazine and was used to treat burns and infections with Staphylococcus aurous. In the animal model, the aqueous and ethanolic extracts of nettle, watercress and burdock root have antimicrobial activity against growth of Staphylococcus aurous.

Results: In this study, aqueous and ethanolic extracts of nettle, watercress and burdock root were prepared in the laboratory. Then, the MIC and MBC of the extract were determined by dilution method in the broth. In the study of the animal model, the bacteria were first inoculated with a concentration of (5×106CFU/ML) to the wound site on Syrian mice. After 24 hours, an ointment prepared with MBC concentration was prepared from extracts of the nettle, watercress and burdock root for 1 g of silver sulfadiazine and was used to treat burns and infections with Staphylococcus aurous. In the animal model, the aqueous and ethanolic extracts of nettle, watercress and burdock root have antimicrobial activity against growth of Staphylococcus aurous.

Conclusion: According to the findings of this study, it can be concluded that the extract of these three plants (nettle, watercress and burdock root) on an animal model has antimicrobial and healing effects on Staphylococcus aurous. It can be used as an anti-inflammatory agent or ointment Bacteria to be raised. In this case, the extract of nettle and burdock root have growth inhibitory and bactericidal activity stronger than watercress extract. And it is hoped that in the future, these plants will be used to treat bacterial infections.

(18503)

Molecular Characterization of Airborne Cladosporium spp Allergens on normal and dust events in Khorramabad, Iran

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Background: Airborne *Cladosporium* spores in different regions of the world are known as the main cause of allergic diseases. This study aimed to identify the airborne *Cladosporium spp* as the most important fungal allergen during Middle Eastern dust (MED) events and normal days in Khorramabad, Iran.

Methods: The samples were collected regularly every six days at three locations during April 2018–March 2019, with additional samplings during MED days. For phenotypic analyses, the Petri dishes were incubated at 25 °C for 72–120 h. Molecular identification of fungi was carried out using polymerase chain reaction (PCR).

Results: At least, 23,741 colonies were counted. 10889 colonies were related to the 8 *various species* in the *genus, Cladosporium*, during dust and non-dust days. The average concentration of *Cladosporium spp* during dust days (9378 CFU/m3) was higher than those in normal days (1511CFU/m3). The average concentration of *Cladosporium cladosporioides, Cladosporium iridis, Cladosporium pseudocladosporioides*, during dust days, (5504 CFU/m3), (1201 CFU/m3), (564 CFU/m3), was higher than those in normal (848 CFU/m3), (242 CFU/m3), (172 CFU/m3). *Cladosporium cucumerinum* was only observed during MED days, not normal days.

Conclusion: Fungal allergens such as Cladosporium spp, were evaluated in a city affected by severe Middle Eastern dust storms during both dust and non-dust days. Dust days showed higher concentrations of fungi.

Keywords: allergens; *Cladosporium* ; dust;

(18726)

A potential marker in brucellosis, long non coding RNA IFNG-AS1

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Background: Brucellosis is the most common bacterial zoonotic infection. This pathogen may survive and sustain in host. The aim of this study is to define relationship between long noncoding (lnc) RNA-*IFNG-AS1* and interferon gamma (IFN-γ) in different groups of patients with brucellosis compared to control group. In this study, associations of lncRNA IFNG-AS1 expression with secretion of IFN-γ level in Sixty patients with brucellosis, which were divided into 3 groups (acute, chronic and relapse groups), as a case group were compared with 20 subjects with negative serological tests and brucellosis clinical manifestation as a control group.

Methods: RNA was extracted from isolated peripheral blood mononuclear cells (PBMCs). LncRNA IFNG-AS1, T-box transcription factor (T-bet) and IFN-γ expressions were detected using quantitative polymerase chain reaction (qPCR). Serum level of IFN-γ was assessed using enzyme linked immunosorbent assay (ELISA).

Results: Expression level of LncRNA IFNG-AS1, T-bet and IFN-γ were increased significantly in all patient groups in compared to healthy subjects ($P < 0.0001$, $P < 0.01$, $P < 0.001$). There was no significant difference in T-bet expression between chronic and healthy groups ($P = 0.98$). Serum level of IFN-γ in acute and relapsed groups was higher than control group ($P < 0.0001$, $P < 0.001$).

Conclusion: The effective role of IFNG-AS1 in many protective actions, including enhancing the expression of IFN-γ in the immune response of brucellosis patients, revealed new potential marker, LncRNA IFNG-AS1 in screening, diagnosis or treatment of brucellosis.

Keywords: Brucellosis, Cytokine, Interferon-gamma, T-bet, lncRNA IFNG-AS1

(16527)

Design of recombinant protein containing conserved epitopes of hemagglutinin H1N1 and H5N1 influenza virus antigen with using bioinformatics methods

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Background: In recent years, with advances in bioinformatics, the design of the influenza vaccine has made considerable progress. This study aimed to design a multifunctional recombinant protein, based on the highly conserved hemagglutinin protein epitopes of H1N1 and H5N1 strains,that they epitopes do not mutate over time.

Methods: For this purpose, according to previous field studies, the sequences of favorite strains were examined and epitopes were selected from these strains that induced the highest humoral and cellular immune responses. Epitope binding score to MHCI and MHCII investigated. After examining the immunogenic and chemical properties of the selected epitopes by the appropriate servers, the recombinant protein structure was determined. The codon optimization was carried out following reverse translation of the above sequence and the optimized sequence was inserted into the PET32a + vector, between two BamHI / XhoI enzymatic regions finally.

Results: The results showed that the recombinant protein in this study has 22451.72 g/mol molecular weight with 214 amino acids. The isoelectric pH of our recombinant protein is 7.25 and has 100% solubility in the prokaryotic system. Also,The extinction coefficient of our structure is 60170 M-1cm-1. Finally, after codon optimization, the protein Codon Adaptation Index (CAI) was calculated and 0.95 reported.

Conclusion: Finally, based on the above data, it has anticipated that the multiepitope structure designed in this study, which has unique and acceptable immunologic properties, can be successfully and reliably expressed in the prokaryotic system and used for immunological studies against influenza A viruses.

Keywords: Influenza Vaccine, Vector, Hemagglutinin, Immunogenesis, Humoral Immunity, Cellular Immunity

(16554)

Evaluation of immune system cytokines in patients with chronic *hepatitis B*

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Background: Immunological factors and host immune system play an important role in the incidence of hepatitis B infection. The different effects of cytokines are indirectly performed by determining the host response pattern and directly by inhibiting viral replication. IFN-γ and IL-4 are secreted from different subset of T (TH1, TH2) cells, respectively. In this study, Association between susceptibility to hepatitis B virus infection and the chronicization with the above factors has been studied.
Methods: In this case-control study, genomic DNA of 140 healthy blood donors as control group and 70 asymptomatic chronic hepatitis B as case group were extracted and gene polymorphism analysis of IFN-γ rs2430561 and IL-4 rs2243250 by ARMS-PCR techniques.
Result : Statistical analysis showed that the frequency of mutant AA and Allele A genotypes of IFN-γ rs2430561 polymorphisms in patients with chronic hepatitis B without symptoms was significantly higher than the control group (P=0.000). Also, CT genotype and T allele polymorphism IL-4 rs2243250 were less abundant in the case group (P=0.000) and (P=0.002).
Conclusion: The results of this study showed that there is a significant relationship between the presence of mutant genotypes and allelices of rs2430561 and rs2243250 cytokines IFN-γ and IL-4 with susceptible to chronic hepatitis B infection.
Key words: Hepatitis B virus, IFN-γ, IL-4, Mutation, Polymorphism

(16559)

Evaluation of *FoxP3* gene polymorphisms in patients with chronic *hepatitis B*

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Background: Chronic hepatitis B infection has different clinical outcomes in different individuals. In addition to the differences in the virus, host genetic characteristics are also involved in the pathogenicity of HBV. Immunological factors and host immune system play an important role in the incidence of hepatitis B infection. Polymorphisms of *FoxP3* gene affect the formation of Treg (Regulatory T cell). In this study, association between susceptibility to hepatitis B virus infection and the Polymorphisms of *FoxP3* gene has been studied.

Methods: In this case-control study, genomic DNA of 140 healthy blood donors as control group and 70 asymptomatic chronic hepatitis B as case group were extracted and gene polymorphism analysis of *FoxP3* rs3761548 by PCR-RFLP techniques.

Result: Statistical analysis of the data showed that mutant genotype rs3761548 polymorphism had higher frequency in case group than control group (P=0.017, OR=4.464).

Conclusion: The results of this study showed that there is a significant relationship between the rs3761548 *FoxP3* with susceptible to chronic hepatitis B infection.

Key words: *FoxP3*, Hepatitis B virus, Mutation, Polymorphism

(18521)

Assessment of the diagnostic value of IL-1β, IL-6, IL-10, and TNF-α in primary HHV-6 infection in asymptomatic children

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Background: Human Herpes virus-6 (HHV-6) is a common childhood pathogen causing primary infection in the early ages of life (so-called Roseola Infantum), which mainly presented by fever and skin rashes. The virus establishes lifelong latency with no clinical manifestations and may reactivates due to the immune weakness leading to a wide variety of associated illness. This study aimed to assess the diagnostic value of IL-1β, IL-6, IL-10, and TNF-α in primary HHV-6 infection in asymptomatic children.

Methods: For this study, we used 17 HHV-6 PCR tested positive throat swabs obtained from children less than 5 years with no signs and symptoms and no history of illness for weeks before the sample collection. Real-time PCR was performed on all throat swabs for evaluating the expression of IL-1β, IL-6, IL-10, and TNF-α using specific primers. Receiver operating characteristic (ROC) curve analysis was used and the area under the ROC curve (AUC) was calculated (95% confidence interval) using GraphPad Prism (Version 8.3.0).

Results: The area under the ROC curve (AUC) was 0.82 for IL-1β (95% CI, 0.8244-1), 0.88 for IL-6 (95% CI, 0.7417-1), 0.87 for IL-10 (95% CI, 0.7207-1), and 1.00 for TNF-α (95% CI, 1-1). ROC curve analysis showed TNF-α with the highest sensitivity and specificity. The other cytokines (in order) would be IL-6, IL-10, and IL-1β in primary HHV-6 infection in asymptomatic children.

Conclusion: The results of our study suggested that TNF-α with AUC=1.00 could be a potential diagnostic biomarker in asymptomatic children with primary HHV-6 infection.

Keywords: Human Herpes Virus-6 (HHV-6), Diagnostic Value, IL-1β, IL-6, IL-10, TNF-α

(18578)

Construction, production, purification and characterization of recombinant hepatitis B e-antigen

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Background: Hepatitis B virus (HBV) is a major health problem worldwide and causes almost one million deaths annually. HBV core gene codes for two related antigens, referred to as core antigen (HBcAg) and e-antigen (HBeAg), sharing 149 residues but have different amino- and carboxy-terminal. HBeAg, is a soluble variant of HBcAg and a clinical marker for determining the disease severity and patients screening. The goal of this study was to construct and purify HBeAg and then generate polyclonal antibodies against this antigen to eventually design an ELISA assay for detection of this antigen.

Methods: The genes coding for HBeAg and HBcAg were separately constructed from HBV infected hepatoma cells, cloned into the expression vector pCold and expressed in Eschercia coli (E. coli). The expressed protein was purified by affinity-chromatography using Ni-NTA resin. To produce anti-HBe polyclonal antibody, rabbits were immunized with HBeAg as an emulsion with Freund's adjuvant. Anti-HBe polyclonal antibodies were conjugated with horseradish peroxidase (HRP), and then a sandwich ELISA was desiged to detect HBeAg.

Results: HBeAg was successfully expressed in *E. coli* Rosettagami strain. SDS-PAGE results showed that the protein was successfully produced and purified by Ni-NTA affinity chromatography with a purity greater than 90%. Western blot analysis of purified HBeAg with sera of patients with chronic hepatitis B infection confirmed that HBeAg is recognized by human anti-HBe antibodies. In addition, reactivity of purified HBeAg with commercial ELISA HBe/Anti HBe kit confirmed the correct conformation of the purified antigen. Rabbit anti-HBe antibody was purified from seum of immunized rabbits and used to design a sandwich ELISA, which specifally detected HBeAg and partially discriminate it from HBcAg.

Conclusion: Our data showed that the conformation of recombinant HBeAg is relatively conserved and the designed ELISA could detect this antigen with high sensitivity.

Keywords: HBeAg, HBcAg, HBV, Anti-HBe polyclonal antibody

(18697)

Thyroid dysfunction (TD) in patients with hepatitis C treated with IFN alpha alone or in combination with ribavirin: A systematic review

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Background: Hepatitis C is a liver disease and in order to cure it (Th1) cytokines (IL-2, IFN-gamma) are needed for host antiviral immune responses. Th2 cytokines (IL-4, IL-10) are inhibitors of Th1 cytokines. Interferon alpha therapy reduces the levels of IL-4 and IL-10 and ultimately helps treat patients. IFN alpha therapy can cause a number of autoimmune diseases such as hypothyroidism, hyper thyroidism and impaired thyroid hormone synthesis. These thyroid disorders develop during or after treatment with IFN alpha alone or in combination with ribavirin. The aim of this study is to investigate the prevalece of TD in untreated and treated patients with IFN alpha and ribavirin in children and adults.

Methods: This systematic review was conducted by using articles from 2018 to 2020 in Google scholar, PubMed and Scopus date bases. I primitively found 24 articles and 8 of them were related to my topic and so were investigated.

Results: The incidence of TD in HCV-treated patients has been reported 2.5% to 42%, which depends on the dose, the duration of treatment and patient characteristics. TD is also common in patients with untreated Chronic Hepatitis C (CHC). TSH increases after combination therapy with IFN alpha and ribavirin. TSH approximately tripled compared to before treatment, while it didn't change in healthy patients receiving treatment. Elevated TSH paves the way for subclinical hypothyroidism in both children and adults. In the first 24 hours of treatment, TSH level decreases and free T3 and free T4 levels remain constant. The incidence of TD is also more pronounced at the end of the treatment.

Coclution: TD is common in both treated and untreated people with CHC. TSH levels increase at the end of the treatment in both children and adults. Subclinical hypothyroidism is more common among thyroid disorders in people being treated.

Keywords: IFN alpha therapy, Ribavirin, Hepatitis C, Thyroid dysfunction (TD).

(18782)

Nigella sativa and Zn potential for treating COVID-19; Immunology aspects of complementary medicine

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Background: The COVID-19 has been stated as a pandemic while there is no promising medicine against its causative agent SARS-CoV-2. Zn supplement and *Nigella sativa* (black seed) can be considered for bioactive components to have anti-viral activity. In this review, we describe immunology aspects of the application of a combination of their components to COVID-19 treatment.
Methods: Published articles were accomplished by PubMed, Google Scholar, Embase, Springer, and ScienceDirect. The literature search was updated to December 2020. Entirely, 46 related articles were found and reviewed.
Results: The SARS-CoV hosts angiotensin-converting enzyme 2 (ACE2). The viral RNA is released in the cytoplasm - a potential site of thymoquinone to stop the release. ORF1a and ORF1ab are translated to RdRP which synthesizes mediate both replication and transcription. Generally, a decreased count of CD4+ and CD8+ lymphocytes, monocytes, and platelets with the increased count of neutrophils were recorded.Remarkably, Zn improves innate and adaptive immunity in microbial infection, whether viral or bacterial. Also involves in NF-κB signaling pathway which influences the expression of cytokines (such as IL-1b, IL-6, IL-8, TNF-α, and MCP-1), chemokines, acute phase proteins (CRP and fibrinogen), matrix metalloproteinases, etc.*N. Sativa* oil produces antinociceptive effects through indirect activation of the supraspinal μ1- and κ-opioid receptor subtypes. *N. Sativa* might be bioactive components to treat COVID-19 patients. Black seed not only blocks the virus entry into pneumocytes and but also providing an ionophore for enhanced uptake of Zn2+ which in turn can enhance host immune response against SARS-CoV-2 as well as inhibit its replication by blocking the viral RdRp.
Conclusions: Zn supplement with N. sativa as its major bioactive components might use as ionophore to allow Zn2+ to enter pneumocytes and inhibit SARS-CoV-2 replication by stopping its replicase enzyme system.

Keywords: COVID-19, Nigella sativa, Zn, complementary medicine

(16668)

A Survey on the Seroprevalence of Toxocariasis and Related Risk Factors in Eosinophilic Children

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Background: Toxocariasis is a serious zoonotic helminthic disease with a considerable impact on public health caused by the nematodes; *Toxocara* species. Clinical manifestations of toxocariasis are depending on the organs affected such as hepatomegaly, pulmonary and ocular symptoms and also blood eosinophilia. Toxocariasis distribution is worldwide with highly-variable seroprevalence (2.4-92.8%) with more occurrences in children. Our cross-sectional study was conducted to determine the seroprevalence of toxocariasis and its association with epidemiological and related risk factors in hyper-eosinophilic children referred to the pediatrics hospital of Qazvin province in 2019-2020.

Methods: A total of 200 serum/plasma samples were collected from eosinophilic children (1-13 years old) referred to the Qods Hospital. Eosinophilia was extracted from the CBC results more than 500 cells/mm^3. Demographic data (age, gender, residential area, parents' occupation and literacy status), clinical symptoms and disease background (hyper-eosinophilia, idiopathic fever, ocular, pulmonary, cutaneous and hepatic disease), and dogs- and soil-contact history was collected. The presence of anti-*Toxocara* IgG antibody was evaluated by *T. canis* IgG ELISA kit.

Results: Anti-*Toxocara* IgG antibodies were detected in 14 (7%) of eosinophilic children and *Toxocara* seroprevalence showed significant correlation regarding the eosinophilia rate and clinical manifestations ($P<0.05$). So, that the highest prevalence of toxocariasis (33.3%) was in children with hyper-eosinophilia above 2000/mm^3. Seroprevalence in asymptomatic eosinophilic-children was 4.4%, while in children with history of idiopathic fever was 21.4%, eye disease 100%, lung disease 13% and in children with liver and skin disease history was zero percent. However, relationship between Toxocara infection with gender, age, soil- and dogs-contact, residential area, parents' occupation and literacy status were not significant ($P>0.05$).

Conclusion: High-prevalence of toxocariasis in eosinophilic children of Qazvin is serious. Therefore, evaluation for *Toxocara* infection is recommended for hyper-eosinophilic children and due to this alarm-situation, the strategies for controlling the disease in dogs and cats are crucial.

Keywords: Seroprevalence, Toxocariasis, anti-Toxocara Antibody, eosinophilic Children.

(16896)

High-throughput protein analysis in the lesions of cutaneous leishmaniasis patients infected with *Leishmania tropica*

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Background: There is currently a lack of information regarding skin human response to anthroponotic cutaneous leishmaniasis (CL) caused by *L. tropica*. In order to understand better the human immune response against *L. tropica* infection, we employed high-throughput proximity extension assay (PEA) and defined protein biomarkers in skin biopsies from ulcerative CL (UCL) and non-ulcerative CL (NUCL) patients.

Methods: The patients had been collected in the CL clinic at Mashhad Medical School, and lesions patients were classified according to their clinical presentation as UCL lesions with the ulcerated epidermis and NUCLs with intact epidermis. The skin punch biopsies driven from patients' lesions and healthy individuals were cultured for 48 h within RPMI and the culture supernatants were used for PEA assay to investigate and compare 92 inflammatory cytokines and chemokines in UCLs and NUCLs relative to healthy controls.

Results: The PEA results showed that 18 and 19 inflammatory proteins were significantly up-regulated (p-value<0.05) in the UCL and NUCL lesions compared to healthy controls, respectively. Among these proteins, both patient groups had high expression of the inflammatory chemokines CCL3, CCL20, CXCL5, CXCL9, CXCL10, CXCL11, monocyte chemotactic protein (MCP) 1, MCP2, MCP3, Oncostatin-M (OSM), T cell surface glycoprotein CD6 isoform (CD6), transforming growth factor alpha (TGF-alpha) and tumor necrosis factor ligand superfamily member 9 (TNFSF9). Unique proteins including Caspase-8 (CASP8), TNFB, urokinase-type plasminogen activator (uPA) and CD40 were up-regulated in UCL patients. The expression of unique inflammatory chemokines (CCL4, CXCL1, CXCL6 and MCP-4) and TNF ligand superfamily member 14 (TNFSF14) were exclusively up-regulated in the NUCL lesions.

Conclusion: A multiplexed inflammatory protein analysis showed differential profiles of inflammatory cytokines, chemokines and surface molecules in the UCL and NUCL lesions. Up-regulation of chemokines was predominant in both patient groups, and PEA also identified Oncostatin-M (OSM) that has not been previously reported for leishmaniasis.

Keywords: Cutaneous leishmaniasis, *Leishmania tropica*, Proximity extension assay, Chemokines, Cytokines

(17999)

Seroprevalence of *Toxocara* infection among asthmatic patients in comparison with healthy children: A case-control study in Shiraz city, southern Iran

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Background: Human toxocariasis is caused by *Toxocara canis* and *Toxocara cati*, the nematodes in the intestine of dogs and cats, respectively. Since the association between asthma and toxocariasis is controversial, the aim of the present study was to investigate the seroprevalence of *Toxocara* infection among asthmatic children in comparison with healthy children.
Methods: This case-control study was conducted on 92 asthmatic and 91 healthy children aged 1-16 years old in Shiraz city, Southern Iran. The serum samples were tested for IgG anti-*Toxocara* antibodies by ELISA method using the *T. canis* larval excretory-secretory (E/S) antigens. The collected data were analyzed using SPSS software.
Results: The seroprevalence of toxocariasis in asthmatic patients was higher than the healthy children with no significant difference in *Toxocara* seropositivity between two groups (9.8% vs 8.8%, P = 0.817). The association between *Toxocara* infection and variables such as gender and age were not statistically significant (p>0.05).
Conclusions: This study indicates that there was no significant association between toxocariasis and childhood asthma. Further study on different regions such as urban and rural areas with a large sample size and using questionnaire for considering risk factors of asthma and toxocariasis is recommended.

Keywords: Seroprevalence, *Toxocara*, Asthma, Iran

(18018)

Seroprevalence and molecular detection of Toxoplasma gondii in healthy blood donors in southwest Iran

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Background: Toxoplasmosis is a cosmopolitan parasitic disease caused by *Toxoplasma gondii* (*T. gondii*). Blood transfusion is a probable route of *T. gondii* transmission. Due to lack of information about seroprevalence of *T.gondii* in healthy blood donors, this study was aimed to determine the chronic and acute infection using serological and molecular methods.

Methods: In this cross-sectional investigation, 380 samples were collected from donated bloods. Anti-*Toxoplasma* IgG and IgM antibodies were examined using enzyme-linked immunosorbent assay (ELISA). Also, all IgG positive samples were tested by IgG avidity test. Eventually, to detection of active infection, DNA was extracted from IgM positive and low IgG avidity samples and then tested using nestedpolymerase chain reaction (PCR).

Results: Among 380 blood donors, 131 (34.47%) were positive for only anti-*T. gondii* IgG, 2 (0.5%) were positive for only anti-*T. gondii* IgM, and 11 (2.9%) were positive for both IgG and IgM antibodies. Then, 142 samples (131 IgG + and 11 IgG +IgM +) were evaluated using IgG avidity test. Of these, 115 (81%) had high avidity IgG indicates past infection; 16 (11.26%) had low avidity IgG representing recent infection, and 11 (7.74%) were equivocal. With nested PCR, 20 samples of 50 seropositive samples were diagnosed positive.

Conclusion: Detected active infection using nested-PCR draws attention to the possibility of *T. gondii* infection via blood transfusion which emphasizes the importance of parasite DNA screening before donation of blood in high risk groups such as: multi-transfused persons, immunosuppressed patient, and pregnant women.

Keywords: *Toxoplasma gondii*, Blood donors, Seroprevalence, PCR, Iran

(18126)

Assessment of inflammatory and antibody responses in the lesion of cutaneous leishmaniasis patients using a non-invasive sampling method combined with a high-throughput protein detection assay and ELISA

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Background: Cutaneous leishmaniasis (CL) is a disease caused by *Leishmania* parasite transmitted through the bite of infected sandflies, which elicits an inflammatory response in the skin. Previously, limited number of inflammation-related proteins along with invasive sampling of blood and skin have been studied. Here, we employed a novel approach based on a non-invasive sampling method combined with a high-throughput protein assay technology called proximity extension assay (PEA) for profiling 92 inflammatory proteins in active and chronic CL patients' lesions caused by *L. tropica*. In addition, specific antibody in the lesions of CL patients was assessed.

Method: Samples were collected by using adhesive tape-discs from lesion and normal skin of 33 *L. tropica* PCR positive patients. PBS added discs were sonicated and used for ELISA and PEA, and data were normalized by inter-plate controls and internal controls.

Result: The anti-leishmanial IgG antibody response of 17 out of 25 acute patients' samples as well as 6 out of 8 chronic cases showed detectable specific IgG antibody. The levels of 34 proteins out of 92 inflammatory proteins were significantly increased in the lesion of CL patients. This includes a group of chemokines, interleukins, surface molecules and receptors as well as other cytokines and proteins.

Conclusion: In summary, we herein employed a novel non-invasive sampling method combined with immunological method for the analysis of the inflammatory proteins and assessment of specific IgG level of the localized lesion of CL patients caused by *L. tropica* parasite. This method may have implication for discovery of biomarkers and treatment follow-up in leishmaniasis. This approach is also applicable for other skin diseases such as cutaneous tuberculosis, lupus vulgaris, psoriasis, and sarcoidosis.

Keywords: Cutaneous leishmaniasis, non-invasive sampling, Proximity extension assay (PEA), ELISA

(18340)

Hydroalcoholic extract of *Glycyrrhiza glabra* and glycyrrhizic acid increased the Interferon-gamma (IFN-γ) secretion in *Leishmania major* infected BALB/c mice

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Background: Cutaneous leishmaniasis is an infectious disease caused by different species of *Leishmania*. It is shown that Interferon-gamma (IFN-γ) produced by T helper cell 1(Th1) plays a critical role in leishmaniasis control. There are natural products like *Glycyrrhiza glabra* extracts and its component which demonstrated to act as immunomodulator and enhance Th1activation. The aim of this study was to explore the effect of hydroalcholic extract of *Glycyrrhiza glabra* and its component glycyrrhizic acid on (IFN-γ) secretion of splenocytes in *Leishmania major* infected BALB/c mice.
Methods: *Leishmania major* infected BALB/c mice were randomly divided into 5 groups; the groups of mice were treated intraperitoneally as follow; 200 or 600 mg/kg of *Glycyrrhiza glabra* extract, its component glycyrrhizic acid (200mg /kg), Glucantime (160 mg/kg) and phosphate buffer saline as a negative control for one month. The mice were scarified and the level of IFN-γ in the supernatant of the splenocytes was measured by ELISA.
Results: The mean of IFN-γ in groups treated with glycyrrhizic acid, Glucantime, and hydroalcholic extract of *Glycyrrhiza glabra* (600 mg/kg) increased significantly compared with the negative control group.
Conclusion: The hydroalcoholic extract of *Glycyrrhiza glabra* and glycyrrhizic acid induced Th1 activation which resulted in as increase in IFN-γ generation in splenocytes of *Leishmania major* infected BALB/c mice.
Keyword: Interferon-gamma, T helper1, *Leishmania major*, *Glycyrrhiza glabra*

(18668)

Immunological effects of nanosilver proteinate (Protargol) on cutaneous lesihmaniasis induced by *Leishmania major* in a BLAB/C mice model

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Background: Leishmaniasis disease is one of the most important tropical zoonotic diseases that caused by an intracellular protozoon. The present study was aimed to evaluate the immunologic effects of nanoparticles of silver proteinate (Protargol) on skin lesion of cutenoues leishmaniasis (CL) caused by *Leishmania major* in the experimental model of BALB/c mice using ELISA method.
Methods: To perform this study, 21 BALB / c mice were purchased, and then 2 $\times 10^6$ promastigotes was injected subcutaneously (except the control group). Then ,the mice were divided randomly into three groups of 7 mice, including Protargol, sham group and the control group. The treatment was performed 3 times daily and for 30 days in all groups. Wound diameter was measured and reported on days 7, 14, 21 and 28 post-treatment in each group. At the end of the treatment, mice were scarified and blood were collected, serum levels of interferon gamma, interleukins (IL) 4 and 12 were then measured using the sandwich ELISA method with commercially available s-ELISA kits (Ready-SET-GO ELISA, ABNOVA, Taiwan) according to the manufacturer's protocol.
Results: Clinical evaluation showed that the wound diameter in the Protargol group was significantly deceased on the second to fourth weeks post-treatment compared to control and sham groups($P<0.001$). The serum levels of interferon gamma, IL-12 and IL-4 expressions in the treatment groups showed a significant increase compared to the control and sham group($P<0.001$).
Conclusion: The findings of the present study showed that increasing of serum levels of INF-γ, IL-12 can elicited stronger Th-1 type cellular immune responses in protatrgol group that can improve the CL lesions induced by *Leishman major* in the BLAB/ c mice model. However, more studies are needed to find the other mechanism of *Arnebia euchroma* on immune responses and T cells.
Key words: cutaneous leishmaniasis, ELISA, cytokines, nanosilver proteinate

(18671)

Immunological effects of *Arnebia euchroma* on cutaneous lesihmaniasis induced by *Leishmania major* in a BLAB/C mice model

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Background: Leishmaniasis is listed as one of the most important of neglected tropical diseases that caused by *Leishmania major* and the number of infected cases has significantly increased in endemic areas. This study was designed to evaluate the immunological effects of *Arnebia euchroma* (*AE*) on cutaneous leishmaniasis (CL) caused by *L. major* in the experimental model of BALB/c mice.
Methods: A total of 30 BALB/ c mice were purchased and divided randomly into three groups including control, sham and *AE* groups. Mice were inoculated subcutaneously (except the control group). The treatment was performed 3 times a day for 30 days and wound diameter was measured and reported on days 7, 14, 21 and 28 post-treatment in each group. At the end of the treatment the serum levels of interferon (INF) gamma, interleukins (IL) 4 and 12 were measured using the sandwich enzyme-linked immunosorbent assay (sELISA) method.
Results: The *AE* group showed significantly deceased wound diameters on the first to fourth weeks post-treatment compared to both the control and sham groups ($P<0.001$). The serum levels of INF-γ, IL-4 and IL-12 were significantly increased in the treatment group compared to the control and sham group ($P<0.001$).
Conclusion: The results of this study showed that *Arnebia euchroma* can improve the CL lesions caused by *Leishman major* in the BLAB/ c mice model by increasing of the serum levels of IL-12 and interferon gamma. However, more studies are needed to find the other mechanism of *Arnebia euchroma* on immune responses and T cells.
Key words: cutaneous leishmaniasis, ELISA, cytokines, *Arnebia euchroma*

(18672)

Improving the Immunostimulatory Effect of FML extracted from Leishmania infantum on Macrophages by Combination with Glycyrrhizin

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Background: The Fucose-Mannose Ligand (FML) of *Leishmania infantum* is a glycoprotein antigen which has not adequate immunogenicity in human. In recent years, adjuvant compounds derived from plants have been used to improve vaccine immunogenicity. Glycyrrhizin (GL) is a natural triterpenoid saponin that has known immunomodulatory activities. In present study, we investigated the effects of a co-treatment with FML and GL on production of cytokines and NO by macrophages, *in vitro*.
Methods: LPS-stimulated murine peritoneal macrophages treated with FML of *Leishmania infantum* and various concentration of GL. After 48h, cell culture supernatants were recovered and the levels of TNF-α, IL-10, IL-12p70 and IP-10 measured by sandwich ELISA and NO concentration by Griess reaction.
Results: Our results indicated treatment of activated macrophages with FML plus GL lead to enhanced production of NO, TNF-α, IL-12p70 and reduction of IL-10 levels in comparison with FML treatment alone.
Conclusion: We concluded that GL can improve immunostimulatory effect of FML on macrophages and leads to polarization of them toward an M1-like phenotype.
Keywords: Fucose-mannose ligand, Glycyrrhizin, Macrophage, Nitric oxide Visceral Leishmaniasis

(18724)

Studying and comparsion serum level of IL-35, 37 and expression of CD8, CD28, CD3, TIM3 surface markers in hydatid cyst

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Background: Hydatidosis is a zoonotic parasitic disease with global distribution, which causes the production process of cytokines to change from Th1 to Th2. The spread of TCD8+ cells and no expression of CD28 cause T cells to differentiate toward senescence, and TIM3 causes immune responses to be adjusted negatively during the chronic inflection as an inhibitory receptor on TCD8+ cells. IL-35 and IL-37 are inhibitory cytokines suppressing the immune system. The purpose of the present study was to investigate cell populations and inflammatory mediators and to direct the response from the immune system in patients with hydatid cysts.

Methods: The PBMCs of patients with hydatid cysts (case) and of healthy subjects (control) were exposed to CD8, CD28, CD3, and TIM3 antibodies (before surgery and positive serum and after separation, respectively), and the values of cell population were examined with the flow cytometry method. The inflammatory cytokines were also examined with the ELISA method after the subjects' blood serums were separated.

Results: The results demonstrated a significant decrease in CD8+CD28- cell population in the patients before surgery and a significant increase in the patients after surgery ($P<0.05$) with respect to the control group. TIM3 lymphocyte markers in the group of patients before surgery exhibited a significant decrease ($P<0.05$) with respect to those in the control group. IL-35 in the two group of patients before and after surgery exhibited a significant increase ($P<0.05$) with respect to that in the control group.

Conclusion: The numbers of senescence T cells in patients with hydatid cysts decrease and hydatidosis can partially inhibit the senescence T cells increases with aging which is related to autoimmune diseases and malignancies. Identification the mechanisms preventing from induction of senescence T cells via hydatid cysts (Echinococcus granulosus) can reveals new therapeutic ways for prevention of aging related diseases such as cancer.

Keywords: Hydatid Cyst, CD8, CD28, TIM3, IL-35, 37

(16653)

Strongyloides stercoralis infection among the patients receiving immunosuppressive drugs in northern Iran; a closer look into risk factors

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Background: Immunocompromised patients are at greatest risk for severe complicated infections with some intestinal parasitic infections especially strongyloidiasis. The objective of this study was to evaluate the prevalence of Strongyloides stercoralis and other intestinal parasites among the patients receiving immunosuppressive drugs and related risk factors in northern Iran.

Methods: This cross-sectional study was conducted among 494 patients receiving immunosuppressive drugs including cancer patients undergoing chemotherapy (n=188) and those treated with prolonged corticosteroid administration (n=306). All fresh fecal samples were examined by direct wet-mount, formalin ethyl-acetate concentration, and agar plate culture techniques.

Results: In total, 16.8% of patients were positive for at least one intestinal parasite among those the helminthic and protozoan infection rates were 5.1% and 12.3%, respectively. The infection rate was significantly higher in corticosteroid treated individuals (19.6%) than cancer patients (12.2%) (P = 0.03). The prevalence rate of S. stercoralis among the patients receiving chemotherapy and those treated with corticosteroids were 4.3% and 5.2%, respectively. The prevalence rate of S. stercoralis infection was significantly higher in older patients (P=0.02).

Conclusion: Strongyloidiasis is one of most common parasites among the patients receiving immunosuppressive drugs in northern Iran. Early diagnosis and proper treatment of these patients are necessary to minimize complications of severe strongyloidiasis.

Keywords: Strongyloidiasis, Immunocompromised patient , Risk factor, Iran

Congress Abstracts

Immunomedulation & Immunoregulation

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18046)

Evaluation of effect of long-term usage of acetaminophen on the gene expression levels of arginase and cyclooxygenase in leukocytes

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Abstract: Acetaminophen (paracetamol) is commonly used to treat many conditions such as headache, arthritis, backache, toothaches, muscle aches, colds and fevers. This drug has been shown to suppress the humoral and cell-mediated *immune responses* at a dose that causes liver injury. Acetaminophen effect on gene expression of arginase and cycooxygenase enzymes in leukocytes is unclear. In this study the effect of long-term usage of acetaminophen on gene expression levels of these enzymes was evaluated in leukocytes. Acetaminophen was orally administrated to Balb/c mice for two months. Afterthat, leukocytes were isolated from acetaminophen-treated mice and control mice. After extraction of RNAs from leukocytes, the gene expression levels of arginase and cycooxygenase were determined using real-time RT-PCR technique. Analysis of data showed that drug altered expression of arginase in leukocytes. But, the expression levels of cyclooxygenase were not significantly different between acetaminophen-treated group and control group.

Keywords: Acetaminophen, Leukocytes, Arginase, Cycooxygenase

(18069)

CTLA-4 FC improves the potency of insulin-producing cells differentiated from mouse bone marrow mesenchymal stem cells.

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Background: Although mesenchymal stem cells (MSCs) are regarded as immunoprivileged and even immunosuppressive, recent evidence suggests that allogeneic immune response might is inevitable in the case of some lineages differentiated from MSCs. Regarding the importance of allogeneic IPCs and MSCs in pre-clinical and clinical studies. The goal of this study was to investigate immunogenic changes during differentiation, potential these possible changes to the stimulation of the immune system in the model of allogeneic murine transplantation, and finally to investigate the impact of CTLA-4 Ig on the survival and efficacy of IPC transplantation in diabetic mice.

Material and methods: Two strains of the mouse, C57BL/6 (H2Db) and BALB / c (H2Dd) were chosen to set an allogeneic model of cell transplantation. Bone marrow MSCs differentiated into IPCs, and flowcytometry used to test the expression of H2D, CD80 and Qa-2 molecules. The IPCs and MSCs were coculters that studied alloreactive response to allogeneic splenocytes. .Then IPCs from C57BL/6 were implanted to streptozotocin (STZ)-induced diabetic BALB/c mice. Blood glucose levels and graft survival time after transplantation were monitored. Moreover, the residual IPCs, infiltrating immune cells and alloreactive cells from the recipients were analysed.

Results: Differentiation results in an increase in immunogenic molecules which ultimately stimulates the alloractive response. IPCs manage glycemia substantially better than MSCs. In contrast to Undifferentiated MSCs, IPCs substantially increase the population of effector cells in both types TCD 4 + and TCD8 +. The proliferation and secretion of IFN-γ cytokine were significantly greater in the IPC group. While, it has been shown that CTLA-4 FC suppresses the alloreactive, this study shown that the strongest regulation of blood sugar and survival with combination of IPC and CTLA-4 FC.

Conclusions: This study shown that IPC could better blood glucose regulation than Undifferentiated MSCs Although this research present signs of an alloreactive to differentiated cells at both stages of the experiment but in differentiated and Undifferentiated allogeneic mesenchymal stem cell recipients were not observed acute rejection of transplants. The CTLA-4FC was suppressed the alloreactive response, and improve the efficiency of allogeneic IPC transplantation.

Keyword: CTLA-4 FC, Mesenchymal stem cell, Insulin Producing Cell, Diabetes, Transplantation

(16757)

Comparison of modulation of microRNAs for human dental pulp stem Cells and human adipose derived mesenchymal stem cells by Crocin

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Introduction: Mesenchymal stem cells (MSCs) are present in different tissue such as bone marrow and adipose tissue, and dental pulp, although there are certain variations between them in their gene expression profile, immune modulation capacity, and the secretion of factors. A lot of research has recently been undertaken to enhance the immunomodulatory function of MSCs and to pick an excellent type of MSC for clinical approaches. MicroRNAs (miRNAs) are small non-coding RNAs that regulate much of the biological activity of MSC cells. Crocin is a carotenoid chemical compound that has anti-oxidant and anti-inflammatory effect. This study aims to evaluate the immunoregulatory related miRNAs level and these target gene in both adipose-derived stem cells (ADSC) and dental pulp stem cell (DPSC) which probably have strong immunomodulatory properties in the presence or lack of Crocin**.**

Methods: ADSCs from adipose tissue were extracted and DPSCs were isolated from dental pulp and then treated with Crocin. Then, the expression of 4 selected immunomudulatory-related micro-RNAs (i.e.-126,-21,-23, and-155) and these targets were assessed by PCR in two MSCs.

Results: Our findings showed that miRNA-23 and miRNA-126 up-regulated by Crocin therapy in MSCs and down-regulated miRNA-21 and miRNA-155 in the other side. As noted, these immuno-regulatory effects of crocin were higher in DPSCs than in ADSCs.

Conclusion: This research suggests that Crocin can suppress the expression of PI3K/Akt/NFKB genes by decreasing the expression of miRNA-23 and miRNA-126 or by increasing the expression of miRNA-21 and miRNA-155 that play a role in the immune regulation pathways in MSCs. These findings can provide an understanding of the mechanisms by which Crocin controls the immunomodulatory feature of MSCs. In addition DPSCs are a better immunomodulator in crocin therapy than ADSCs. It may be helpful for modulation or treatment of autoimmune disorders.

Keyword: Mesenchymal stem cell, micro-RNA, miRNAs, Immunoregulatory, Crocin, Compar.

(18156)

The Effect of hydroalcoholic extract of Ferula assa-foetida L. oleo-gum-resin on serum levels of IL-6 and TNF-α cytokines and oxidative stress parameters in animal model of rheumatoid arthritis

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Background: Rheumatoid arthritis is a chronic inflammatory and auto-immune disease that affects the synovial tissue in multiple joints and is characterized by joint swelling, cartilage damage, synovial and bone erosion. Potential side effects of current treatments for RA have limited their use, therefore, interest in replacing anti-inflammatory treatments has reappeared. The aim of this study was to evaluate the anti-inflammatory and antioxidant activity of Ferula assa-foetida L. resin extract in collagen-induced arthritic mouse model.

Methods: Rheumatoid arthritis was induced by collagen type 2 and adjuvant in female 8-10 weeks old Wistar rats. 30 rats were randomly divided into 6 groups: healthy control, negative control, positive control, dose of 100 mg / kg of extract, 300 mg / kg of extract and group of mixed. Extract was administered in gavage form and dexamethasone as an intraperitoneal injection for 24 days and their effects were assessed using subjective evaluation of arthritis, serum levels of inflammatory cytokines (IL-6 and TNF-α), oxidative stress indices (NO and TAC), and histopathology parameters.

Results: The study indicate that oral administration of extract has reduced the level of inflammatory cytokines (IL-6 and TNF-α). Protective effects of assafoidita resin in RA also showed a decrease in the score of arthritis and joint histology, so that for the inflammation index, the dose of 300 of extract could reduce 63.63% than patient group. In general, this group was able to reduce the total score of the histopathologic symptoms of the disease 65.78% compared to patient group ($p < 0.03$). But no significant results were observed in the oxidative stress parameters (NO and TAC).

Conclusion: Regarding the improvement of tissue symptoms and the comparative reduction of inflammatory cytokines, this extract can be considered as a suitable candidate for further study, clarification of mechanisms and ultimately therapeutic use.

Keywords: Rheumatoid Arthritis, Ferula assa-foetida L .resin, Inflammatory Cytokines, Collagen Induce Arthritis

(16662)

Immunomodulatory Potential of Murine Adipose-Derived Mesenchymal Stem Cells is enhanced Following Culture on Chitosan Film

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Background: Recent studies show that the effects of paracrine on mesenchymal stem cells (MSCs) are mediated by the secretion of interleukin-10 (IL-10), transforming growth factor beta (TGF β), nitric oxide (NO), and arginase. Preconditioning of mesenchymal stem cells improves their immunomodulatory features. Chitosan is a biopolymer that has low immunomodulatory properties, low toxicity and biodegradability. The aim of this study was to evaluate the effect of cultured mesenchymal cells on chitosan film on immune responses.

Methods: In this study, MSCs were isolated from abdominal adipose tissue of BALB/c mice. Flow cytometry was used to confirm the identity of mesenchymal stem cells. Chitosan film was prepared at 3% w/v and then MSCs were cultured on it. After 24 h, cells were stimulated by 10 ng/mL LPS. The concentration of IL-10 and TGF-β was measured by ELISA, and the concentration of NO and IDO enzyme activity in mesenchymal cells were measured by spectrophotometry.

Results: In this study, with the regard of the effect of chitosan film on mesenchymal cells culture, it was shown that the level of IL-10,NO and IDO in MSc cells cultured on LPS-stimulated chitosan film was 29.56 pg / mL, 82.17 µmol / mL and 37.63 µmol/ mL respectively. These values increased significantly compared to mesenchymal cells cultured alone ($P < 0.0001$, $P < 0.0001$ and $P = 0.0431$).

Keywords: Chitosan film, Mesenchymal stem cell

(17958)

Crocin improves the immunomodulatory capacity of dental pulp stem cells via up-regulation of CD200 glycoprotein

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Background: Dental pulp stem cells (DPSCs) are a new type of mesenchymal stem cells (MSCs) with the high capacity for multi differentiation, tissue regeneration and modulation of immune responses. Therefore due to the unique capabilities, they are potential candidate for clinical applications, especially treatment of degenerative and immune-related diseases. Recently, studies have focused on the gene expression change strategy to improve therapeutic effectiveness and stemness status of these MSC cells. Crocin is known for its beneficial effects in reducing immune responses and helping to repair tissue damages. This study was conducted to investigate the surface expression of CD200 glycoprotein in DPSCs (possibly for the first time) and followed by effect of crocin on it, which is known to be one of the most important immune regulation factors.
Methods: The MTT method was used to determine an optimal-nontoxic concentration of crocin for DPSCs. Also, flow cytometric procedure was performed to assess the expression change of CD200 after treatment with crocin. Finally, the data was analyzed with SPSS software (version 26).
Results: In the study, it had been successfully detected the cell surface expression of CD200 glycoprotein in the DPSCs and revealed that cell treatment with crocin (400 µM) significantly increased the positive cell percentage up to 1.36, 3.34 and 2.7 fold compared to control groups after 24, 48 and 72h ($P < 0.05$, $P < 0.001$ and $P < 0.001$, respectively).
Conclusion: The research suggested that crocin can enhance immunomodulatory capacity of DPSC cells through up-expression of CD200 biomarker.

Keywords: Dental pulp stem cell, Crocin, CD200, Immunomodulation

(18416)

Evaluation of the regulatory axis of long non-coding RNA NEAT1/ miR199a-5p/heat shock protein A5 gene expression in patients with diabetic neuropathy

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Background: Neuropathy is one of the most common microvascular complications of diabetes, seen in 50% of patients and leads to foot ulceration and amputation. One of the factors involved in the pathogenesis of diabetic neuropathy (DN) is endoplasmic reticulum (ER) stress. The key regulator of ER stress is heat shock protein A5 (HSPA5), which acts as a chaperone, regulating the response of unfolded proteins. In the current study, we assessed the expression of HSPA5 and its regulatory axis long non-coding (lncRNAs) NEAT1/miR-199-5p.

Methods: The peripheral blood from twenty patients with or without diabetic neuropathy was obtained. The expression levels of the lncRNA NEAT1 and HSPA5 gene were assessed using qPCR. miR-199a-5p assessed by LNA method.

Results: The gene expression level of NEAT1, as well as HSPA5, increased significantly in the diabetic neuropathy subjects compared to the non-DN group (P=0.01). The expression level of miR-199a-5p in patients with diabetic neuropathy was significantly lower than the non-DN subjects (P=0.04).

Conclusion: Considering the inflammatory and neurodegenerative role of NEAT1, it can be said that increased NEAT1 expression may be played a role in the pathogenesis of neuropathy. Also, decreased level of miR-199a-5p gene expression and consequently increased HSPA5 expression may indicate the role of endoplasmic reticulum stress mediators in diabetic neuropathy under chronic stress induced by hyperglycemia. According to this data, it can be expected that by targeting this pathway, positive effects can be observed in improving the condition of DN patients.

Keywords: Diabetic neuropathy, HSPA5, lncRNA, miR-199a-5p

(16883)

Immunomodulatory effects of phytosomal curcumin are associated with downregulating miR-155 and miR-126a in dental pulp stem cells

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Background: Recent evidence has demonstrated that dental pulp-derived stem cells (DPSCs) may represent a source of pluripotent progenitors capable of regulating the immune system and therefore have application in reconstructive medicine and treatment of many diseases. Today, there are various ways to improve the performance of DPSCs in the clinic, one of them is the alteration in the degree of expression of their genes. Although microRNAs (miRNA/miR) can act as a modulator of the immune system in DPSCs. Phytosomal curcumin (PC) is a nanoparticle form of curcumin that eliminates the disadvantages of curcumin. Curcumin is notable for its pleiotropic medicinal benefits, like its anti-inflammatory activity. The target of this paper was to ascertain the immuno-regulatory role of PC in DPSCs and the alleged links of two key miRNAs in the immune system.

Methods: MTT assay was employed to the evaluation of cell viability in PC-treated DPSCs. Real-time quantitative (RT-PCR) showed the expression levels of miRs in PC-treated and untreated groups. Statistical analysis is carried out utilizing SPSS (version 16).

Results: PC (30 µM) treatment in DPSC could ameliorate its immunoregulatory property, presented by reduced expressions of miR-126 (at 24 h and 48h, 0.407 and 0.007 fold respectively, $P < 0.001$), as well as decreased expression miR-155 expression (at 24 h and 48h, 0.009 and 0.003 fold respectively, $P < 0.001$). Moreover, PC was more effective than curcumin in improving the immune modulation of DPSCs ($P < 0.01$).

Conclusion: Evidence in this study suggested that PC mediates immunoregulatory in DPSC via miR-155 and miR-126, which may provide a theoretical basis for PC in the treatment of many diseases.

Keywords: dental pulp stem cell, microRNA, immunoregulatory or immunomodulatory, phytosomal curcumin

(16880)

Enhancement of the Immunomodulatory Properties of Dental Pulp Stem Cells by Crocin through Up-expression of HLA-G5 and STAT3 Genes

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Background: Dental pulp stem cells (DPSCs) are a new population of adult stem cells located in the oral cavity. Recently, these cells have been identified with potential properties for tissue repair/regeneration and also modulation of immune responses. Change in the target genes expression through co-culture method with different stimulants is one of available opportunity to enhance the cell's capacity in research and clinical uses. Crocin is the most famous effective compound of saffron plant with beneficial effects in tissue repair and minimizing the immune responses. The aim of this study was to evaluate the effects of Crocin on the relative expression of HLA-G5 and STAT3 biomarkers which are among the most important factors in modulating immunity by these cells.

Methods: The Crocin effects on DPSCs viability were evaluated by MTT test. Quantitative real-time PCR technique was accomplished in order to assess the relative expression change of STAT3 and HLA-G5 under cell treatment condition with Crocin. Eventually, the data was analyzed by SPSS program (version 26).

Results: According to the Real-Time PCR results, cell treatment with Crocin(400 µM) significantly induced time-dependent increased expression of of HLA-G5 gene ($P < 0.001$), while the expression of STAT3 was significantly upregulated in 72h (expression= 1.38-fold, $P < 0.001$) after a statistically remarkable reduction in 24h (expression= 0.59-fold, $P < 0.001$).

Conclusion: The study suggests that Crocin is able to specifically optimize the DPSCs and enhance their efficacy for immunomodulatory applications.

Keywords: Dental pulp stem cell, Crocin, HLA-G5, STAT3, Immunomodulation

(16881)

Curcumin modulate inflammatory pathways by upregulation of microRNA-23b in dental pulp stem cells

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Background: Dental pulp stem cells (DPSCs), as one type of mesenchymal stem cells (MSCs), have the capability of selfrenewal, multipotency, as well as immunosuppressive properties. They are ideal candidates for regenerating damaged dental tissue and treating many diseases. Recently, genetic variation is one of the methods to improve the immunomodulatory activity of MSCs. MicroRNAs (miRNAs) are small noncoding RNAs that control most of the cell's biological activities. They have been proved in previous studies to play a significant role in the regulation of MSC immunomodulatory activity. Curcumin is known for its pleiotropic medicinal properties, via its anti-inflammatory and anti-oxidant effects. This study is to investigate the effect and underlying mechanisms of curcumin on the immunoregulatory function of DPSCs.

Methods: Cell viability rate was observed in DPSCs after treatment of curcumin by MTT assay. Real-time quantitative (RT-PCR) was applied to estimate the expression of MicroRNA-23b after treatment of curcumin at 24 h and 48 h. Statistical analysis is carried out utilizing SPSS (version 16).

Results: Curcumin (6 μM) treatment in DPSC could improve its immunoregulatory capacity. The qPCR results showed that miR-23 had a significant increase compared to the untreated group (at 24 h and 48h, 18.5 and 20.2 fold respectively, $P < 0.001$)

Conclusion: Curcumin can modulate inflammatory pathways via miRNA-23overexpression in DPSCs. These results may provide insight into the mechanism underlying the regulation of the immunomodulatory activity of DPSCs by Curcumin.

Keywords: MicroRNA 23b, Immunoregulatory, Immunomodulatory, Curcumin, mira

(18414)

The effects of adipose tissue mesenchymal stem cell-derived exosomes with conditioned media on neutrophil function and apoptosis

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Background: Neutrophils are short-lived cells of the innate immune system that have an important role in defending against pathogens by producing reactive oxygen species (ROS). Effective strategies for increasing neutrophil viability and function may be beneficial, especially in many conditions such as immunodeficiency diseases. Some studies suggest using mesenchymal stromal cells (MSCs) and MSC-conditioned media (MSC-CM) for this aim. But, there is no study on using MSC-derived exosomes for improving neutrophil's viability and function. So, we examined the effects of MSC-exosomes and also MSC-CM on neutrophil function and survival and compared them with each other.
Methodology: Exosomes and CM were isolated from human adipose tissue MSCs. Exosomes were characterized. Neutrophils were isolated from five healthy donors, and the effects of the two independent treatments on neutrophil apoptosis were measured by Annexin V-PI method, then neutrophil function was evaluated using NBT and phagocytosis assays.
Results: It was recognized that exosomes decreased neutrophils apoptosis and increased their phagocytosis capacity. MSC-CM augmented neutrophil's phagocytosis and ROS production, but it couldn't decrease neutrophil's apoptosis.
Conclusions: This report showed that the use of exosomes and CM might be useful for increasing immunity by improving neutrophil function and survival.
Keywords: Mesenchymal Stem Cell, Neutrophil, Exosome, Conditioned Media

(15477)

The effect of Platelet Rich Plasma (PRP) on the B92 Glial Cell

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Background: In previous studies, the crosstalk between some cancer cells and platelets have been documented. The purpose of the present study was to evaluate the effects of platelet-rich plasma (PRP) on B92 glial cancer cells.

Methods: In this experimental study, 1×10^6 B92 cells were treated with Platelet-rich plasma (PRP) for different of 0, 5, 10 and 20 percent of cutler media for 24 h. The morphological changes of the treated cells were evaluated by inverted light microscopy. The effects of PRP on the proliferation rate of cells were measured using the tetrazolium salt reduction test (dimethyl thiazole-diphenyltetrazolium bromide, MTT). QRT-PCR technique was used to evaluate the expression level of TNFα, IL-10 and BCL-2 genes.

Results: The results of the MTT reduction test showed that PRP promotes B92 glial cell growth in a dose-dependent manner. PRP in a dose-dependent manner also increased BCL-2 gene expression. The expression of the TNF-α cytokine gene was decreased in a non- percent -dependent manner after the treatment of B92 glial cells with PRP. Treatment of B92 glial cells with PRP promoted a significant increase in the expression level of the gene of anti-inflammatory IL-10 cytokine.

Conclusion: In the microenvironment of cancer, platelets promote the growth and proliferation of B92 glial cells and their escape from immune responses.

Key Words: Platelet-rich plasma (PRP), B92 glial cells, IL-10, TNF-α, BCL-2.

(16568)

Thymectomy May Be Leading to Reduction of Tc17 and Th17 Cells in Myasthenia Gravis Patients.

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Background: Myasthenia gravis (MG) is an autoimmune disease mediated by autoantibodies against the neuromuscular junction. The thymus has an important role in the pathogenesis of MG because most patients have thymic pathology, and thymectomy (TE) can reduce the severity of the disease.
Methods: In this study, the frequency of Th17 and Tc17 cells was studied in 12 MG patients (pre-TE and 6 months post-TE) and in 12 healthy controls (HC).
Results: The frequency of Tc17 cells in the pre-TE patients was significantly higher than in the HC ($p < 0.05$), and after TE, these cells had significantly decreased compared to before TE ($p < 0.05$). The frequency of Th17 cells in pre-TE patients was significantly higher than in the HC ($p < 0.05$), and after TE, these cells had significantly decreased compared to before TE ($p < 0.05$).
Conclusion: Our findings indicated a possible role of Tc17 and Th17 in MG pathogenesis.
Keywords: Myasthenia gravis, Thymectomy, Th17, Tc17

(18704)

The role of uremia and miR-24-3P expression in immune dysfunction in end-stage renal disease

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Background: Immune dysfunction involving both innate and adaptive immune responses are common in end stage renal disease (ESRD) patients. This disorders, which is caused by uremia in these patients, leads to suppression of the immune system and increases the prevalence of infection. It also leads to inflammation by increasing the activation of the immune system, which may be associated with an increased risk of cardio vascular disease (CVD). The results of previous studies show that uremia alters the expression of microRNAs. The present study aimed to investigate the changes in the expression of microRNAs, small non coding RNAs containing 18-24 nucleotides in the serum of hemodialysis patients in order to find the microRNA associated with immune dysfunction.

Method: Real Time PCR method was used to evaluate the expression of miR-24-3P in serum. Data analysis was performed using Graph Pad Prism version 7. In all analyses, $p \leq 0.05$ was considered statistically significant.

Results: The expression of miR-24-3P in hemodialysis patients was significantly higher than the healthy subject. WBC count was significantly higher in the healthy subject compared to hemodialysis patients ($P = 0.02$). The results of bioinformatics studies using databases such as miR TAR and Target Scan showed that this microRNA targets the TGFβ gene and the results of KEGG studies using DIANA TOOLS - miR Path v. showed that this microRNA affects the TGFβ and MAPK pathways.

Conclusion: The results of this study showed that a decrease in WBC count in these patients could be associated with impaired immune function and an increased risk of infection in these patient. It is also possible that miR-24-3P may suppress the immune system by affecting TGFβ expression and the TGFβ pathway. And, it may increase inflammation in these patients by affecting the MAPK pathway.

Keywords: MicroRNA, ESRD, Uremia, Immune dysfunction

(18150)

Evaluation of regulatory axis of lncRNA MALAT1/miR-1-3p/CXCR4 in the peripheral blood; A comparison between patients with and without diabetic neuropathy

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Background: The pathogenesis of diabetic neuropathy (DN), the most common complication of diabetes mellitus, is not yet fully understood. According to recent findings, C-X-C Motif Chemokine Receptor 4 (CXCR4) has been reported can be involved in the development and maintenance of pain in patients with diabetic neuropathy. In this study, we evaluated the expression of CXCR4 and its regulatory axis long non-coding (lncRNAs) MALAT1/miR-1-3p.

Methods: Peripheral blood samples were obtained from twenty DN patients and twenty diabetic patients without neuropathy (non-DN). RNA expression of MALAT1 and CXCR4 was assessed using RT-qPCR. The expression level of miR-1-3p was evaluated by real-time PCR using locked nucleic acid (LNA) method.

Results: Significant increase in expression of MALAT1 and CXCR4 was observed in DN patients compared to non-DN subjects ($P < 0.05$ and $P < 0.05$, respectively). analysis of miR-1-3pexpression demonstrated a significant decrease in DN patients ($P < 0.05$).

Conclusions: The MALAT1/miR-1-3p/CXCR4 axis might be involved in the pathogenesis of DN and these molecules could be useful biomarkers for DN.

Keywords: Diabetic neuropathy, MALAT1, miR-1-3p, CXCR4

(18759)

Effect of Lactobacillus acidophilus on IL-6 production by peripheral blood mononuclear cells of endometriosis patients

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Introduction: The presence of endometrial tissues outside the uterine cavity, known as endometriosis, is affected by environmental, genetic, hormonal and immunological factors. Among the disease immunological symptoms are inflammation and an increase in inflammatory cytokines. Lactobacillus acidophilus, as a probiotic flora, has been used for the treatment of many inflammatory diseases, and reduction of inflammatory factors. Here, we investigated the impact of Lactobacillus acidophilus treatment on IL-6 secretion by mononuclear cells obtained from endometriosis patients. **Materials and Methods** A standard sample of Lactobacillus acidophilus from the regional center of the Iranian Collection of Industrial Fungi and Bacteria (PTCC) and peripheral blood samples from endometriosis and non-endometriosis patients were used. Ficoll-separated peripheral blood mononuclear cells (PBMCs) were cultured in the presence and absence of PHA with a certain concentration of bacteria. The supernatant level of IL-6 was measured by ELISA in cultures of endometriosis and non-endometriosis samples. **Results** IL-6 production by endometriosis PBMC was higher compared to the control group in absence of Lactobacillus acidophilus; this difference was even more pronounced upon admixture of PHA to the cultures. Of note, Lactobacillus acidophilus addition to the cultures increased IL-6 level in the first 24 hour of co-culture, while it significantly reduced the cytokine concentration after 48 hours. **Conclusion** Depending on the treatment period, Lactobacillus acidophilus could exert either stimulatory or inhibitory impacts on the expression of the typical inflammatory cytokine, IL-6, by endometriosis-derived PBMC. According to previous studies, bacteria have the capacity to balance/modulate the immune system responses as related to the level of cytokines; more favorable modulatory impacts could be achieved with expanded treatment time periods. This study highlights the need for further research on the exact mechanisms involved in the interaction between Lactobacillus acidophilus and immune cells from endometriosis patients.

Keywords: Lactic acid bacteria, Immunomodulation, Endometriosis, PBMC.

(16884)

Bumetanide combined with Enalapril modulate macrophage-induced humoral and contact hypersensitivity responses in mice

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Background: The over-activated inflammatory responses of macrophages (Mph) likely increases the risk of hypertension development, while clinically relevant bumetanide administered alone or in combination with enalapril may possibly exert the immunomodulatory effects. Thus, we investigated the impact of these drugs on macrophage-mediated immunity in mice.
Methods: mice were treated i.p. with enalapril (5 mg/kg) with or without bumetanide (5 mg/kg) by 8 days. On the third day, mice were i.p. injected with mineral oil and 5 days later Mph were harvested to assess the generation of reactive oxygen species (ROS) and nitric oxide (NO). Mph were also pulsed with sheep red blood cells (SRBC) or hapten and transferred to mice for evaluation of their ability to induce humoral or contact hypersensitivity (CHS) reactions, respectively.
Results: Bumetanide, when administered alone or with Enalapril, enhanced ROS, but decreased NO production by Mph. SRBC-pulsed Mph from mice treated with Enalapril combined with Bumetanide increased the secretion of antigen-specific antibodies by recipient B cells, while Mph of mice treated with Bumetanide with Enalapril increased the number of antigen-specific B cells. Enalapril reduced CHS ear swelling response and this effect was augmented by Bumetanide.
Conclusion: Bumetanide with or without enalapril modulate the humoral and allergic cell-mediated immune responses by affecting the function of Mph. Further studies should investigate the clinical effect of these observations.
Keywords: Bumetanide, Enalapril, Humoral, Hypersensitivity

(16569)

High Frequency of Tc22 and Th22 Cells in Myasthenia Gravis Patients and Their Significant Reduction after Thymectomy.

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Background: Myasthenia gravis (MG) is an autoimmune disease accompanied by a thymic pathology and in most patients thymectomy (TE) is used as the therapeutic approach. Both B and T cells play an important role in MG pathogenesis.
Methods: Twelve pre- and post-TE MG patients and 12 healthy controls (HCs) were enrolled. The mean percentages of Th22 and Tc22 cells were evaluated in MG patients (before and 6 months after TE) and HCs.
Results: The mean percentage of Tc22 cells in pre-TE patients was significantly higher than in HCs ($p < 0.05$), and after TE Tc22 cells significantly decreased compared to pre-TE ($p < 0.05$). The frequency of Th22 cells in pre-TE MG patients was not significantly different from HCs, but after TE Th22 cells were significantly decreased compared to pre-TE ($p < 0.05$).
Conclusion: Our findings suggest a possible role of Th22 and Tc22 in MG pathogenesis.
Keywords Myasthenia gravis , Thymectomy , Th22 cells , Tc22 cells

Congress Abstracts

Immunopharmacology & Medicinal Plants

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18703)

Tranilast:A NLRP3 Inflammasome Inhibitor Drug for COVID-19

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Background: SARS-CoV-2 is a type of beta-CoV that develops acute pneumonia, which is an inflammatory condition. A cytokine storm has been recognized as one of the leading causes of death in patients with COVID-19. ALI and ARDS along with multiple organ failure have also been presented as the consequences of acute inflammation and cytokine storm.
Evidence acquisition: directory of open access journals, google scholar, PubMed, EBSCO and web of science were searched.
Results: it has been previously confirmed that SARS-CoV, as another member of the beta-CoV family, activates NLRP3 inflammasome and consequently develops acute inflammation in a variety of ways through having complex interactions with the host immune system using structural and non-structural proteins. Numerous studies conducted on Tranilast have further demonstrated that the given drug can act as an effective anti-chemotactic factor on controlling inflammation, and thus, it can possibly help the improvement of the acute form of COVID19- by inhibiting some key inflammation-associated transcription factors such as NF-κB and impeding NLRP3 inflammasome. Several studies have comparably revealed the direct effect of this drug on the prevention of inappropriate tissue's remodeling; inhibition of neutrophils, IL-5, and eosinophils; repression of inflammatory cell infiltration into inflammation site; restriction of factors involved in acute airway inflammation like IL33-; and suppression of cytokine IL13-, which increase mucosal secretions.
Conclusion: Tranilast may be considered as a potential treatment for patients with the acute form of COVID-19 along with other drugs.
Keyword: Coronavirus, COVID-19, Tranilast, NLRP3 Inflammasome, Inflammation, SARS-CoV-2

(18544)

Immunomodulatory activities of extracts and essential oils of two Oregano species (*Origanum Vulgare* L. and *Origanum Majorana* L.)

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Background: Medicinal plants with therapeutic properties improve the body's resistance against disease partly by their effects on immune cells. In this study, we evaluated the immunomodulatory properties of essential oil and extract of *O.Vulgare* and *O.Majorana in vitro.*

Methods: Plant samples were purchased and the ethanolic extract and essential oil from plant leaves were prepared using Maceration and Clevenger methods. The splenocytes and peritoneal macrophages were isolated from BALB/c mice. After mitogen stimulation (Con-A and PMA) cells were cultured with extract and essential oil for 24 h. MTT assay to evaluate the cell viability was measured. The enzymatic pathways iNOS or arginase of macrophages were examined using NO and urea assays respectively. The production IFN-γ, IL-4, IL-10 in supernatants of splenocytes was determined by ELISA.

Results: We revealed that *O.Vulgare* extract and *O.Majorana* essential oil resulted in a significant increase in macrophage proliferation 66% and 46% respectively. Among the compounds, only *O. Majorana* extract increases the ratio M1/M2 up to about 14-fold compared with a control group. Significant improvement of Th1/Th2 ratio (15-fold by *O.Vulgare* extract and 3-fold by essential oil and extract of *O.Majorana*, and *O.Vulgare* essential oil) a result from upregulation of Th1 and downregulation of Th2 markers. The amount of IFN-γ, IL-4, IL-10 produced by lymphocyte treated with essential oil of *O.Vulgare* and *O.Majorana* strongly enhanced compared with non-treated cells. Although the extract of *O.Vulgare* and *O.Majorana* reduced the production of IL-4. Thus both essential oils cause an imbalance of Th1/Treg by increasing IFN-γ to IL-10 ratio.

Conclusion: We showed in this comparative study that extracts were more effective than essential oils in moderately direct the immune response to Th1 and M1 without Th1/Treg imbalance and are more suitable choices to modulate the immune response toward anti-cancer or other stronger inflammatory responses. However, the detailed mechanisms remain to be investigated.

Keywords: Immunomodulatory, Oregano, M1/M2 Polarization, Th1/Th2, Th1/Treg Balance

(18459)

Anti-tumor effects of the aqueous seed extract of *Trachyspermum ammi (L.) sprague* on human cancer cell lines

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Background: Medicinal herbs are being increasingly used for the treatment of cancers. Despite a wide range of the pharmacological activities reported for the seeds of *Trachyspermum ammi (L.) sprague*, its potential anti-tumor effects are unknown. Herein, we evaluated the potential cytotoxic effect of the aqueous seed extract of *T. ammi* on human cancer cell lines. Moreover, the potential inhibitory effect of the aqueous seed extract on the expression level of Transforming growth factor beta (TGF- β), a prominent tumor progressive cytokine, was also investigated.

Methods: Cytotoxic activity of the aqueous seed extract *of T. ammi* on two human cancer cell lines including, breast and ovarian cancer cell lines was evaluated by MTT assay. Potential inhibitory effect of the seed extract on the expression level of TGF-β was evaluated by real-time polymerase chain reaction assay.

Results: MTT results showed the seed extract of *T. ammi* possessed a significant cytotoxic activity on the ovarian cancer cells compared to the untreated cells (p value < 0.05). Moreover, a significant reduction in the expression level of TGF-β was observed in both treated breast and ovarian cancer cells compared to the untreated cells (p value <0.05).

Conclusion: The seed extract of T. ammi can possess cytotoxic effect on human cancer cell line. Moreover, it may potentially inhibit tumor growth and proliferation by reducing TGF-β.

Keywords: Cytotoxic effect, Transforming growth factor beta, Trachyspermum ammi, Tumor.

(16759)

Impact of Berberine on anti-apoptotic Bcl-2 protein expression in patient with B-Chronic Lymphocytic Leukemia

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Background: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world that is characterized by an expansion of small and mature malignant $CD5^+/CD19^+/CD23^+$ B lymphocytes in blood, bone marrow as well as secondary lymphoid tissues. The treatment of CLL patients is still exposed to fail, and most of them show subsequently relapse. Berberine is a natural isoquinoline alkaloid that has been shown to inhibit the proliferation and induce apoptosis in a wide variety of tumor cells. However, the molecular action mechanism of berberine in CLL cells is unknown. The previous studies have shown that berberine leads to reduced viability and elevated levels of apoptosis in PBMCs of CLL patients. CLL cells are characterized by remarkable expression of Bcl-2. Here we investigated the anti-cancer effects of berberine on peripheral blood mononuclear cells (PBMCs) of CLL patients through anti-apoptotic protein BCL2.

Methods: In order to analyze the expression of anti-apoptotic proteins using flow cytometry and western blot, PBMCs of 12 CLL patients were isolated by Ficoll-paque then cultured in the four groups including treated with berberine (25 µM), untreated (control group), DMSO (vehicle control), and venetoclax (VEN) (as a positive control as Bcl-2 inhibitor) for 24 hours**.**

Results: Examination of treated cells demonstrated that berberine decreases Bcl-2 levels. Although western blot results did not show any change in Bax as a pro-apoptotic protein, an increased Bax/Bcl-2 ratio indicated that mitochondrial pathway is involved in berberine-induced apoptosis of CLL cells. Furthermore, berberine and ventoclox induced similar suppression effects on Bcl-2 expression in CLL patients. Also, we showed that berberine could reduce CD19 expression in lymphocytes of a treated group in comparison to control groups.

Conclusion: Our findings describe some of the molecular mechanisms of berberine by decreasing Bcl-2 which may be considered as a novel apoptosis inducer in CLL cells.

Keywords: Chronic lymphocytic leukemia; Berberin; Bcl-2

(16532)

Evaluation of chemical content, antioxidant, anti-inflammatory and anti-proliferative effects of *Ferula assa foeitida* gum essential oil on MDA-MB-468 breast cancer cell line

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Background: The inflammatory process can induce oxidative stress. The production of oxidants can upset the balance of the antioxidant system and cause mutations in vital molecules such as DNA. These mutations can lead to a variety of cancers, including breast cancer. The purpose of the present study was to investigate the content of chemical compounds, antioxidant power and anti-proliferative effects of *Ferula assa foeitida* essential oil on MDA-MB-468 breast cancer cell lines.
Methods: In this study, the essential oil of *Ferula assa foeitida* chemical composition was evaluated by GC-MS method. The phenolic and flavonoid content was determined by Folin-Siocato and Aluminum Chloride methods, respectively. The antioxidant power was evaluated using FRAP and DPPH methods. The anti-inflammatory effects were evaluated using Griess assay on Raw 264.7 macrophage. The anti-proliferative effect was evaluated by MTT assay on MDA-MB-468 breast cancer cell lines.
Results: Phenolic and flavonoid contents were 238.75 ± 18.26 µg GAE/mg and 91.02 ± 15.46 µg EQ/mg respectively. The chemical compounds Z-1-propenyl sec-butyl disulfide and E-1-propenyl sec-butyl disulfide were reported to be 24.93% and 36.25%, respectively. The monovalent antioxidant power was 56.25 ± 3.25 µmolFe^{2+}/g. The highest effect of total antioxidant power was reported at a concentration of 5000 ppm and 8.41%. The highest anti-inflammatory effects were reported at concentration of 600 ppm (38.28%) after 24 hours of Incubation. The highest anti-proliferative effect was reported at concentration of 400 ppm (31.12%) after 72 hours of Incubation.
Conclusion: *Ferula assa foeitida* gum essential oil has a significant content of chemical compounds. It has relatively high effects in inhibiting free radicals. Therefore, it can have anti-inflammatory and anti-proliferative effects on MDA-MB-468 triple negative cell line of breast cancer. Therefore, it is a good combination to inhibit inflammation and inhibit the proliferation of cancer cells.
Keywords: GC-MS, DPPH, FRAP, MTT assay, Raw 264.7, Ferula assa foeitida.

(18711)

Apoptotic Mode of Action of *Hemiscorpius lepturus* Scorpion Venom in K562 Human Chronic Myelogenous Cells

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Background: Apoptosis is a complex programmed metabolic interaction initialed by a cascade of intracellular events resulting in elimination of normal cells and is dysregulated in cancer cells. The objective of this study was to determine whether the cytotoxic effects of the venom from *Hemiscorpius lepturus* scorpion is related to induction of apoptosis and to clarify its mode of action.
Methods: Initially the IC_{50} concentration of the venom against K562 cancer cells was estimated after 24 h exposure. Changes in the expression of caspase-3 and survivin were quantified by real-time PCR. For evaluation of the apoptotic capacity, Annexin V/PI staining on flow cytometery was employed following exposure to 7, 14, 28 µg/ml of venom for varying durations (12, 24 and 48 h).
Results: Exposure to *H. lepturus* scorpion venom induced 50% cell death at 14 mg/ml. Caspase-3 expression was upregulated in a concentration and duration of exposure manner. Concurrently, expression of survivin was also upregulated. The rate of apoptosis increased in a concentration and duration of exposure manner.
Conclusion: These results suggest that *H. lepturus* scorpion venom induces apoptosis in K562 cancer cells and is mediated by capsase-3-dependent pathway. Further studies for identifying the responsible active constituent are prudently required.

Keywords: *H. lepturus* scorpion, Apoptosis, Caspase-3, Survivin, K562 cells.

(18604)

Effectiveness of topical administration of *Cinnamomum verum* hydroethanolic extract on wound healing in streptozotocin-induced diabetic mice

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Abstract: This study evaluated the effectiveness of an ointment prepared from *Cinnamomum verum* hydroethanolic extract on wound healing in diabetic mice. Two circular full-thickness excisional wounds were created. Wound contraction ratio, histopathology parameters and mRNA levels of *cyclin* D1, insulin-like growth factor 1 (IGF-1), glucose transporter-1 (GLUT-1), total antioxidant capacity and malondialdehyde of granulation tissue contents were evaluated to investigate the effect *C. verum* on wound healing. The HPLC data for cinnamon hydroethanolic extract identificated cinnamaldehyde (11.26%) and 2-hydroxyl cinnamaldehyde (6.7%) as the major components. A significant increase was observed in wound contraction ratio, fibroblast proliferation, collagen deposition, re-epithelialization and keratin biosynthesis in the C. verum-treated groups in comparison to the diabetic non-treated group ($p < 0.05$). The expression of cyclin D1, IGF1, GLUT 1 and antioxidant capacity were elevated in *C. verum*-treated groups in comparison to control group ($P<0.05$). Topical administration of C. verum accelerated wound healing and can possibly be employed in treating the wounds of diabetic patients.

Keywords: Cinnamomum verum, Antioxidant activity, Collagen deposition, Cinnamaldehyde, Re-epithelialization, keratin biosynthesis.

(18602)

Anti-inflammatory effect of Ferula assa-foetida L. oleo-gum-resin hydroalcoholic extract in animal model of acute inflammation

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Background: The Plants have been a constant source of drugs. Due to side effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs, recently, much emphasis has been placed on finding novel therapeutic agents from medicinal plants. Ferula asafoetida Linn. is a main source of asafoetida, a strong, tenacious and sulfurous odor, and oleo- gum resin of medicinal and nutritional importance. Recent pharmacological and biological studies have shown several activities of this plant.In this study, the anti-inflammatory effect of Ferula assa-foetida oleo-gum-resin hydroalcoholic extract in animal model of acute inflammation (xylene- induced mice ear edema) was investigated.

Methods: Ear edema was induced by applying xylene on the surface of the left ear 30 min after intraperitoneal administration of Ferula assa-foetida hydroalcoholic extract (100 and 300 mg/kg), dexamethasone (5 and 10 mg/kg) and the vehicle (negative control group). The ear edema was evaluated after 30 min of xylene application based on the increase in ear weight (mg), obtained by the difference between the left ear (inflamed) and the right ear (noninflamed).

Results: The group treated with 100 mg/kg concentration of Ferula assa-foetida extract significantly ($p<0.02$) inhibited the ear edema.

Conclusion: The results suggest that Ferula assa-foetida L. oleo-gum-resin hydroalcoholic extract may be effective as an anti-inflammatory agent acute inflammation.

Keywords: Ferula assa-foetida L., acute inflammation

(18402)

Immunomodulation in multiple sclerosis by *phytotherapy*

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Abstract: Multiple sclerosis is a chronic inflammatory and demyelinating disorder of the central nervous system (CNS) that can cause cognition, mobility, and sensory impairments. Studies have shown that the immune system through inflammation and autoreactive T cells are involved in the progression of MS. The present article aimed to review the potent anti-inflammatory, antioxidant, and immunomodulatory agents that could modulate the immune response in MS. In the herbal medicine, various medicinal plants including Olive, Silybum marianum, Grape, Pomegranate peel extract, Nigella sativa, Turmeric, Green tea, Aloysia citrodora, Boswellia papyrifera, Boswellia serrate, Ruta graveolens, and Andrographis paniculata are known with therapeutic benefits in MS patients through immunoregulation and reduction of major symptoms.

Keywords: Multiple sclerosis, Immunomodulatory plants, Herbal medicine, Alternative medicine

(18375)

Therapeutic Efficacy of Urtica dioica in Patients with Rheumatoid Arthritis: A Randomized Double-Blind, Placebo-Controlled Clinical Trial

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Background: Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease. In recent years, new drugs with novel targets have been developed to increase the efficacy of drugs in the treatment of RA. The pharmacological therapy of RA is often symptomatic to mitigate pain and inability with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), drugs with defined side effects and risks. Complementary medicines might decrease the signs of RA and reduce the need for these medicines. In the present study, we studied anti-inflammatory and antioxidant effects of medicinal plants Urtica dioica, in patients with RA. Moreover, the effects of these herbal medicines on IL-17 production has not been investigated in RA patients.

Methods: This randomized, double-blind, controlled trial selected 60 eligible RA patients for three months, and randomly divided them into Urtica dioica, and placebo groups. Moreover, the potential effect of these herbal medicines on Disease Activity Score (DAS) 28, Total Anti-oxidant Capacity (TAC), IL-17, Rheumatoid Factor (RF), anti-cyclic citrullinated peptide antibodies (Anti-CCP), C Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) before and after clinical trial were evaluated.

Results: A concise summary of the major findings of the experiment or study. Sufficient data must be provided to permit evaluation by the reviewers and public reading of the abstracts. Statements such as “additional information to be presented at the meeting” are not acceptable.

Conclusion: Medicinal plant Urtica dioica appeared to decrease the symptoms and inflammatory factors, and can improve the signs of RA. Thus, Urtica dioica has a great potential as a complementary therapy in patients with RA and other chronic inflammatory diseases.

Keywords: Rheumatoid Arthritis, Urtica dioica, Clinical Trial, IL-17, TAC

(18313)

Evaluation of proliferative activity of Galic Acid combined with Doxorbicin in jurkat cell line

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Background: Acute lymphoblastic leukemia (ALL) is one of the malignant proliferations of lymphoid cells in the early stages of differentiation and accounts for ¾ of all cases of childhood leukemia. .Available treatment cannot completely treat this disease. Gallic Acid, is a polyhydroxyphenolic compound that widely distributed in the natural plants, Fruits and food and has a wide range of biological functions.The aim of the present study was the evaluation of the effect of Galic Acid combined with Doxorbicin on proliferation in jurkat cell line.

Methods: Jurkat cells were cultured and then treated with DOX and GA in combination or alone for 48 hours. The viability of cultured cells was measured by MTS assay.

Results: We observed the dose-dependent anti proliferation effect of GA and DOX alone against Jurkat cells. But, the combination of GA with DOX not anti-proliferation effect and demonstrated antagonistic effects

Conclusion: Our findings suggest that combination therapy with GA and DOX does not enhance anti-leukemic efficacy of standard.

Key words: Gallic Acid, proliferation, Jurkat cells, acute lymphoblastic leukemia, MTS, DOX

(18201)

Efficacy and mechanisms of medicinal plants as immunotherapy in treatment of allergic rhinitis: a systematic review

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Introduction: Allergic rhinitis is a common disease of immune system that negatively affects general health, quality of life, and social relationships. In the recent years, many studies have been conducted to discover novel treatments for this disease particularly using natural products. Here, we review findings of recent studies that harness medicinal plants and phyto-therapies in oriental medicine that have effectively reduced allergic rhinitis complications. We also assess the use of medicinal plants and their derivatives in oriental medicine to treat allergic rhinitis.

Search strategy and Study design: As a main medical database in English language, Pubmed was searched using the following keywords: ethno-medicinal plants, ethnobotanical study, ethnopharmacology, phytotherapy, herbal treatments, and allergic rhinitis or respiratory allergy to retrieve relevant publications from 2010 until November, 2016. The data was collected independently by two authors. By using the above search terms, 546 articles, of which 58 articles were duplicates, were retrieved. After evaluation of the titles and abstracts of the retrieved articles, 35 articles that devoted to the effects of medicinal plants on allergic rhinitis were selected. Only articles with accessible full text in English language were selected for more evaluation. Accordingly, twenty-one articles were included in the final analysis.

Conclusion: Nowadays, with the raised level of public health, infectious diseases have declined but instead allergic diseases have become a main health issue of the community. Meanwhile, growing research is being conducted to develop new treatments based on a more in-depth understanding of the immunologic mechanisms of allergic diseases. Recovering hemostatic immune responses is the main feature of these treatments. In this regard, medicinal plants should not be disregarded because they are a rich source of compounds some of which have not yet been identified. The medicinal plants, used in oriental medicine and in different ways, induce anti-allergy effects through affecting immunoglobulins and inhibiting different cytokines and interleukins. These plants also prevent inflammation in nose and respiratory tract through exerting anti-inflammatory effects. The plants used in oriental medicine, especially Chinese medicine, can, in combination or separately, be used as complementary and even, in some cases, alternative treatment to chemical drugs. Altogether, this review confirms the value of a great number of medicinal plants used in oriental medicine to treat allergic rhinitis, which can represent a rich source for drug discovery in the future.

(18128)

Ferula lutensis Oleo-Gum-Resin attenuates TNF-α-induced ROS generation, ECAMs expression, and PBMCs adhesion in Human Umbilical Vein Endothelial Cells (HUVECs)

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Background: Inflammation is a defense of the body against endogenous or exogenous stimulants, resulting in chronic inflammation if it persists. Recent studies have demonstrated several anti-inflammatory properties of assafoetida. In this paper we studied the anti-inflammatory effects of the ethanolic extract of assafoetida (EEA) in TNF-α-stimulated human umbilical vein endothelial cells (HUVECs).

Methods: *Ferula lutensis* Oleo-Gum-Resin (assafoetida) was gathered from the Tabas region (Southern Khorasan, Iran). HUVECs were cultured in a flat-bottom plate, followed by treated with EEA and recombinant human TNF-α. We used the MTT test to assess cell survival. Intracellular reactive oxygen species (ROS) and adhesion of peripheral blood mononuclear cells (PBMCs)-HUVECs were evaluated with DCFH-DA and CFSE fluorescent probe, respectively. Gene expression of intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin and surface expression of ICAM-1 protein were measured using Real-Time PCR and flow cytometry methods, respectively.

Results: Pre-treatment of HUVECs with EEA significantly reduced intracellular ROS formation and PBMCs adhesion to TNF-α-induced HUVECs. Moreover, EEA pre-treatment decreased VCAM-1 gene expression and ICAM-1 surface expression in the target cells.

Conclusions: The results indicate that EEA prevented the generation of ROS, triggered by TNF-α, and inhibited the expression of VCAM-1 and ICAM-1, leading to reduced PBMCs adhesion. These findings suggest that EEA can probably have anti-inflammatory properties.

Keywords: Assafoetida, HUVECs, Inflammation, Tumor necrosis factor-alpha.

(18011)

Implications for glycosylated compounds and their anti-cancer effects

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Abstract: Glycosylated compounds are major secondary metabolites of plants, which have various therapeutic effects on human diseases, by acting as anti-cancer, antioxidant, and anti-inflammatory agents. Glycosylation increases stability, bioactivity, and solubility of compounds and improves their pharmacological properties. Two well-known examples of glycosylated compounds include cardiac and flavonoid, the anti-tumor activities of which have been emphasized by several studies. However, little is known about their role in the treatment or prevention of cancer. In this review, recent studies on antitumor properties of cardiac and flavonoid glycosides, and their mechanisms of action, have been investigated. More specifically, this review is aimed at focusing on the multifactorial properties of cardiac and flavonoid compounds as well as their correlation with signaling pathways in the treatment of cancer.

Keywords: Glycosylated compounds; cardiac glycoside; flavonoid glycoside

(16897)

Medicinal properties of some Asteraceae family plants on immune system: A review article

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The Asteraceae is the most and largest cosmopolitan family of flowering plants. Plants of this family were widely used in the past and are still used as medicinal herbs. In this article, we reviewed the medicinal properties of five genera of Asteraceae family plants (Artichoke (Cynarascolymus L.), Chichory (Cichoriumintybus L.), Calendula (Calendula officinalis L.), Burdock (Arctiumlappa L.), and Feverfew (Tanacetumparthenium L.)) which affects the immune system. Asteraceae family plants contain different components which flavonoids are the most important ingredient. Previous studies suggest that plant flavonoids may be health-promoting, disease-preventing dietary compounds. Using of Asteraceae family plants can influence the immune system. The anti-inflammatory effect is the most important effect which is observed in all Asteraceae family plants. Plants of this family reduce pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and other acute-phase proteins like C - reactive protein (CRP). It seems that Asteraceae family plants reviewed in this article are good candidates for studying in clinical trials of inflammatory diseases in which modulating the immune system is needed.

Keywords: Asteraceae, Immune system, CRP, TNF-α

(15476)

Investigate macrophage function in response to combination of Silybum marianum and Nigella Sativa extracts in inflammation

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Background and Aim: lipopolysaccharide-induced RAW 264.7 cell and peritoneal inflammatory macrophages are regulated by Nigella sativa and Silybum marianum extract.

Methods: The safe dose and toxicity of the prepared extracts was evaluated by MTT assay and acute toxicity test. Then, nitric oxide production determined by Griess assay on the supernatant of inflammatory macrophages. To evaluate the gene expression of tumor necrosis factor (TNF)-α, interleukin (IL)-6, transforming growth factor (TGF)-β, and IL-10, RNA extracted from macrophages and Real-time PCR was performed. Finally, to investigate regulatory role of prepared extract, regulatory T cells (Treg cells) count were analyzed by flow cytometry.

Results: Silybum marianum methanolic extract (SME), Nigella sativa ethanolic extract (NEE), and their mixture (SME+NEE) decreased NO level significantly both in-vitro and in-vivo. NEE has significant increase gene expression of IL-10 ($P = 0.0001$) and showed a significant decrease in IL-6 and TNF-α expression on cell line ($P = 0.0015$ and $P = 0.0001$, respectively). In peritoneal macrophages, the SME+NEE group has shown a statically significant increase in IL-10 and TGF-β expression ($P = 0.0045$ and $P = 0.037$, respectively) while decrease of IL-6 and TNF-α expression was showed ($P = 0.034$ and $P = 0.010$, respectively). And in line with the immunoregulatory effects of the SME+NEE, the percentage of Treg cells was significantly higher than the control group ($P = 0.015$).

Conclusion: These results suggest that SME+NEE group, have anti-inflammatory and immunomodulatory activities in in-vivo. Thus, the mixture can be of value in the treatment of inflammatory diseases.

Keywords: Cytokine, Inflammation, Nigella sativa, Nitric oxide, Silybum marianum

(18249)

Balance Between Cytokines in rats Treated With Scorpion Venom.

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Background :Scorpion venom consists of a very complex of molecules and demonstrates cellular activities capable of stimulating immune functions in vivo. The purpose of this study was to analyze the effects of Scorpion venom on the balance of cytokines in rat.
Methods: cytokines were assayed by enzyme-linked immunosorbent assay .
Results: Significant differences were observed in the time-course of cytokine levels. The balance of pro- and anti-inflammatory cytokines were significantly higher in injected rats group when compared with those obtained for non-injected group. The effect of immunization with
0.5 ml of Scorpion venom on the balance of pro- and anti-inflammatory cytokines was measured. The maximum levels of cytokines were observed on 4h and 24h after immunization. These ratios may possibly reflect the balance of pro- and anti-inflammatory cytokines in plasma. which may by manifested in the inflammatory status during the envenoming processes.
Conclusion: an increase in the plasma of pro- and anti-inflammatory cytokines may be a useful marker for scorpion envenomation.

Keywords: Cytokines, Scorpion Venom, rats, Khuzestan,iran

Congress Abstracts

Oral and Mucosal Ommunity

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18251)

Immunomodulatory properties of osteogenic differentiated dental pulp stem cells

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Background: Dental pulp stem cells (DPSC) showed great differentiation and immunomodulatory effects. As they are attractive alternative for regular cell therapies including adipose derived mesenchymal stem cells (AD-MSCs) and bone marrow mesenchymal stem cells (BM-MSCs), DPSCs have been used in several cell therapy clinical trials. However, their immunomodulatory capacity after differentiation into the different cell lineage have not been studied. In the present study we aim to investigate the immunomodulatory effects DPSCs after osteogenic differentiation.
Methods: DPSCs have been extracted from 6 human third molars. DPSCs were characterized using flow cytometry and differentiation potential tests. DPSCs and osteogenic differentiated DPSCs were co-cultured (1:1 and 1:5 ratio) with allogenic Peripheral blood mononuclear cell (PBMC). Proliferation of PBMCs were measured using 5-Bromo-2'deoxyuridine (BrdU) proliferation test. The amount of IL-6, IL-10, PGE2, and TGF-β were measured using ELISA. The expression of HLA-G, HGF and IDO were analyzed with Real-time RT-PCR. The production of NO was measured by Griess assay.
Results: The results indicated that osteogenic differentiated DPSCs inhibited PBMC proliferation in both 1:1 and 1:5 ratios ($P<0.05$). The amount of, IL-6, TGF-β and PGE2 cytokines increased significantly ($P<0.05$) in osteogenic differentiated DPSCs. The production of NO also increased during osteogenic differentiation. The expression of HGF, IDO and HLAG genes remained unchanged after osteogenic differentiation.

Conclusion: This study indicated that osteogenic differentiated DPSCs have the same immunomodulatory properties as undifferentiated DPSCs in terms of function. However, the mechanism of immunomodulation is changing during differentiation process.
Keywords: dental pulp stem cell, immunomodulation, oral immunology, regenerative medicine

(18319)

Correlation between gingival expression of IL-33, ST2 and LL37 and periodontal diseases

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Background: In this study we aimed to investigate the potential changes in mRNA expression of IL-33, ST2 and LL37 in gingival tissues with periodontal diseases compared with healthy gingiva.
Methods: 18 patients with early gingivitis (EG), 19 with moderate to severe chronic periodontitis (CP) and 23 healthy control subjects were enrolled in our study. Clinical attachment level (CAL) was assessed. Collected gingival tissue samples post-surgery were used to collect RNA using mini spin column principle. cDNA was manufactured and Real Time PCR was utilized for a relative measurement of gene expression.
Results: Kruskal Wallis test showed no significant difference in gene expression for all genes between 3 study groups. A correlation was found in gene expression of IL-33 and ST2 among the 3 groups, as well as for ST2 and LL37. In individual groups, IL-33 expression was correlated with ST2, only in CP group. ST2 and LL37 expression also showed a correlation in control, EG and CP. No correlation was observed between CAL and gene expression of the target genes in chronic periodontitis group.
Conclusion: we found no significant difference in gene expression of IL-33, ST2 and LL37 in patients with periodontal diseases compared to healthy subjects. No correlation was observed between gene expression and CAL.

Keywords: Periodontitis, Gingivitis, Inflammation, Interleukin-33, Antimicrobial Cationic Peptides, Interleukin-1 Receptor-Like 1 Protein

(18579)

Chemokine mission in oral cavity health and periodontal disease

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Background: Inflammation is a biological response in the immune system that can be caused by various factors such as pathogens, cells, toxic compounds, etc. Periodontitis is made up of two words: periodont means structure around the tooth and itis means inflammation. The host response to this inflammation involves both mechanisms of innate and acquired immune responses. Inflammatory responses, periodontal pathogenic microorganisms stimulate the cells that make up periodontal tissues, forcing them to produce a variety of inflammatory mediators, especially cytokines and chemokines.
Research method: Published articles were accomplished from PubMed, Google Scholar, Wiley, Springer, Science Direct, and Elsevier from 2012 to December 2020. Entirely, 50 relevant articles were found and reviewed.
Results: Numerous chemokines during inflammation of gum play a varied role in the oral cavity. CCL2 and CCL5 stimulated macrophage migration that affected the release of IL-8. CCL3 and CXCL13 motivate B cells and T cells to discharge RANKL and accelerate bone resorption. CCL20 targeting T helper 17 and enhancement rate of inflammation in the oral cavity.
Conclusion:
In periodontal disease, chemokine has multiple roles in inflammation progress. Indeed, chemokine affects the gum and alveolar bone with stimulate innate and adaptive immune cells. These cells release immune mediators and increase inflammation incite.

Keywords: chemokine, periodontitis, inflammation, oral

(18333)

Comparing the gingival expression of MMP-1, MMP-9 (matrix metalloproteinase) and HBD-3 (human beta defensing-3) in healthy individuals and patients with moderate to severe chronic periodontitis.

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Background and purpose: Periodontopathic bacteria stimulate the cells that make up periodontal tissues, forcing them to express a variety of inflammatory mediators such as inflammatory cytokines. These inflammatory mediators can stimulate the matrix metalloproteinases and prostaglandins. It has also been seen that defensins, which are antimicrobial peptides, are highly expressed in the oral cavity and the expression of these peptides is decreased in periodontal tissues. Therefore, the aim of this study was to compare the expression of MMP-1, MMP-9 and HBD-3 genes in gingival tissue between healthy and moderate to severe chronic periodontitis which is to help with timely identification and diagnosis and treatment.

Analysis method: The collected samples of gingival tissue were homogenized by TRIzol and transferred to special columns for purification of RNA with more purity. After quantitative and qualitative analysis of purified RNA, cDNA was manufactured and the expression of genes was examined using Real Time PCR.

Results: Expression of MMP-1 and HBD-3 genes showed a significant difference between the three groups using Kruskal Wallis test, but in terms of MMP-9 gene expression, no statistically significant difference was observed in the different groups studied. By comparing the pairs of the studied groups in terms of MMP-1 and HBD-3 expression using Games-Howell Post Hoc statistical test, there was a statistically significant difference between healthy groups and those with severe chronic periodontitis in terms of MMP-1 gene expression. There is not statistically significant direct correlation was found between the expressions of the three genes in the three groups. In examining the correlation between each of the genes with the clinical index (Clinical attachment loss) CAL using Spearman correlation coefficient test, we found a direct and statistically significant correlation only in the expression of HBD-3 and CAL genes.

Conclusion: Comparing the three groups in terms of MMP-1, we found a statistically significant difference between the three groups, so that the mean of gene expression in the group of severe chronic periodontitis was higher than the others and in the healthy group was lower than the others. By comparing the two groups, it was found that this difference is especially between the severe chronic periodontitis group and the healthy group.

Keywords: Periodontitis, Gingivitis, Matrix Metalloproteinase 1, Matrix Metalloproteinase 9, DEFB103 protein, human.

(18103)

The role of tolerogenic dendritic cells subsets in the screening of celiac disease

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Background & Aims: Recently, dendritic cells have received much consideration in celiac disease because of their importance in gut homeostasis by processing peripheral antigens such as gluten and by identification of tolerance to self-antigens. The important role of CD11c+, CD103+, CD207 and indoleamine 2,3-dioxygenase dendritic cells in the generation of T regulatory cells differentiation has been recognized. In this study, we explore the mRNA and protein expression of introduced markers in intestinal of patients with celiac disease compared to healthy control.

Methods: Biopsy were collected from 60 celiac disease and 60 healthy. Total RNA was extracted by a standard commercial kit. The mRNA expression of genes was quantified by relative Real-time polymerase chain reaction with β2 microglobulin as a reference gene. Moreover, paraffinized intestinal tissues were investigated for CD11c+, CD207+and CD103+ by immunohistochemistry

Results: CD11c, CD103, CD207 and indoleamine 2, 3-dioxygenase were significantly elevated in celiac disease patients compared to the controls group ($P<0.001$). Moreover, immunohistochemistry results showed that only CD103 significantly increased in celiac disease patients compared to controls ($P <0.001$).

Conclusions: According to our results, CD103 and CD207 may be suggested as diagnostic markers in the screening for celiac disease.

Keywords: Celiac disease, gene expression, dendritic cells, indoleamine 2, 3-dioxygenase

(18603)

Assessment the expression of CXCL13, and CCL28 chemokines in gastric biopsy specimens of individuals with Helicobacter pylori-infected

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Background: Chemokines play an important role in invoking immune cells to sites of inflammation, and it seems that their association with bacterial pathogens can help promote and exacerbate inflammation. Therefore, in this study we investigating the relationship between Helicobacter pylori pathogens and mRNA expression of CXCL١٣, and CCL٢٨ chemokines in patients with gastrointestinal problems.

Methods: Forty-three individuals infected with Helicobacter pylori with gastritis and thirty-eight healthy individuals were selected for this study. The mRNA expression of CXCL١٣, and CCL٢٨ chemokines in gastric biopsy was assessed by Real-Time PCR and bacterial pathogens were assessed by PCR.

Results: The mRNA expression of CXCL١٣, and CCL٢٨ chemokines was significantly increased in the gastric mucosa of infected individuals in compare to the healthy groups.

Conclusion: In people infected with Helicobacter pylori, increased expression of CXCL13 and CCL28 chemokines may be associated with the development of gastritis by invoking B, T, and other immune cells to the site of inflammation.

Keywords: Helicobacter pylori, chemokines, gastritis

(16744)

Role of Th22 cells in Helicobacter pylori-related gastritis and peptic ulcer diseases

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Helicobacter pylori (H. pylori) has been shown to be one of the leading causes of peptic ulcer diseases (PUDs) and gastritis. T helper-22 (Th22) cells and its most important cytokine, interleukin-22 (IL-22) are importantly active in inflammation and inflammatory tissues. Since inflammation is one of the main attributes of infection caused by H. pylori and resulting complications (gastritis and gastrointestinal ulcer), this study was designed to evaluate the Th22 cells count and the IL-22 protein expression in people suffering from PUD and gastritis. The present study was conducted on 55 patients with gastritis, 47 patients with PUD and 48 uninfected subjects. After preparation of section and extraction of protein from antral biopsies, immunohistochemistry and western blot methods were used to evaluate the Th22 cells and IL-22 protein expression level, respectively. According to findings, the Th22 cells count and the IL-22 protein expression level in the infected subjects were significantly more than in the uninfected subjects. It should be noted that the Th22 cells count and the IL-22 protein expression level in the infected subjects with PUD were significantly greater than those in the infected subjects with gastritis. In addition, the Th22 cells count had positive correlation with the density of H. pylori, chronic inflammation score and acute inflammatory score in the infected subjects with PUD. The Th22 cells count had positive correlation with the Th17 cells count and inverse correlation with the Treg cells count in the infected subjects with PUD and gastritis. Our data demonstrated that abnormal hyper-activation of Th22 cells as well as its correlation with the Th17 cells during infection caused by H. pylori might damage tissues through immunopathological responses.

(16886)

Fecal Microbiota Transplantation as a novel approach

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Conclusion: Microbiota and immune system collaborate together and regulate each other. Fecal Microbiota Transplantation can be one of the novel therapeutic approaches for gastrointestinal and non- gastrointestinal disorders like inflammatory bowel disease, obesity, etc. For this reason, recently physicians and researchers are tending to use it to cure gastrointestinal and non- gastrointestinal disorders. The immune system regulates by microbiota, so its imbalance may cause disorders. Currently, this therapeutic method suggests by The US Food and Drug Administration for people suffering from Clostridioides difficile who do not respond to standard therapies. Rarely Fecal Microbiota Transplantation has been used for the cure of other diseases like inflammatory bowel disease but it's efficient for some patients. Although it has many applicants, still there are concerns about side effects, so it is better to do more researches for conclusions. The aim of this review article was to gain insight link between gut microbiota and immune system in various diseases, roles of Fecal Microbiota Transplantation in several disorders.

Keywords: Gut microbiota; Fecal Microbiota Transplantation; Immune system

(18027)

The Circulating Midkine in the Newly Diagnosed Celiac Disease: Clinical Implications

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Background: Celiac disease (CeD) is a chronic inflammatory small intestine disorder caused by an abnormal immune response to an array of the epitopes of the wheat gluten and related proteins of rye and barley in genetically susceptible individuals. Midkine (MK) is an angiogenic cytokine, chemotactic in the direction of polymorphonuclear neutrophils and macrophages, and a T-regulatory cell suppressor. So far a possible relationship with CeD has not yet been explored. Diagnosis of CeD is, based on serologic test in a clinical setting suggestive of CeD and confirmatory histologic examination of the duodenal biopsy. Sometimes genetic testing of human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 may be needed. The objective of this study was to measure and compare the circulating MK in the celiac patients and healthy individuals.

Methods: 20 newly untreated CeD cases and 20 normal controls were enrolled in this study. The Enzyme-linked immunosorbent assay (ELISA) was used to measure the circulating MK in the celiac patients and controls.

Results: There was insignificant difference in the circulating MK between the patients and controls ($P>0.05$).

Conclusions: The study results suggest that the MK marker does not have any diagnostic value in CeD activity to be used at the time of diagnosis or during follow-ups.

Keywords: Celiac disease, Midkine, Serum, Enzyme-linked immunosorbent assay, Inflammation, Tissue transglutaminase.

(18412)

Association of HLA genes with susceptibility to idiopathic Achalasia

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Background: The association of HLA class II genes with idiopathic achalasia as a relaxing dysfunction of the lower esophageal sphincter is studied for several years. However, factors responsible for the genetic predisposition of this disease have not been clearly understood. In this study, our goal was to investigate the association between HLA-DRB1 and HLA-DQ subtypes with idiopathic achalasia in the Iranian population.

Material and methods: HLA typing performed among 63 idiopathic achalasia patients and 71 healthy controls using PCR amplification, employing sequence-specific primers (PCR-SSP). The DRB1and DQ frequencies determined in the patients and controls.

Results: HLA-DRB1:01 was significantly higher in healthy controls than the idiopathic achalasia (*P=0.007*). Furthermore, HLA-DRB1:11 and HLA-DRB1:15 were significantly higher in idiopathic achalasia patient than the healthy controls (*P =0.05* and *P =0.001*).

Conclusion: Our results show that the HLA-DRB1*11, *15 have a susceptible risk factor for idiopathic achalasia, while the HLA-DRB1*01 shows a protective role against the disease

Keywords: Achalasia, HLA-DRB1, HLA-DQ

(18424)

Interleukin-22: A Regulator of Intestinal Immune Responses in Cancer and Autoimmunity

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Abstract: As a member of IL-10 family cytokines, IL-22 is an important regulator of intestinal homeostasis which is secreted by Th-22 cells. Also, various cell types are capable of producing IL-22, including fibroblasts, hepatocytes, epithelial cells and keratinocytes. IL-22 is involved in both inflammatory and protective immune responses in cancer, allergy, infection and autoimmunity. Maintaining epithelial barrier integrity, expression of tight junction proteins and intestinal inflammation could be targeted by IL-22 function. In vivo and in vitro studies demonstrate that IL-22 can both promote and suppress gut inflammation. Several researches are designing to clarify the exact role of IL-22 in the intestinal immune responses. Recombinant IL-22 therapy or anti IL-22 therapy are 2 different therapeutic choices that are dependent on the IL-22 function in each inflammatory and anti-inflammatory conditions. This paper discusses the current knowledge on this issue and tries to clarify the potential of IL-22 to be used in the future therapeutic approaches of intestinal disorders including inflammatory bowel diseases and colon cancer.

Keywords: IL-22, Intestinal inflammation, Autoimmunity, Colon cancer

(18118)

Comparison of treatment process of children with adenotonsil hypertrophy by surgery and medication

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Background: Adeno-tonsillar hypertrophy is one of the most common causes of airway obstruction in the upper respiratory tract. Tonsillectomy is the most common surgical intervention in children. It has been suggested that drug treatment in allergic cases may reduce the size of adeno-tonsil hypertrophy. Therefore, the aim of this study was to evaluate the results of two treatments (surgery and medication) among children with adeno-tonsil hypertrophy with allergic background.

Methods: In a clinical trial study, 68 children were identified by Prick and Past allergic tests with adeno-tonsil hypertrophy and referred to Tabriz University of Medical Sciences Hospital. They were divided into two groups and matched based on age, sex, symptoms and initial complications. Each bite was treated with one of two surgical or pharmacological treatments. Finally, they were compared based on treatment results.

Results: In the surgical group, 34 children with a mean age of 6.3 ± 2.3 years, including 25 boys (71.9%) with 9 girls (29.1%) with 34 children in the drug treatment group with a mean age of 6.8 ± 2.1 years including 24 boys (70.7%) and 10 girls (29.3%) were compared. There was no significant difference between the two groups in the improvement of clinical signs and complications; however, in the group treated with medication in 3 patients (8.8%), the size of the tonsil did not decrease. No recurrence of the disease was observed in the surgical group; however, in the group treated with drug therapy in 6 patients (17.6%) we saw the recurrence of the disease.

Conclusion: Based on the results of our study, although both pharmacotherapy and surgery are highly effective in inhibiting adeno-tonsil hypertrophy in children; However, recurrence of the disease may occur in children treated with medication. The decision to treat should be based on the patient's condition. Drug treatment has a long duration and surgery also faces risks such as bleeding.

Keywords: Adeno-tonsil, Tonsillectomy, Inflammation, Surgery, Medication

(18213)

The Relationship between Salivary and Serum IgA & IgG Levels and Dental Caries in Adults

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Background: Dental caries is one of the most common microbial infectious disease. The important method for assessment of oral health status is DMFT (Decayed, Missing, and Filled Teeth). Recent studies have shown conflicting results regarding the relationship of antibodies with dental caries. This study aimed to investigate the salivary and serum IgA and IgG levels in adult's caries.
Methods: This cross-sectional study was conducted on 96 patients with dental caries who referred to the specialized dental clinic in Yasuj. Based on the DMFT index patients were divided into three groups. DMFT index in group 1, 2 and 3 were 0, 1-3 and more than 3, respectively. Salivary and serum levels of IgA and IgG were measured by nephelometric method. Data were analyzed using SPSS software, chi-square and paired t-test.

Results: The mean salivary IgA level in group 1, 2 and 3 were 0.259±0.118, 0.264±0.175, and 0.169±0.106 mg%, respectively (p=0.001). Also, the mean salivary IgG level in group 1, 2 and 3 were 1.3600.350±1.320 ,316± and 1.3200.370 ± mg% (p=0.929). The mean serum IgA level were 1.4430.518 ±1.805 ,0.433± and 1.7900.700± gr% in group 1, 2 and 3, respectively (p=0.363). Also, the mean serum IgG level in group 1, 2 and 3 were 9.2751.658±10.257 ,1.899± and 10.5893.113± gr% (p=0.451).
Conclusion: This study showed that by decreasing the level of salivary IgA, the rate of dental caries and DMFT index increase and this indicates the protection mechanism against dental caries by IgA.
Keywords: Dental caries, DMFT, IgA, IgG

Congress Abstracts

Psychoneuroimmunology and Immunoendocrinology

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(16693)

Evaluation of the Immunological Factor Hepcidin in Ischemic Stroke Patients Receiving the tissue-Plasminogen Activator (t-PA)

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Background: Ischemic stroke (IS) is an acute pathological event depending on the inflammatory process of the nervous system. t-PA is only one FDA-approved item within 3.5 to 5 hours of the onset of symptoms. Hepcidin protein is the iron homeostasis, the main regulator. Its source in the brain is both localized and supplied from the bloodstream by the inflammation effect. This study aimed to measure the hepcidin at the time of admission and 72 hours after, to improve the IS patient's prognosis.

Method: In this case-control study, considering the inclusion criteria, 31 patients were admitted to the Valiasr center with a diagnosis of IS, and 10 patients were included in the study as a control group. Blood samples were taken from patients at baseline and 72 hours after t-PA injection. Blood levels of hepcidin protein in both samples were measured by ELISA. Previous medical history, routine tests, and CT scan results of patients were collected. All data were entered into SPSS software and analyzed.

Result: The age of the subjects had a mean of 73.24 and a standard deviation (SD) of 10.44 in t-PA positives, a mean of 68.6, and an SD of 11.43 in t-PA negatives. Serum hepcidin levels increased significantly after t-PA injection (P-value = 0.007). Changes in hepcidin levels at the onset of IS were significantly different from serum hepcidin levels in the control group (P-value = 0.022). There was no significant relationship between serum hepcidin levels at arrival and patients' NIHSS (P-value = 0.724).

Conclusion: Our study showed that the hepcidin serum concentration increases after t-PA injection, which could mean the t-PA anticoagulant function, the restoring blood flow, and inflammation effects on IS micro-environment in the brain. Introducing a suitable factor can be an effective clinical application for neurologists to achieve the desired results in the treatment of stroke patients.

Keywords: Ischemic Stroke, Immunological Factor, Hepcidin, Tissue plasminogen Activator (t-PA).

(16900)

Assessment of plasma Osteopontin level in relapsing- remitting multiple sclerosis patients

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Background: Multiple sclerosis (MS) is autoimmune and immune-mediated disorders of the central nervous system (CNS). Osteopontin (OPN) is a pleiotropic cytokine with an important role in cell-mediated immunity, infections, inflammation, and cancer. OPN acts as a pro-inflammatory cytokine in autoimmune conditions. Since the exact immune pathogenesis of MS is not well defined and many factors are involved, the need to detect more contributing biomarkers may help in setting new therapeutic strategies. The aim of the present study was to assess the plasma level of OPN in RRMS patients in Isfahan and compared them with healthy individuals.

Methods: A total of 40 cases of relapse- remitting multiple sclerosis (RRMS) patients and 40 healthy subjects as a control group enrolled in this study. The plasma level of OPN was measured by Enzyme-linked immunosorbent assays (ELISA).

Results: Our results showed that the plasma OPN level was significantly higher in RRMS patients (41.55 ± 11.69 ng/ ml) compared with the control group (32.35 ± 16.43 ng/ml) (P-value ≤0.05). Our results also demonstrated that there was no statistically significant difference in the mean of plasma OPN level among RRMS patients who were treated with IFN-ß and those who were not (P-value ≥0.05). Also, no correlation observed between plasma OPN level and duration of disease, age of onset, and EDSS score of the patients.

Conclusion: This study showed that RRMS patients had higher mean plasma level of OPN compared to healthy control group and treatment with IFN-ß had no significant effect on the plasma level of OPN. It can be concluded that OPN may not be a specific marker for MS, but targeting it might present a promising therapeutic effect to MS patients.

Keywords: Multiple sclerosis, relapse- remitting multiple sclerosis, Osteopontin, ELISA

(18755)

Immunologic Effect of Tissue-Plasminogen Activator (t-PA) on Interleukin-10 (IL-10) in Acute Ischemic Stroke Patients

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Background: To date, stroke is the second cause of mortality worldwide. The most common type of stroke is an ischemic stroke which occurs due to the obstruction in the cerebral-feeding arteries. Tissue-Plasminogen Activator (t-PA) is the only FDA-approved treatment for acute ischemic stroke. Additionally, an inflammation process happens in the stroke environment. Interleukin-10 (IL-10) is the main anti-inflammatory cytokine. In this study, we aim to determine the immunologic effects of t-PA through analyzing the levels of IL-10 in stroke patients.

Method: In this case-control study, 25 patients with the diagnosis of acute ischemic stroke were included on the basis of inclusion criteria. 15 of the patients had indication to receive t-PA (tPA-positive) and the residual of the patients (n=10) had not received t-PA (tPA-negative). The patients' blood samples were given two times, on admission and after 72 hours. The specimens (n=50) were analyzed by the ELISA.

Results: On admission, the IL-10 serum levels were higher in tPA-negative group compares to tPA-positive patients. However, in the first 72 hours, the amount of IL-10 placed on the same range in both groups. Accordingly, within 72 hours the levels of IL-10 became higher in tPA-positive and decreased in tPA-negative (p-value<0.05). The changes of IL-10 levels in the first 72 hours represented the immunosuppression of the stroke-related inflammation and increasing the expression of anti-inflammatory cytokines in tPA-positive patients; However, the IL-10 reduction in tPA-negative patients has demonstrated that the inflammation still exists in the stroke environment and the expression of anti-inflammatory mediators have not increased yet.

Conclusion: According to the alteration of the IL-10 levels, we can conclude that t-PA has immunologic role in treating stroke patients, beside its thrombolytic effect. Notably, t-PA can reduce the stroke-related inflammation, ameliorate the focal neurologic deficits, and improve the clinical outcome in the ischemic stroke patients.

Keywords: Ischemic Stroke, Interleukin-10 (IL-10), Tissue plasminogen Activator (t-PA), Inflammation

(18105)

IL-38; as an early predictor marker for the ischemic stroke prognosis

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Background: Ischemic stroke, the most common type of stroke, is caused by a sudden neurological defect following a vascular occlusion and elicits a local and systemic inflammation in brain tissue. Interleukin-38 is an anti-inflammatory cytokine associated with ischemic and inflammatory diseases. This study was performed to evaluate the effect of tPA therapy on interleukin-38 serum level changes and the prognosis of ischemic stroke patients in the next three months.
Methods: We enrolled 29 ischemic stroke patients confirmed by a neurologist based on radiologic and clinical manifestation between 2019 September to 2020 February. The patients who had NIHSS more than 6 with no underlying inflammatory diseases were selected for tPA therapy. On admission and 24 hours after tPA therapy, the IL-38 serum level was measured by ELISA kit.
Results: The results showed that serum levels of IL-38 were significantly increased after tPA therapy (p-value <0.001). A significant relationship was observed between the modified Rankin Score (mRS) and IL-38 serum changes in response to tPA therapy (p-value<0.001). Besides, IL-38 serum changes following tPA was dramatically related to NIHSS at hospitalization (p-value=0.007). Also, our analysis poses a positive relation between NIHSS at hospitalization and mRs criteria (p-value=0.023). No notable relation has been observed between IL-38 serum levels before and after tPA and mRs (p-value=0.601, p-value= 0.074). Furthermore, there is no evidence for the relation between NIHSS at hospitalization and IL-38 levels before and after tPA(p-value=0.457, p-value= 0.105).
Conclusion: The results indicate that tPA could meaningfully increase the IL-38 serum level. Also, a negative correlation has been found between IL-38 serum changes in response to tPA and mRS. Since the lower changes in IL-38 serum level result in a poorer prognosis, we conclude that IL-38 serum changes might be a novel early predictor factor for ischemic stroke prognosis.
Keywords: Ischemic Stroke, Interleukin-38, tPA therapy, Prognosis, Neuroimmunology

(16805)

The effect of chronic social stress (deprivation stresses) and oxytocin on the number and cytotoxicity of peripheral blood and spleen NK cells in male rats

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Introduction: Natural killer cells are innate immune lymphocytes that play an important role in defense against tumor and viral infections. Many factors, such as social stress, act on the immune system. Oxytocin is a 9amino acid hormone that plays an important role in response to stress, and its injection reduces anxiety and depression caused by stress. The aim of this study was to evaluate the effect of chronic social stress and oxytocin on the number and activity of NK cells in rats exposed to this stress.

Methods: WISTAR rats were exposed to food deprivation, stress for 21 days. From the 11th day a series of rats, Received 20 µl, and another 40 µl oxytocin with a concentration of 1 mg/ml and control group Received, Normal saline intranasal And one group was considered as healthy control. At the end of the study, the animals were anesthetized and killed. Blood samples and spleen tissue were collected. The number of NK cells was counted by flow cytometry with two CD3-CD161 + markers and cytotoxic activity was evaluated by lactate dehydrogenase (LDH) release assay.

Results: Corticosterone concentration increased significantly in stress group compared to the control group and oxytocin treatment decreased it but nonsignificant.. The number of NK cells in peripheral blood was not significantly different in the stress group and the oxytocin treated groups compared to the control group. In the spleen, the number of NK cells in the deprivation stress group treated with doses of 20 was significantly higher than the control group. cytotoxic activity was increased in the ratio of 50/1 and 25/1 in deprivation stresses Received 40 µl. (P-value <0.05)

Conclusion: In the stress group, corticosterone level has increased in the deprivation group that treated with oxytocin, the number and function of NK cells increased significantly.

Keywords: Natural killer cell, chronic stress, oxytocin

(16894)

Assessment of plasma soluble CD137 level in relapsing-remitting multiple sclerosis patients

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Background: Multiple sclerosis (MS) is a high-prevalence chronic neuroinflammatory disease, affecting the central nervous system. Co-stimulatory molecules such as CD137 (4-1 BB) play a major role in the activation of lymphocytes in the CNS. Based on the role of sCD137 in autoimmune diseases, in this study, we aimed to assess sCD137 in peripheral blood from patients with MS in Isfahan province and compare it with healthy controls.

Methods: In this study, we enrolled two groups of participants, consisting of 36 patients with relapsing-remitting multiple sclerosis (RRMS) and 52 age and sex-match healthy controls. Plasma sCD137 level was measured by enzyme-linked immune sorbent assays (ELISA).

Results: Assessment of plasma sCD137 level showed that the mean of sCD137 in RRMS patients was significantly higher than the control group (1021.75±296.12 ng/L versus 892.18±184.21 ng/L) (P value≤ 0.05). The logistic regression model was performed by adjusting for the confounding variables, such as age, education level, and job in both groups. The results showed that the risk of MS increases by 30% for every 100-unit increase in sCD137, which is statistically significant. Our results also showed no correlation between mean of sCD137 and EDSS score, age of onset, duration of disease as well as serum 25 (OH) D concentrations of patients.

Conclusion: In conclusion, we investigated the plasma sCD137 level in RRMS patients and compared with healthy controls in Isfahan province. Our result demonstrated that the mean plasma sCD137 level was higher in RRMS patient than the healthy controls. Since the elevation of sCD137 has been confirmed in other autoimmune diseases, it is not a specific marker for MS. Further investigations might be able to clarify its role in the pathogenesis of MS.

Keywords: Multiple sclerosis, relapsing-remitting multiple sclerosis, CD137, autoimmune disease

(17995)

Expression analysis of long non-coding RNAs in peripheral blood mononuclear cells from multiple sclerosis patients

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Background: Long noncoding RNAs (lncRNAs) have important roles in regulating autoimmunity, and immunity balance. Many lncRNAs are defined as the regulators of NF-κB pathway that is involved in modulation of immune responses. In this study, we evaluated expression levels of lncRNAs involved in regulation of the NF-κB pathway including *HOTAIR*, *THRIL*, *H19*, *NKILA*, and *ANRIL* in patients with Multiple Sclerosis (MS) to determine their roles in the pathogenesis of MS.
Methods: The quantitative Real -Time PCR method was used to assessment of the relative expression of lncRNAs in Peripheral Blood Mononuclear Cells (PBMCs) of 60 relapsing-remitting MS (RRMS) patients in comparison with 30 control subjects.
Results: It was evidenced, *HOTAIR*, *THRIL*, and *H19* were up-regulated and *NKILA* was down-regulated in relapse phase patients compared to remitting phase patients and controls. However, *ANRIL* was increased in relapse phase patients compared to controls, but was decreased compared to remitting phase patients.
Conclusion: Findings of this study revealed that, Importantly, *HOTAIR*, *THRIL*, and *H19* were related to disease attacks in patients with RRMS, while *NKILA* as an anti-inflammatory factor was linked to stable phase in patients. However, *ANRIL* was related to both relapse and remitting phases of disease.

Keywords: Long noncoding RNA, relapsing-remitting MS (RRMS), Peripheral Blood Mononuclear Cells (PBMCs), NF-κB

(18725)

CXCL12/CXCR4 axis in patients with Parkinson's disease

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Background: Parkinson's disease (PD) is one of the most prevalent diseases of the central nervous system. There is strong evidence that inflammation is associated with PD pathogenesis. Many studies have shown that chemokines and their receptors mediate neuroinflammation. The role of CXCL12 and its receptor, CXCR4, has not been fully examined in PD. The purpose of this study was to investigate the role of CXCL12/CXCR4 in the peripheral blood of patients with PD and healthy controls.
Methods: This study was carried out on 30 patients with PD and 40 healthy controls. Healthy volunteers were matched to PD patients for sex and age. Exclusion criteria were acute or chronic inflammatory diseases and infection. Patients were also excluded if they had received anti-inflammatory treatment in the last 2 months. The study was approved by the Ethics Committee at Rafsanjan University of Medical Sciences and subjects signed a written informed consent before enrollment in the study. CXCL12 serum levels and CXCR4 mRNA levels were measured using ELISA and real-time PCR, respectively.
Results: Our findings showed that CXCL12 levels in the peripheral blood samples of patients with PD and control group were 140.8 ± 14.87 and 59.50 ± 3.049, respectively. The difference between the two groups was statistically significant ($P < 0.0001$). In addition, we observed that the expression of CXCR4 was significantly increased in PBMCs from PD patients compared with control group ($P < 0.0001$).
Conclusion: The finding of our study may emphasize the importance of CXCL12/CXCR4 in PD. CXCR4 expression in PBMCs or CXCL12 serum levels may be potential biomarkers of inflammation in PD patients. Although a higher expression of circulating CXCL12 can be observed in PD patients, CXCR4 surface expression on different subpopulations within PBMCs should be investigated to hypothesize that CXCL12/CXCR4 may be involved in the pathogenesis of the disease.

Keywords: Parkinson's disease, CXCL12, CXCR4, Inflammation

Congress Abstracts

Reproductive Immunology

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(16525)

Contraceptive and molecular function of a novel recombinant vaccine based human leukemia inhibitory factor on Balb/c mice: An experimental in vivo study

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Background: Various factors involved in the establishment and maintenance of the pregnancy can be targeted for antifertility vaccine design. The functional competence of leukemia inhibitory factor (LIF), as immunocontraceptive vaccine in Balb/c mice, was investigated in this experimental study.
Methods: Female Balb/c mice were divided into two groups of vaccinated and controls. The recombinant human LIF (rhLIF) protein and phosphate buffer saline was emulsified with Freund's adjuvant and injected into vaccinated and control groups, respectively. The inhibition of implantation was evaluated in mice uterine. To evaluate the cellular immunity of mice underwent rhLIF vaccine, the concentration of secreted interferon-γ (IFN-γ) and interleukin (IL)-4 were measured in cultured splenocyte of mice stimulated by rhLIF. The expression of immune responsive gene 1 *(IRG-1)*, cochlin *(COCH),* amphiregulin *(Ar)*, and heparin-binding EGF-like growth factor *(HB-EGF*) genes were determined for assessed the impacts of active immunization on the expression of specific genes involved in LIF signaling. Mice were evaluated for inhibition of fertility after delivery, reversibility of immune response against rhLIF, and survival rate.
Results: Active immunization of Balb/c mice with rhLIF resulted in reduction of the implantation and fertility rate up to 80.49% and 75%, respectively. All mice produced a high titer of anti-rhLIF antibodies in serums and vaginal fluids washes after 16 weeks. The concentration levels of IFN-γ and IL4- in culture supernatant of splenocytes stimulated with rhLIF were significantly higher in vaccinated group (P <0.05). A significant down regulation in mRNA levels of *IRG-1*, *Ar* and *HB-EGF* was observed in vaccinated group compared to control group; however, no significant change in the expression profile of *cochlin* gene was detected.
Conclusion: The results showed that rhLIF prevented pregnancy in a high percentage of female mice. Although the immunization of female Balb/c mice with rhLIF inhibited fertility and expression of genes associated with this molecule, further studies are needed to support this protein as a suitable candidate for contraceptive vaccine.
Keywords: Leukemia inhibitory factor, Contraceptive vaccine, Active immunization, Immune responsive gene 1, Amphiregulin, heparin-binding EGF-like growth factor

(16837)

Evaluating the Frequency of CD8$^+$HLA-G$^+$ T cell in primary Unexplained Infertile Females

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Background: Most of the findings have focused on the importance of CD4$^+$HLA-G$^+$ and CD8$^+$HLA-G$^+$ regulatory T cells (Treg) during pregnancy. It has been demonstrated that these HLA-G$^+$ T cells subsets could induce maternal immune tolerance against semi-allogenic conceptus during pregnancy. There are only a few experiments regarding the Treg cells in the context of unexplained infertility (UI).

Methods: 35 participants including 18 primary unexplained infertile and 17 fertile females were enrolled in this study. 3-5 ml blood samples were taken and Peripheral blood mononuclear cells (PBMCs) were separated by Ficoll. Using a flow cytometer, the frequency of CD4$^+$HLA-G$^+$ and CD8$^+$ HLA-G$^+$ T cells was assessed in the peripheral blood samples of primary unexplained infertile and fertile females.

Results: Our results showed that the frequency of CD8$^+$HLA-G$^+$ Treg cells was significantly lower in primary unexplained infertile females than fertile females (p= 0.048). Although the frequency of CD4$^+$HLA-G$^+$ Treg cells in the primary unexplained infertile females was lower than fertile females, the difference was not statistically significant (P= 0.25).

Conclusion: Regarding the important role of CD8$^+$HLA-G$^+$ Treg cells during pregnancy and its decrease in females with primary UI, it seems that reduced CD8$^+$ HLA-G$^+$ Treg cells could be a leading immunological factor in the context of infertility. Nevertheless, more researches are needed in this field.

Keywords: CD8$^+$HLA-G$^+$ T cell, CD4$^+$HLA-G$^+$ T cell, unexplained infertility, Immune system

(18077)

Ameliorative effect of *Alpinia officinarum Hance* extract on nonylphenol-induced reproductive toxicity in male rats

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Background: Nonylphenol (NP), an environmental contaminant, has been considered an endocrine-disrupting chemical that interferes with reproductive function and induces oxidative stress in different organs, testis, and prostate. *Alpinia officinarum Hance* (ALP), a plant species of the Zingiberaceae family has proven antioxidant properties. This study aimed to evaluate the effect of alcoholic extract of ALP treatment on NP-induced reproductive toxicity and oxidative stress in male rats.
Methods: Our experimental groups were defined as follow: oil treatment (control), NP 10 mg/kg, Alp 2.5 mg/kg (ALP LD), Alp 5 mg/kg alone (ALP HD), NP + Alp 5 mg/kg (NP + ALP LD), and NP + Alp 10 mg/kg (NP + ALP HD). In this study, MTT assay were used to assess cytotoxicity. Also, total antioxidant capacity (TAC), superoxide dismutase (SOD), malondialdehyde (MDA), and testosterone levels were assessed in the serum of the rats. Moreover, histopathological and immunohistochemical analyses were performed on the testis and prostate tissue samples.
Results: NP administration resulted in significant cytotoxicity revealed by cell viability assay. Also, NP exposure resulted in a significant increase in lipid peroxidation and oxidative stress, represented by a remarkable reduction in total antioxidant capacity. In contrast, no significant changes in SOD levels have been observed. Moreover, NP induced a significant increase in prostate-specific antigen (PSA) levels accompanied by a significant reduction in testosterone levels. On the other hand, the relative of the testis of both NP + ALP LD and NP + ALP HD groups were significantly decreased compared to the control group, but no significant changes in the prostates' relative weight were observed. Histopathological evaluations also revealed destructive effects in testis and prostate tissue samples. NP-induced cytotoxicity was remarkably ameliorated, followed by ALP administration. Furthermore, the administration of ALP reduced the oxidative stress and destructive effects of NP in male rats.
Conclusion: In conclusion, ALP can protect against NP-induced oxidative stress toxicity and reproductive dysfunction in male rats.
Keywords: *Alpinia officinarum Hance*, Nonylphenol, Oxidative stress, Reproductive system, Testosterone, Toxicity

(18119)

Evaluation of CD3 CD56 NKT cell percentage and function and its relationship with serum vitamin D levels in women with recurrent spontaneous abortion

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Background: Women with recurrent spontaneous abortion (RSA) may have immune abnormalities. Vitamin D is known to play a role in the function of immune system. The aim of this study was to evaluate the percentage and function of natural killer T (NKT) cells and its relationship with serum vitamin D or 1,25-dihydroxy vitamin D3 (active form of the vitamin) level in women with RSA.
Materials & methods: In this case-control study peripheral blood was obtained from patient and healthy control groups. The percentage of NKT CD3 + CD56 + cells and activated NKT CD3 + CD56 + CD69 + cells were investigated using flow cytometry technique. Serum levels of IFN-γ and vitamin D were also measured using the ELISA technique.
Results: The mean percentage of NKT cells in women with RSA increased significantly compared to the healthy control group ($P<0.018$). There was no significant difference in CD69 marker expression between the patient and healthy control groups. Serum IFN-γ levels in women with RSA showed a significant increase compared to the control group ($p<0.031$). Serum levels of vitamin D showed a significant decrease in RSA group compared to the control group.
Conclusion: As a result, we found that an increase in the percentage and inflammatory function of NKT cells was associated with recurrent miscarriage. Decreased vitamin D can also lead to immune system dysfunction and pregnancy problems.
Keywords: Natural killer T (NKT) cells, recurrent spontaneous abortion (RSA), recurrent implantation failure (RIF), interferon- γ, vitamin D

(18221)

Preeclampsia-Exosomes: Their role in Th17/Treg axis imbalance in healthy pregnant women

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Background: Pre-eclampsia (PE) is defined as new-onset pregnancy with high blood pressure and proteinuria. Exosomes have critical roles in physiological and pathophysiological processes, they could also be one of the reasons for the alterations of maternal immunological response in pregnancy. Herein, we assessed the possible effects of PE-exosomes in the pathophysiology of preeclampsia in healthy pregnant women.

Methods: In this study, exosomes were isolated from PE patient's serum according to the ultra-centrifugation protocols and incubated with peripheral blood mononuclear cells (PBMCs) of healthy pregnant women. Exosomes from healthy pregnant women utilized as control. The effects of PE-exosomes on the frequency of Th17 and Treg cells, mRNA expression of their transcription factors and cytokines were evaluated by flow cytometry, real-time polymerase chain reaction (PCR) and Enzyme-linked immunosorbent assay (ELISA), respectively.

Results: PE patients indicated a decreased Treg cells number and increased Th17 cells. Also, Th17/Treg ratio significantly increased in these patients. Moreover, our results demonstrated that PE serum-derived exosomes in the PBMCs of healthy pregnant women lead to significant decrease in, TGFβ, and IL-10 mRNA expression; While, the expression of RORγt, IL-17, IL-23, IL-6, and IL-1β were significantly increased. No meaningful difference in the expression of FoxP3 was observed. Additionally, our data exhibited increased IL-6, IL-17, IL-23 and IL-1β levels, and decreased IL-10 level in the supernatant of cultured PBMCs from healthy pregnant women following PE-exosome intervention. Conversely, no meaningful difference in TGF-β level was observed.

Conclusion: Based on our findings, PE-exosomes are able to alter Th17/Treg ratio as well as their related gene expression and cytokine profiles. These findings support the probable role of PE-exosomes in PE pathogenesis. Importantly, our results bring up PE-exosomes as a novel target in the treatment of PE patients.

Keywords: Pre-eclampsia, Exosomes, Regulatory T cells, T helper 17 cells

(18231)

Evaluation of Toll-Like Receptors 6-10 Gene expression Levels in Endometriosis

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Background: Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissues outside the uterine cavity. Some studies have shown that failure to regulate innate immune responses may play a role in the pathogenesis of endometriosis. The goal of this study was to evaluate the gene expression levels of Toll-Like Receptors 6-10 (TLRs 6-10) in ectopic (EESCs) and eutopic (EuESCs) endometrial stromal cells of patients with endometriosis compared with endometrial stromal cells (ESCs) from non-endometriotic controls (CESCs).
Methods: Ectopic and eutopic endometrial tissues were collected from 36 patients with endometriosis during laparoscopic surgery. Endometrial tissues of 26 non-endometriotic patients used as control. Following cell characterization by flow cytometry using a panel of antibodies, the total RNA was isolated from the cultured cells and analyzed for the expression of the TLRs 6-10 genes by specific primers using real-time PCR assay.
Results: Significantly lower gene expression levels of TLR8 ($P<0.05$) and TLR9 ($P<0.001$) were found in EESCs and EuESCs compared with CESCs. The gene expression of TLR7 in EESCs was significantly lower compared with those of EuESCs ($P<0.05$). The gene expression of TLR6 and TLR10 in EESCs, EuESCs, and CESCs was not statistically significant.
Conclusion: These findings suggest TLRs may be involved in the pathogenesis of endometriosis.
Keywords: Endometriosis, Endometrial stromal cells, TLR

(18365)

Proteome Analogy in the first-trimester and Term Human Placentas

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Background: Placenta is a complex organ that plays a significant role in the maintenance of pregnancy health. It is a dynamic organ that undergoes dramatic changes in growth and development at different stages of gestation. In the first-trimester, the conceptus develops in a low oxygen environment that favors organogenesis in the embryo and cell proliferation and angiogenesis in the placenta; later in pregnancy, the higher oxygen concentration is required to support the rapid growth of the fetus. This transition, which appears unique to the human placenta, must be finely tuned through successive rounds of protein signature alterations. This study compares placental proteome in the normal first-trimester (FT) and term human placentas (TP).

Methods: Normal human first-trimester and term placental samples were collected and differentially expressed proteins were identified using two-dimensional liquid chromatography-tandem mass spectrometry.

Results: Despite the overall similarities, 120 proteins were differently expressed in first and term placentas. Out of 120 proteins differentially expressed in two groups, expression of 72 proteins was up-regulated and expression of 48 was down-regulated in first and term placenta. Of 20 proteins sequenced, seven showed increased (GRP78, PDIA3, ENOA, ECH1, PRDX4, ERP29, ECHM), eleven decreased (TRFE, ALBU, K2C1, ACTG, CSH2, PRDX2, FABP5, HBG1, FABP4, K2C8, K1C9) expression in first-trimester compared to the full-term placentas and two proteins exclusively expressed in first-trimester placenta (MESD, MYDGF).

Discussion: According to PANTHER and Reactome, these proteins were mostly involved in response to chemical stimulus and stress, regulation of biological quality, response to stress, programmed cell death, hemostatic and catabolic processes, protein folding, cellular oxidant detoxification, and coagulation and retina homeostasis. Elucidation of alteration in protein signature during placental development would provide researchers with a better understanding of the critical biological processes of placentogenesis and delineate proteins involved in regulation of placental function during development.

Keywords: Placenta, proteomics, first-trimester, full-term, 2D LC-MS/MS

(18455)

An Invisible Pattern of Autoantibodies in the of Women with Recurrent Spontaneous Abortion

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Background: Recurrent spontaneous abortion (RSA) is one the most common pregnancy disorders. Several factors play critical role in pathogenesis of RSA and one of the most important of them are autoimmune responses related factors. The relationship between autoantibodies without a certain systemic autoimmune disease, with infertility and RSA is not well established yet. This study is designed to investigate the profile of autoantibodies in Iranian women with RSA to determine the most common types of anti-nuclear antibodies (ANA) in these women.

Methods: Fifty non-pregnant RSA subjects were included in the study. The subjects had three or more unexplained recurrent miscarriage before 20 weeks of gestation and low (negative) ANA titer. ANA titer was determined by ELISA method and autoantibodies intensity was assayed through immunoblotting technique.

Results: According to the immunoblotting results, anti-nuclear antibodies against SS-A native, Ro-52 recombinant, histone and ds-DNA were the most common autoantibodies in women with RSA, respectively. However, in positive results, the intensity of autoantibodies against SS-A native and Ro-52 recombinant was significantly more than ds-DNA and histones ($P<0.005$).

Conclusion: We found a hidden layer of autoimmune reactions with a specific pattern in women with unexplained abortion, which was different from healthy women. This pattern *might be a useful predictive factor* for detection of the risk of miscarriage in women in the pre-pregnancy stage.

Keywords: antinuclear antibody, recurrent spontaneous abortion, immunoblotting

(18568)

It is defective decidualization not aberrant immune system that triggers abortion in CBA/J x DBA/2 mating

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Background: Recurrent pregnancy loss (RPL) remains a distressing problem to couples. At window of implantation, considerable modifications in endometrium and endometrial immune cells take place. One of such modifications is decidualization through which transcriptome, secretome and proteome profile of endometrial stromal cells (ESCs) is extensively altered. The main aim of this study is test whether correction of decidualization in CBA/J female mice could normalize abortion rate in CBA/J x DBA/2 abortion model.

Methods: Estrus was induced by successive subcutaneous injection of 17β estradiol and ESCs were isolated and verified by cytokeratin and vimentin immunofluorescent staining. ESCs were *In vitro* decidualized (IVD) by treatment with cAMP and MPA and validated by real time analysis of *Prl* and *Pgr* expression. The impact of IVD on proteome profile of ESCs including 111 cytokines, adhesion molecules, chemokines and growth factors was investigated by membrane-based array. As pre-clinical step, CBA/J mice was received *in utero* infusion of either decidualized ESCs (CxD/D), non-decidualized ESCs (CxDND) or PBS (CxD/P) 12 days before mating with DBA/2 mice. Control mice were not manipulated and mated with DBA/2 (CxD) or BALB/c (CxB). At day 13.5 of pregnancy mice were sacrificed and reproductive parameters, frequency of Tregs in para-aortic/renal and inguinal lymph nodes and proliferation of splenocytes in response to stimulation with either DBA/2 or BALB/c splenocytes was assessed by flow cytometry.

Results: The isolated ESCs expressed vimentin but failed to express cytokeratin. Decidualization led to more than 500-fold increase in expression of *Prl* gene. Decidualization induced higher levels of IL-6 and IL-11, CCL11 and CXCL12 expression, while reduced the production of Endoglin, and IL-1α. This process was also associated with an increase in growth factors and growth factor binding proteins including G-CSF, M-CSF, IGFBP2-6, while reduced the expression of FGF-21 and osteopontin. We also found that decidualization caused increased expression of chemerin and decreased expression levels of coagulation factor III, MMP-9 and RBP4. Different experimental groups showed no difference in number of implantation sites. Those groups with surgery (CxD/D, CxD/ND and CxD/P) had litters with lower weight. In CxD/D group, the resorption rate was normalized to the levels observed in CxB group. Frequency of inguinal lymph node Tregs in all groups was comparable, while in CxD/D mice the frequency of Tregs in paraaortic/renal lymph nodes increased to the level

observed in non-abortion group (CxB). No significant changes in proliferation of splenocytes from pregnant CBA/J mice was observed in treated group compared to CxD group.

Conclusion: Our results showed for the first time that it is defective decidualization and not aberrant immune responses that trigger abortion in CBA/J x DBA/2 mating. In this regard, attributing abortion in CBA/J x DBA/2 model to immunological defects seems to be oversimplification.

Key words: Pregnancy loss, Regulatory T cells, Decidualization, Endometrium, Pregnancy parameters

(18609)

Decidualization-incompatible mating in CBA/J x DBA/2 model: Does quality of seminal plasma play a role?

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Background: Pregnancy is a complex and a finely-tuned process in which different systems including immune and endocrine systems work together in a coordinated manner. Nonetheless, new insights has unraveled the potential role of seminal plasma in promoting pregnancy success by modulating cellular and molecular adaptions of the maternal environment. In this research, differential effects of seminal plasma from mice of different strains on parameters associated with endometrial receptivity and decidualization and proteome profile of endometrial stromal cells (ESCs) has been investigated to puzzle out the mystery of abortion in CBA/J x DBA/2 mating.

Methods: Estrus was induced in CBA/J female mice by 17β estradiol injection. ESCs were isolated off the uterine tissue and characterized by cytokeratin and vimentin immunofluorescent staining. Extracts from seminal vesicle, prostate and epididymis of BALB/c, CBA/J and DBA/2 male mice were prepared and pooled. Protein profile of each extract was then assessed by conventional and 2D gel electrophoresis and compared. Differential effect of seminal plasmas from different male strains on endometrial parameters including cell cytotoxicity, wound healing and migration was tested in the next step. The impact of seminal plasma on proteome profile of ESCs including 111 cytokines, adhesion molecules, chemokines and growth factors was investigated by membrane-based array. Metabolome of seminal plasma was explored by LC-MS/MS analysis. The effect of seminal plasma on expression of genes associated with cell migration, motility, proliferation and apoptosis in ESCs was investigated by real time PCR at the final step.

Results: The purity of isolated ESCs was reasonably high. Isolated cells expressed vimentin but failed to express cytokeratin. Extracts of male reproductive organs showed different protein concentrations, with seminal vesicle having the highest concentration. SDS-PAGE electrophoresis revealed different protein profile in reproductive organs of mice from different male mice strains. The results of 2D gel electrophoresis showed seminal plasma of DBA/2 mice have only about 68% similarity with those from BALB/c and CBA/J mice. Toxicity assessment showed that 5% of seminal plasma from DBA/2 mice had cytotoxicity on ESCs at all time periods tested, while those from BALB/c and CBA/J mice exerted cytotoxicity only when exposed to ESCs for 24 h. Seminal plasma of DBA/2 mice inhibited wound healing of ESCs, while those from BALB/c and CBA/J mice accelerated this

process. The same pattern was also obtained in migration assay. Protein profiling by membrane-based array clearly showed that seminal plasma induced pro-inflammatory proteins and chemokines such as IL-6 and CXCL1, CXCL16, CCL2 and seminal plasma of DBA/2 mice induce significantly higher levels of inflammatory mediators compared to other strains. Seminal plasma of BALB/C and DBA/2 mice down-regulated the expression of *BCL-6*, while only DBA/2 seminal plasma upregulated the expression of *Inha*. LC-MS/MS analysis showed decidualization-friendly metabolome in BALB/c seminal plasma.

Conclusion: Our results showed for the first time that seminal plasma from different mice strains have differential effects on key endometrial parameters associated with embryo implantation. Seminal plasma of DBA/2 mice significantly triggered higher production of inflammatory mediators and arrested cell migration and wound healing. Our results suggest that prolonged and excessive inflammation of endometrium of female CBA/J mice following insemination by male DBA/2 mice is the primary factor for defective decidualization in CBA/J mice leading to abortion.

Keywords: Pregnancy loss, Decidualization, Endometrium, Seminal plasma, Wound healing, Inflammation

(18669)

Expression levels of monocyte chemoattractant protein-1, hepatocyte growth factor, and insulin-like growth factor-1 in endometriotic patients compared with non-endometriotic controls

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Abstract: To study the concentrations of monocyte chemoattractant protein-1 (MCP-1), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1) in peritoneal fluid (PF) and serum, and to evaluate their expressions by PF and peripheral blood mononuclear cells (PFMCs and PBMCs, respectively), and ectopic and eutopic endometrial stromal cells of patients with endometriosis (EESCs and EuESCs, respectively) compared with controls. The concentrations of MCP-1, HGF, and IGF-1 in serum and PF of 70 endometriosis patients and 70 controls were determined by ELISA. PBMCs, PFMCs, as well as EuESCs and EESCs from 30 endometriosis patients, and their counterparts in 15 non-endometriotic controls were cultured and the gene and protein expressions of these cytokines were evaluated by RT-qPCR and ELISA, respectively. The levels of MCP-1, HGF, and IGF-1 in serum and PF in women with endometriosis were significantly higher than the control group ($P < 0.05$-$P < 0.001$). Gene expression of MCP-1 and IGF-1 in the PFMCs, PBMCs and EESCs also showed an increased level compared to controls ($P < 0.05$-$P < 0.0001$). The protein expressions of MCP-1 and IGF-1 by PFMCs were statistically more noticeable in endometriotic women ($P < 0.05$ and $P < 0.01$, respectively). The gene and protein expression of HGF in PFMCs and its gene expression by EESCs were significantly higher in endometriotic women compared to controls ($P < 0.05$-$P < 0.01$). The higher concentrations of MCP-1, HGF, and IGF-1 in serum and PF and their higher expressions by PFMCs and EESCs in endometriosis patients may contribute to the development of endometriosis.

Keywords: Endometriosis, MCP-1, HGF, IGF-1, PFMCs, PBMCs, ESCs, Ectopic.

(18739)

Effect of Different Concentrations of Leukemia Inhibitory Factor on Gene Expression of Vascular Endothelial Growth Factor-A and Transforming Growth Factorbeta-1 in Trophoblast Tumor Cell Line

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Background: Several studies have shown that leukemia inhibitory factor (LIF) is one of the most important cytokines in the process of embryo implantation and pregnancy, but so far the role of this cytokine in angiogenesis and trophoblast invasive process has not been fully investigated.
Objective: To examine the effect of LIF on gene expression of vascular endothelial growth factor(VEGF) and transforming growth factor beta 1 (TGF-β1) in choriocarcinoma cell line (JEG-3) as a trophoblast cell.
Methods: JEG-3 choriocarcinoma cells stimulated with different concentrations of LIF for 6, 12, 24, 48 and 72 hours. The expression of VEGF and TGF-β1 analyzed by real-time PCR. Delta CTs were subjected to one-way analysis of variance (ANOVA) and a post hoc Tukey's test by SPSS version 25.0 software for data analyzing.
Result: In stimulated cells, different concentrations of LIF caused the significant decrease of VEGF gene expression ($p<0.05$) at 12, 24 and 48 hours, but the gene expression increased after 72 hours. Also different concentrations of LIF caused a significant reduction of TGF- β1 gene expression depending on the dose ($p <0.05$) and times ($p <0.05$).
Conclusion: Gene expression of VEGF and TGF-β1 in trophoblast cells treated with LIF decreased, indicating this cytokines plays an important role in angiogenesis and invasive process in placentation. So, this study showed that further studies are needed to determine the effect of LIF on other angiogenic factors in trophoblast cells.

Keywords: LIF, VEGF-A, TGF- β1, Trophoblast, JEG-3

(18330)

Thyroid Peroxidase in Human Endometrium and Placenta: A Potential Target for Anti-TPO Antibodies

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Background: Autoimmune thyroid disease (AITD) is the most common endocrine disorder during pregnancy. Thyroid auto-antibodies (TAs) have been suggested to serve a role in implantation failure and spontaneous abortion. Until now, there is no data on the potential interaction of TAs with human reproductive organs. Here, we set out for the first time to test this hypothesis by studying the expression of thyroid peroxidase (TPO) at gene and protein level in human reproductive organs.

Methods: Endometrial samples were taken from normal women and placenta tissues were collected after full term caesarian section. Expression of TPO messenger RNA (mRNA) was investigated by qRT-PCR. In addition, polyclonal anti-TPO antibodies were produced and the expression of TPO protein in mentioned tissues was evaluated by immunohistochemistry (IHC) and Western-blot analysis. The reactivity of anti-TPO antibody in human embryos was evaluated by Immunofluorescent staining (IF).

Results: For the first time, our study showed that TPO is expressed at gene and protein levels in endometrium and placenta. TPO expression was mainly localized to glandular and luminal epithelial cells in the endometrium. In placenta, the syncytiotrophoblasts and invasive trophoblast cells were the main cell types that expressed TPO protein. Specific band of approximately 110 kDa was observed in all endometrial and placental tissues by Western blot analysis. However, no expression of TPO protein was observed in human embryo.

Conclusion: TPO expression in endometrium and placenta may explain higher frequency of abortion and infertility in patients with thyroid autoimmunity.

Keywords: TPO, Endometrium, Placenta, Embryo, Abortion, Thyroid autoimmunity

(18279)

Evaluating Chronic Endometritis in Women with Recurrent Implantation Failure and Recurrent Pregnancy Loss by Hysteroscopy And Immunohistochemistry

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Background: The identification of less invasive methods with acceptable diagnostic value for evaluating intrauterine abnormalities can improve the satisfaction of patients and physicians. Although hysteroscopy plus biopsy has favorable predictive and diagnostic values, limited studies have evaluated its value, and the exact value of this method is not completely understood. The aim of this study was to evaluate the prevalence of chronic endometritis in patients with recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) by hysteroscopy and immunohistochemistry.
Interventions: Hysteroscopy on the third to fifth day after finishing the menstruation cycle and then a biopsy for immunohistochemistry by a specific monoclonal antibody against the CD138 marker.
Measurements and Main Results: In total, 85 patients with a mean age of 36.08 § 5.76 years underwent hysteroscopy on the third to fifth day after finishing the menstruation cycle. At the end of hysteroscopy, a biopsy was taken and assessed using immunohistochemistry. Immunohistochemical staining findings of >5 plasma cells per 20 high-power fields were considered the gold standard. The prevalence of chronic endometritis (CE) in both groups and the diagnostic value of hysteroscopy were evaluated. All data were analyzed using the Fisher exact test and analysis of variance. The prevalence of RIF-related CE was 23.4% (11); 21.3% (10) of the cases were diagnosed by hysteroscopy. The prevalence of RPL-related CE was 36.8% (14) and 31.6% (12) based on hysteroscopy and immunohistochemistry staining, respectively. Subsequently, 10 patients (RIF/RPL-related CE with a positive hysteroscopic outcome) were selected randomly for in vitro fertilization therapy, and 3 (30%) of them eventually became pregnant. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy in diagnosing CE were 86.36%, 87.30%, 70.37%, and 94.82%, respectively.
Conclusion: Hysteroscopy is a reliable diagnostic technique in patients with RIF after in vitro fertilization and RPL that can reliably diagnose chronic endometritis.

Keywords: Hysteroscopy; Immunohistochemistry; Endometritis; Recurrent implantation failure

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran
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(18466)

Effect of autoimmune thyroiditis on women infertility

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Background: Autoimmune diseases are one of the main causes of primary ovarian failure and infertility in women. In this study, the relationship between ovarian hormones and thyroid hormones in women was investigated.

Methods: 50 women in a cross-sectional study was conducted at the infertility Center of kermanshah University of Medical Sciences. Women with thyroid-stimulating hormone (TSH) > 3 mIU/L were included in the study with convenience sampling. TSH, thyroxine (T4), anti-TPO antibody hormones were measured by ECL methods. Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Prolactin (PRL) and anti-Mullerian hormone (AMH) were measured by IRMA methods. Data were collected by a form containing demographic data, body mass index.

Results: As shown in table 1, there was no significant difference between the groups in the mean age (P=0.88), body mass index (BMI) (P=0.64), mean T4 (P=0.17), prolactin (P=0.56), LH (p=0.11) and FSH levels (P=0.08). Ovarian reserve characteristics: anti-Mullerian hormone (AMH) levels in hypothyroid and normal group was 1.77±1.45 and 2.99±1.68, respectively.

The effect of autoimmune thyroiditis on ovarian reserve was determined as differences in AMH and FSH levels between the groups. There were significant differences between the two groups on Anti TPO (P <0.01), TSH (p=0.05) and AMH (P=0.03).

Conclusion: Patients with hypothyroid were at higher risk for decreased ovarian reserve. They need more care and counseling before pregnancy.

Keywords: Infertility, Hypothyroid, Anti-Mullerian hormone

Table 1: Clinical characteristics of patients and normal groups

Variable	Hypothyroid (N=30)	Normal (N=30)	P value*
	mean±SD	mean±SD	
Age (year)	32.22±5.40	32.40±4.69	0.42
BMI (kg/m2)	24.92±3.15	24.33±3.55	0.77
Anti TPO	45.88±11.15	10.98±6.44	0.001
TSH (mIU/L)	5.88±3.95	2.62±1.02	0.05
T4 (µg/dL)	7.24±3.57	9.15±2.54	0.17
LH (mIU/mL)	7.33±4.64	6.06±3.24	0.11
Prolactin (µg/L)	14.25±6.55	15.29±5.52	0.56
FSH (mIU/mL)	8.58±5.04	6.55±3.05	0.08
AMH (ng/mL)	1.77±1.45	2.99±1.68	0.03

(18085)

Effect of Maternal LPS Exposure during Pregnancy on Expression of Immunomodulatory MicroRNAs in Placenta-Derived Exosomes

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Background: Expression pattern of microRNAs in placenta-derived exosomes play a crucial role in the regulation of immune responses and inflammation at the fetal-maternal interface. Concerning the immunomodulatory properties of miR-17 and miR-29a, we determined expression levels of them in placenta-derived exosomes in a lipopolysaccharide (LPS)-induced abortion mice model.
Methods: Pregnant BALB/c mice, aged 6-8 wk, were divided randomly into two groups (n=7/each) on gestation day 11.5. The mice in experimental group treated with LPS, and whereas mice in control group treated with Phosphate buffered saline. Five hours after treatment, the placental cells were isolated and were cultured for 48 hr. Then cell culture supernatants were collected and used for isolation of exosomes. Isolated exosomes confirmed by Western Blot and scanning electron microscopy. Then miRNAs extracted from exosomes, and cDNA synthesized. The expression levels of miR-17 and miR-29a evaluated by quantitative real-time PCR analysis.
Results: Our results showed that expression levels of miR-29a in placenta-derived exosomes obtained from the LPS group significantly increased compared to the control group. We also found that expression levels of miR-17 in placenta-derived exosomes obtained from the LPS group decrease, but did not show significant changes compared with the control group.
Conclusion: We concluded that inflammatory reactions at the fetal-maternal interface can alter miRNAs expression patterns into placenta-derived exosomes, especially miRNAs with, immunomodulatory effects such as miR29a.
Keywords*:* Exosome; miR-17; miR-29a; Placenta; Inflammation.

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran
ICIA 2021 AHVAZ IRAN

(17936)

Gene Expression of *SOCS3* and *SOCS4* in Granulosa Cells of PCOS Women

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Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women, affecting 5% to 10% of women of childbearing age. In this syndrome, the oocytes do not reach full maturity and are not released from the ovaries during menstruation which increases the number of immature oocytes. PCOS is a multifactorial disorder in which hormonal, genetic and environmental factors are involved. Inflammation plays a role in the pathogenesis of PCOS, therefore cytokines e.g. interleukins, interferons and their downstream signaling pathways maybe also involved in its development. Some regulatory proteins, such as the SOCS (Suppressors of Cytokine Signaling) family members, are involved in the negative regulation of cytokine signaling. All members of the SOCS protein family are expressed in the ovaries, however the expressions of SOCS3 and *SOCS4* are higher and mostly play an important role in ovulation process.
The aim of this study was to compare the gene expression of *SOCS3* and *SOCS4* in granulosa cells of women with PCOS in compare to women with normal ovulation.
Methods: In this case control study, 20 women with PCOS (PCOS group) and 20 women with normal ovulation (control group) who underwent ovarian stimulation were enrolled. Granulosa cells were isolated from follicular fluid. RNA extraction and cDNA synthesis were done. *SOCS3* and *SOCS4* gene expression was measured by Real Time PCR. GAPDH was used as housekeeping gene.
Results: The results showed that the expression of *SOCS3* and *SOCS4* were higher in granulosa cells of PCOS group compared to controls.
Conclusion: It seems over expression of *SOCS3* and *SOCS4* genes in granulosa cells of PCOS women may be involved in prevention of follicular maturation and ovum release via their negative regulatory effects on cytokine signaling pathway. The study with larger sample size is recommended.
Keywords: Polycystic ovary syndrome, Granulosa cells, SOCS, Cytokine, Inflammation

(18072)

Vitamin D receptor expression in sperm of male with unexplained infertility

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Background: Vitamin D has been linked to several disorders like infertility. The purpose of this study was to investigate the level of vitamin D and mRNA expression of vitamin D receptor (VDR) in the sperms of male subjects with unexplained infertility.

Methods: In this case-control study, 24 unexplained infertile men as the case group and 22 healthy fertile men as the control group were recruited. Men completed special questionnaires, and semen samples were obtained. Vitamin D levels were evaluated in the seminal fluid using ELISA. Afterwards, the swim-up test was performed for the isolation of motile sperm cells. From these cells, RNA was extracted, cDNA was synthesized, and mRNA expression of VDR gene was evaluated with quantitative Real-time PCR.

Results: A decrease in VDR mRNA expression levels was detected in case group in comparison to the control group, but this reduction was not statistically significant. Besides, the level of vitamin D in seminal fluid was not detectable in both groups.

Conclusions: The data from our preliminary study indicated that the sperms of unexplained infertile men express the VDR gene mRNA lower than fertile men, although there was no vitamin D in seminal samples. Hence, dysregulation of vitamin D;VDR signaling might take part in etiopathogenesis of unexplained infertility in men.

Keywords: vitamin D receptor, unexplained infertility, vitamin D, mRNA expression

(18109)

Gene expression of SIRT1 in endometrial tissues of women with endometriosis

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Background: Endometriosis as an estrogen dependent gynecological condition, is associated with progesterone resistance and cell proliferation. This disease characterized by the presence of endometrial tissue outside the uterus cavity. Autoimmune regulator (AIRE) is one of the immune-inflammation genes that its expression changes in endometriosis. AIRE plays role in central immunological tolerance via regulating the expression of tissue restricted antigens (TRA) with using several partners. Sirtuin1 (SIRT1) as one of AIRE partners, is a histone deacetylase which activates AIRE via its deacetylation. In this study, we investigated gene expression levels of SIRT1 in endometrial tissues of women with endometriosis in compare to controls.

Materials and Methods: In this case-control study, 10 women with endometriosis (endometriosis group) and 15 women without endometriosis (control group) were enrolled after diagnostic laparoscopy. Eutopic endometrial tissues of endometriosis and control groups were taken by pipelle. Ectopic endometrial samples were collected from women with endometriosis during laparoscopy. RNA extraction and cDNA synthesis were done and real-time PCR was used for *SIRT1* gene expression analysis.

Results: *SIRT1* gene expression was decreased in ectopic tissues in compare to eutopic and control endometrial samples, although these differences were not statistically significant.

Conclusion: It seems that mRNA expression of *SIRT1* is dynamic in endometriotic tissues, while further studies with larger sample size are recommended.

Keywords: Endometriosis, SIRT1, Gene expression, Ectopic, Eutopic.

(18184)

Investigation of NK cells in the uterine tissue

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Background: Probably one of the most important reasons for failure in the treatment of pregnancy disorders and infertility is the lack of accurate diagnosis of the cause of these problems. Patients are usually screened for anatomical disorders, hormonal disorders, anti-cardiolipin antibodies, anti-ß2-glycoprotein, and coagulation factor deficiency. In many cases, people do not have these disorders. Uterine biopsy can be one of the best samples to diagnose infertility in these people.
Methods: In the present work, we stained NK cells of uterine samples in a 32 women taken by a specialist doctor from women with pregnancy abnormalities (repeated abortions, IVF failure) by immunohistochemistry and compared them with 16 samples from healthy individuals.
Results: UNK cells were significantly higher in patients compared to the control group. (patients: 18.14±7.14, controls: 11.71±6.17, P=.004).
Conclusion: NK cells play an important role in the pregnancy process. Increase in these cells leads to pregnancy abnormalities. But many of these investigations have focused on NK cell blood samples, while several studies have determined large differences between the phenotype and function of blood NK cells and uterine NK (uNK). To calculate the number of uNK cells, the number of positive cells in the total stromal cells was counted. This method is more accurate, because uNK cells are reported as a percentage. Prednisolone, IVIg, and lymphocyte therapy are treatments that can increase the chances of a successful pregnancy by acting on uNK. These methods can be useful in treatment of the people with high uNK.
Keywords: uNK, Pregnancy, IVF failure, Infertility

(18260)

Relationship between age and consanguineous marriage with the number of abortions

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Background: Fetal mortality has many causes but obviously genetic factors play a more important role. The age of pregnant women and consanguineous marriage are the most important factors in pregnancy. The aim of this study was to investigate the relationship between age and consanguineous marriage with the number of abortions.

Methods: This study was performed in 1398 on 46 pregnant women referred to Taleghani Hospital in Ilam province. Data analysis was performed using SPSS software (Spearman correlation test) (P value < 0.05).

Results: There was a positive correlation between age and the number of abortions. There was no significant correlation between consanguineous marriage and the number of abortions.

Conclusion: Increasing the age of pregnant women is one of the most important factors affecting recurrent miscarriage

Keywords: gestational age, consanguineous marriage, abortion, pregnancy

(18261)

Relationship between vitamin D level and the number of abortions

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Background: One of the most common complications of pregnancy is spontaneous abortion. Vitamin D has strong anti-inflammatory effects at the maternal and fetal levels and increases Th2 responses. The aim of this study was to investigate the relationship between vitamin D levels and the number of abortions in pregnant women.
Methods: This study was performed in 1398 on 46 pregnant women referred to Taleghani Hospital in Ilam province. Blood samples were evaluated for vitamin D levels. Data analysis was performed using SPSS software (Spearman correlation test) (P value < 0.05).
Results: There is a negative correlation between vitamin D levels and the number of abortions.
Conclusion: Low serum levels of vitamin D can be considered a risk factor for miscarriage.

Keywords: number of abortions, vitamin D

(18384)

The effect of hydro-alcoholic and hexane extract of Foeniculum vulgare on female sex hormones in female mice

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Background: Foeniculum vulgare belongs to the family Apiaceae, used in traditional medicine for a wide range of diseases such as digestive, respiratory and reproductive disorders.
Objectives: The aim of this study was to compare the different effects of hydro-alcoholic and hexane fennel extracts on female sex hormones estrogen, progesterone, LH and FSH. This may help us choose the best solvent for this plant to achieve a more efficient outcome in treatment.
Methods: In this experimental study, 64 female mice (balb/c) were divided into two control groups and six groups receiving different concentrations of oral hexane or hydro-alcoholic extract. After 20 days, the plasma levels of these four sex hormones were assessed by ELIZA.
Results: the results showed that both extracts had the same effect on the increase of progesterone (P-value <0.0001) and decreased endogenous estradiol (P-value <0.006), however, the hydro-alcoholic extract had a slightly stronger effect than the hexane type. Although decreased LH was not observed in the hydro-alcoholic (P-value group 9 = 0.084) and hexane extracts (P-value> 1.6). Additionally, Concentrations of FSH reduced in either hexane (P-value = 0.03) and hydro-alcoholic (P-value = 0.05) extracts just in 150 mg/kg concentrate, but hexane groups had a more severe decrease than hydro-alcoholic groups.
Conclusions: the two extracts seem to be different not only in concentration but also in composition. Therefore, the effect of these extracts on female sex hormones is different.
Keywords: Foeniculum vulgare, Hexane extract, Hydro-alcoholic extract

(18438)

Alteration in gene expression of VEGF in endometrial tissues of women with endometriosis

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Background: Endometriosis is one of common benign diseases in women of reproductive age**.** It is characterized by the growth of endometrial-like tissue outside the uterus**.** Endometriosis is considered as a multifactorial disease affected by genetic and epigenetic factors. Neoangiogenesis is a major element in the pathogenesis of endometriosis**.** So vascular endothelial growth factor (VEGF) may have important roles in its pathogenesis**.** VEGF plays main role in endothelial proliferation, vasodilation and increases vascular permeability. The aim of this study was to evaluate the expression levels of *VEGF* gene in endometrium of women with endometriosis.

Methods: In this case-control study, 12 endometrial samples (eutopic) and 12 endometriotic lesions (ectopic) of women with endometriosis and 12 endometrial control samples were analyzed. Control samples were obtained from women who had no evidence of endometriosis during diagnostic laparoscopy in Royan Institute. Control and eutopic endometrial samples were obtained by pipelle. Ectopic samples were obtained during laparoscopy procedure. All women signed the informed consent form and did not receive any hormonal treatments during the last three months. After endometrial tissues collection, RNA extraction and cDNA synthesis were done. Real-time PCR technique was used for quantitative gene expression of VEGF and P-value less than 0.05 was considered statistically significant.

Results: Gene expression of VEGF was increased in eutopic tissues of endometriosis group in compared with control group. Gene expression level of VEGF was lower in ectopic lesions versus eutopic and control endometrial samples. These differences were not statistically significant (P>0.05).

Conclusion: The findings of this study suggest that overexpression of VEGF in eutopic endometrium of endometriosis could indicate a higher angiogenic activity, which might contribute to the increased capability of endometrial cell implantation at ectopic sites.

Keywords: Endometriosis, Angiogenesis, VEGF

(18720)

Vitamin C and E supplementation effects on secretory and molecular aspects of VEGF derived from peritoneal fluids of patients with endometriosis

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Background: Endometriosis is an extremely heterogeneous disease and affects about ten percent of the female population during their reproductive years. Recent studies showed that endometriosis is an angiogenesis-dependent disease. Antioxidants play a key role in the inhibition of oxidative stress-induced damages and the reduction of pelvic pain in patients with endometriosis. Vitamin E and vitamin C are the main components in neutralizing free radicals. Antioxidant consumption such as vitamin C and vitamin E in women with endometriosis showed an inverse correlation between antioxidant intake and endometriosis pathology. Peritoneal macrophages are a well-characterized source of vascular endothelial growth factor (VEGF). The aim of this study was to determine the VEGF gene expression and production in peritoneal macrophages of patients with endometriosis under the effects of vitamins C and E in comparison with control.

Methods: The lab trial study carried out on 50 patients undergoing laparoscopy and peritoneal fluid samples were collected from them. We compared the VEGF gene expression and production in peritoneal macrophages among groups by using real-time PCR and ELISA methods, respectively.

Results: Our findings showed that gene expressions influenced by vitamin C increased in different concentrations and incubation times, except for the incubation time after 48 h. In the case of vitamin E, this was evident with the exception of vitamin E 50 **µM** after 24 h and vitamin E 100 **µM** after 48 h.

Conclusion: Our results indicated that vitamin C and E in different concentrations and incubation times altered VEGF gene expression in the peritoneal macrophages but they had not affected on VEGF productions. Further studies are needed to determine the effects of C and E vitamins in different concentrations on vascular endothelial growth factor gene expression and production in peritoneal macrophages and the possible roles of these vitamins in treating endometriosis.

Keywords: Endometriosis, Peritoneal macrophages, VEGF, Vitamin C, Vitamin E

(18723)

Association of IL-17 and IL-23 follicular fluid concentrations and gene expression profile in cumulus cells from infertile women at risk for ovarian hyperstimulation syndrome

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Background: This study determined the association between the levels of interleukin (IL)-17 and IL-23 in follicular fluid (FF), as well as their mRNA levels in cumulus cells from infertile women at risk for ovarian hyperstimulation syndrome (OHSS).
Methods: In this case-controlled study, the control group (n = 40) was infertile women whose partners had male factor infertility, whereas the case group (n = 40) was infertile women at risk of OHSS. IL-17 and IL-23 concentrations in FF were measured using an enzyme-linked immunosorbent assay method, whereas the mRNA expression levels of IL-17 and IL-23 of cumulus cells were determined using RT-PCR.
Results: Significantly higher levels of IL-17 were seen in the case group ($p = 0.04$), whereas there was no significant difference in IL-23 concentrations between the two groups ($p = 0.3$). The mRNA levels of IL-17 and IL-23 showed no significant differences. In the case group, there was a positive significant correlation between the IL-23 concentration in FF and the oocyte maturation rates ($p = 0.01$). In the case group, the number of follicles, MII oocytes, immature oocytes, fertilized oocytes and number of embryos were significantly higher than the control group ($p < 0.05$).
Conclusion: Our findings showed that the mRNA expressions of IL-17 and IL-23 were similar in the two groups, and IL-17 was increased in the case group.
Keywords: IL-17, IL-23, OHSS, Follicular fluid, Gene expression

(18727)

Assessment polymorphisms of -634C/G & +936C/T VEGF gene and their relationship with serum level VEGF in women suffering preeclampsia

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Background: Vascular endothelial growth factor (VEGF) an angiogenic factor, plays a significant role in vascular permeability and vascular proliferation. Prior studies demonstrated that a circulating imbalance of angiogenic factors occurred several weeks before the clinical manifestations of preeclampsia. In this study the VEGF -634 C/G and +936 C/T polymorphism and its relationship with the VEGF serum levels in pregnant women with preeclampsia were assseed.

Methods: In this case control study two groups of pregnant women with preeclampsia and healthy pregnant women were parcipitated. DNA was extracted from the peripheral blood lymphocytes using phenol-chloroform extraction method. The genotypes of the VEGF -634 C/G and +936 C/T polymorphism were detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). The VEGE serum levels were measured by ELISA technique.

Results: In this study the maternal age, gestational age, maternal hemoglobin and maternal BMI were significantly associated with risk of ($P<0.05$). There was no significant difference between the case and control groups regarding VEGF -634 C/G and +936 C/T polymorphism ($P>0.05$). Also, the case group showed an increase level of VEGF serum level compared with the control group ($P < 0.001$).

Conclusion: Despite the significant increase in VEGF serum level in preeclampsia patients, it seems that VEGF -634 C/G and +936 C/T polymorphism are not associated with preeclampsia. Further studies are necessary to more fully assess the different factors associated with preeclampsia.

Key words: Preeclampsia, Polymorphism, VEGF, ELISA

(18793)

The prevalence of Sexually Transmitted Diseases (STDs) among 25-60 years old men in Iran

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Background: Sexually Transmitted Diseases (STDs), especially in men, could lead to multiple morbidities, as well as facilitate the transmission of serious pathogens such as HIV. The present study used data from a nation-wide survey on male morbidities to estimate the prevalence of STDs among men in Iran.

Methods: This cross-sectional study used data from a nation-wide project on male reproductive morbidities in 2007. 2296 men with age of 25 to 60 years old were recruited by systematic cluster sampling across four provinces (*Golestan*, *Hormozgan*, *Kermanshah*, *and Isfahan*). Data on symptoms of STDs including genital secretion, pushing out, itching or genital ulcers, and lymphadenopathy of the inguinal area after sexual contact was collected by trained urologists. Data analysis was done using SPSS. Independent samples T-test and Chi-squared tests were used for the analysis.

Results: 2296 men with the mean (SD) age of 39.95 (10.3) years were interviewed. Two-thirds of all subjects (75%) were aware of using condoms in suspected sexual relationships; while only 69% of them actually used condoms in those circumstances. Overall, 14 subjects (0.6%) had one type of STDs at the time of the study. One-Hundred and ten subjects (4.7%) answered "yes" to the question of whether they were referred to a physician for sexual problems.

Conclusion: The prevalence of STDs is still low among male population in Iran. Careful and well-designed surveillance system to monitor the incidence of STDs and implementation of proper preventive measures to restrict the spread of sexually transmitted pathogens are amongst proposed recommendations.

Keyword: Sexually Transmitted Diseases, Male, Iran, population-based survey

(18258)

The relationship between FBS/GTT of non-diabetic pregnant women and their newborn weight

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Background: Infant weight is one of the most important factors associated with infant death. On the other hand, one of the factors affecting the macrosomic occurrence of the fetus is Gestational diabetes. High maternal FBS/GTT, which increases insulin production increases infant mortality.
Methods: In this study, in order to evaluate fasting blood sugar levels in the first trimester, 24-28 weeks of pregnancy and 50 g one hour screening test in non-diabetic pregnant women and its effect on their neonatal weight in 1398 in one of the hospitals affiliated to the University of Science Ilam medicine has been performed. Samples were selected from 50 pregnant women aged 24-28 weeks who underwent fasting blood glucose testing in the first trimester of pregnancy and its value was less than 105 mg / dL. For samples, 50 g glucose tolerance test was performed in the fasting state. Intravenous blood samples were taken before and after eating 50 g of glucose. After delivery in the semester (37-41 weeks), the baby was weighed and its sex and weight were recorded.
Result: There is a weak and significant negative relationship between infant weight and maternal GTT.FBS ($P < 0.05$)
Conclusion: Thus, FBS and GTT values of the first trimester and 24-28 weeks can be used to predict birth weight
Keywords: Fasting blood sugar (FBS), Gestational diabetes screening (GTT), Infant weight, Non-diabetic pregnant women

Congress Abstracts

Research & Development

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

18676

Characterization of 6D6 hybridoma clone producing Monoclonal Antibody reactive with Bladder Cancer Cell lines

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Background: Hybridoma technology has been used for some decades to produce monoclonal antibodies against tumor-associated antigens that can be applied for the diagnosis or treatment of cancer.
Methods: In the present study a newly established bladder cancer cell line, JAM-ICR, was used to immunize BALB/c female mice. Following the protocol of fusion, high reactive hybridoma producing antibodies were selected by flow cytometry and ELISA techniques. The hybridomas were screened with breast mesenchymal stem cells, peripheral blood mononuclear cells of healthy individuals, and a panel of cell lines of epithelial origin.
Results: Among a series of hybridoma, 6D6 was selected based on no reaction to hematopoietic cell lineage and the cells of mesenchymal origin but reactive with JAM-ICR bladder cancer and other epithelial tumor cells. The western blot analysis indicates that 6D6 recognizes a glycoprotein on the epithelial tumor with a molecular weight of about 50-60 kilodaltons. In order to specify the target of this monoclonal antibody, the 2dimentional gel electrophoresis and mass spectrophotometry are under investigation.
Conclusion: Considering the extent of the use of a monoclonal antibody in clinical oncology we are hoping that this clone will be available for further study of bladder cancer both in diagnosis, and prognosis of bladder cancer in the future.
Keywords: Bladder cancer, Hybridoma, Monoclonal antibody

(18789)

miR-622 serves as a tumor-suppressive and impairs motility through inhibiting metastatic genes in prostate cancer

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Background: Recent evidence suggests that microRNAs (miRNAs) are involved in prostate cancer (PCa) metastasis and hold great promise as therapeutic targets. Herein, we transfected the miR-622 mimic into PC3 cells and evaluated the effects of this interference on these tumor cells' growth and migration repression and the expression of targeted genes.
Methods: Transfecting of miR-622 mimic and inhibitor, negative control (NC), and NC inhibitor were established using Lipofectamine™ 2000. The expression levels of miR-622 were evaluated using the qRT-PCR. Cytotoxic effects of miR-622 assessed by MTT. A scratching test will be applied to determine the impact of miR-622 on cell migration. Apoptosis was detected by Flow cytometry. Gene and protein expression levels of K-Ras, c-Myc, MMP2, MMP9, and CXCR4 as metastatic genes evaluated using the RT-qPCR and Western blot, respectively.
Results: miR-622 is down-regulated in PC3 cells. As expected, miR-622 relative expression levels were as follows: miR-622 mimic > NC and NC inhibitor > miR-622 inhibitor ($P< 0.01$). Importantly, we showed that transfected miR-622 mimic could suppress the motility of PC3 cells, while transfected miR-622 inhibitor could promote cell proliferation ($P< 0.01$). Furthermore, overexpression of miR-622 resulted in enhanced apoptotic rate in the miR-622 mimic group compared with the miR-622 inhibitor group. Also, overexpression of miR-622 could increase significantly down-regulated the MMP2, MMP9, CXCR-4, c-Myc, and K-Ras expression levels ($P< 0.05$).
Conclusion: Our findings demonstrate a novel mechanism by which miR-622 modulates the metastasis of PCa cells. These results confirm the tumor-suppressive effect of miR-622 in PC3 cell line by reducing cell migration and metastasis.
Keywords: Prostate Cancer; miR-622; Migration; Metastasis.

(18427)
Expression analysis of beta-secretase 1 (BACE1) enzyme in peripheral blood of patients with Alzheimer's disease

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Background: Recent evidence has indicated that beta-secretase 1 (BACE1) is involved in the production of amyloid beta (Aβ) in patients affected with Alzheimer's disease (AD). Therefore; the purpose of this study was to measure mRNA and plasma levels of BACE1 in AD patients, as an early diagnosis biomarker for such individuals.

Methods: A total number of thirty AD patients and thirty normal subjects as controls were recruited in the present study. Plasma levels of BACE1 were then examined via enzyme-linked immunosorbent assay (ELISA) and also mRNA expression of BACE1 in total blood was measured using real-time PCR technique.

Results: The findings revealed a significant difference in gene expression of BACE1 in the peripheral blood of AD patients compared with that in controls ($p<0.0001$). Additionally, elevated plasma levels of BACE1 were found in AD patients compared with those in normal subjects ($p<0.01$). Statistical analyses also demonstrated no correlation between expression (mRNA and protein) of BACE1 in both AD patients and controls and age or the results of Mini-Mental State Examination (MMSE) scale ($p>0.05$).

Conclusion: Given the importance of early diagnosis of AD patients, it was suggested that the measurement of plasma levels and also mRNA expression of BACE1 might be a valuable blood-based biomarker used in preference to other invasive diagnostic methods such as cerebrospinal fluid (CSF) analysis.

Keywords: Alzheimer's disease; Beta-Site APP-Cleaving Enzyme 1; Biomarker.

(18016)

Effect of Dimethyl fumarate Loaded-PLGA Nanoparticles on Expression of *IL-1, IL-6, and TNF-α* Genes in Murine Splenocytes

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Introduction: Conventional systems for drug delivery in the body have a number of problems and limitations. Therefore, in pursuit of an approach to overcome these limitations, controlled and targeted drug delivery systems were proposed, which have several benefits such as reduced period of drug consumption by the patient, a more uniform effect of medication, decreased drug side effects and so forth. The aim of this study was to design and synthesize a PLGA formulation targeted with CD40 monoclonal antibody, which has suitable physicochemical properties as a DMF drug delivery system having minimal cytotoxicity. Therefore, this research was performed to determine the effect of Anti-CD40mAb-DMF-NPs on the expression of IL-1β, IL-6 and TNF-α cytokine genes in mouse splenocytes.

Materials and Methods: In this experimental study, mouse splenocytes were first purified and cultured. Then, PLGA nanoparticles containing dimethyl fumarate conjugated with CD40 antibody were designed and tested for the first time. The loading efficiency of DMF within nanoparticles as well as their physicochemical characteristics was measured and the morphology of PLGA and complexes formed with DMF were examined by scanning electron microscopy (SEM). The toxicity of different groups, namely free PLGA, free DMF, DMF-containing PLGA, PLGA conjugated with DMF-containing antibody, was evaluated by MTT assay. QRT-PCR method was subsequently used to assess the effect of the mentioned groups on the expression of IL-1β, TNF-α and IL-6 genes.

Results: In the present study, a new low-risk method was investigated that may be effective in treating MS. PLGA formulations conjugated with mAbCD40 were loaded with DMF drug that showed little cytotoxic effect against mouse splenocytes. After treatment of the cells with DMF alone or with polymer carriers, the expression of IL-1β, IL-6 and TNF-α cytokine genes was significantly reduced. The decrease in expression was higher in the antibody-targeted nanoparticles group relative to other treatment groups.

Discussion and Conclusion: There is a two-way communication between the nervous system and the spleen, and the activity of immune cells is regulated by noradrenaline released in the spleen. In turn, the activity of the nervous system is adjusted by IL-1 and TNF-α splenic cytokines. According to these evidences, the therapies based on targeted drug-carrying nanoparticles are expected to be an effective system for multiple sclerosis and other inflammatory diseases such as splenic rheumatoid arthritis. Such drug delivery system is targeted, safe and applicable as a new systematic treatment method. Our results in this area are promising and provide a good basis for further future studies in this regard.

Keywords: Spleen Cells, PLGA, DMF, Multiple Sclerosis, mAbCD40

(16622)

The effect of targeted DMF loaded-PLGA nanoparticles on the pattern of cytokine expression in dendritic cells

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Background: Poly (lactideco-glycolide) (PLGA) nanoparticle can be used for drug delivery to enhance drug bioavailabity and bioresident through active targeting by nanoparticle antibody Conjugation. Dimethylfumarate (DMF) is an approved drug for MS treatment with immune-modulating effects on dendritic cells (DCs) and CD40 is a proper candidate for DCs targeting. In this study, we assessed the anti-inflammatory effect of targeted PLGA-nanoparticles containing DMF on murine bone marrow DCs (BMDCs).

Methods: DCs derived from C57BL/6 bone marrow stem cells using recombinant IL-4 and GM-CSF growth factors and confirmed by Flow cytometry. PLGA nanoparticles containing DMF was designed as a targeted carrier using CD40 monoclonal antibody performed by EDC and NHS using random-orientation conjugation. DMF entrapment and release, physicochemical and morphological characteristics and cytotoxicity were measured. The expression levels of IL-12p35, IL-23p19, IL-6 and IL-10 were measured by qRT-PCR after 24 and 48 hours.

Results: Treatment of BMDCs with the synthesized nanoparticles had no toxic effects on the cells and led to a decrease in the expression of IL-12p35, IL-23p19 and IL-6 inflammatory genes and to some extent an increase in IL-10 gene expression after 24 and 48 hours.

Conclusion: This study shows that DMF can effectively encapsulated by PLGA nanoparticles and delivered to DCs. We have shown that sufficient amounts of these nanoparticles can regulate the expression of inflammatory and modulatory genes in BMDCs.

Keywords: Multiple Sclerosis (MS), Dimethyl Fumarate (DMF), PLGA Polymer, Targeted delivery, Dendritic Cells.

(18116)

Coinhibition of CD73 and EZH2 molecules suppresses the growth and development of 4T1 breast cancer cells, in vitro

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Background: Account for 15-20% of all breast cancer cases, triple-negative breast cancer (TNBC), is one of the most aggressive types of breast cancer with poor prognosis, high metastatic potential, and invasiveness, and about 40% mortality rate during the first 5 years after diagnosis with limited therapeutic options which mean age at incidence is found to be 47.52±3 years. Emerging evidence reveals that EZH2 and CD73 are both overexpressed in breast tumors which lead to elevation of cancer hallmarks containing tumor proliferation, metastasis, and invasion through some important signal pathways including PI3K/Akt and Wnt/β-catenin pathways. Therefore, the present study aims to evaluate triple-negative breast tumor behaviors during targeted therapy by co-inhibition of EZH2 and CD73 molecules.

Method: In this study, by using well-characterized hyaluronate-PEG-Chitosan-Lactate (H-PCL) nanoparticles (NPs) which encapsulating CD73/EZH2 specific siRNA molecules, we repressed EZH2/CD73 biomarkers in 4T1 murine breast cancer cell line and investigate the effect of combination therapy on tumor cell properties comprises proliferation, metastasis, migration, apoptosis, and angiogenesis in vitro.

Results: our results demonstrated optimum physicochemical properties of the generated NPs cause to efficient delivery and release of siRNAs in target cancerous cells and consequently suppression of EZH2/CD73 expression. Here we reported that combination therapy with listed biomarkers impressively diminished cancer colony formation, metastasis, migration as well as angiogenesis. Furthermore, apoptosis was significantly induced in 4T1 cancer cells.

Conclusion: These findings support the hypothesis that silencing of EZH2/CD73 biomarkers can be a potent therapeutic method for TNBC treatment in vitro which should be further considered in vivo studies in the future. We believe that this research would offer novel clues into biomarker candidates for the treatment of TNBC patients.

Keywords: Nanoparticle, EZH2, CD73, Breast cancer

(18449)

Efficient neutralization of tetanus toxin by a single chimeric monoclonal antibody

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Background: Tetanus is a life-threatening disease characterized by muscle spasm caused by the neurotoxin of *Clostridium tetani*. Given the potential risks of the current passive immunotherapy of tetanus with human anti-toxin polyclonal antibody (PAb) and the limitation of this preparation, neutralizing monoclonal antibodies (MAbs), especially chimeric or human ones with reduced immunogenicity, might be considered as an alternative source.
Methods:A mouse-human chimeric MAb, designated c-1F2C2, was generated and its specificity with various recombinant fragments of tetanus toxin generated in E. coli was determined. In vivo toxin neutralizing capacity of c-1F2C2 was evaluated and compared with that of the commercially available human anti-toxin PAb in a mouse model. The possible mechanisms of the toxin neutralizing activity of the MAb were investigated by assessing its inhibitory effect on the toxin receptor binding, including GT1b ganglioside receptor and those expressed on PC12 cells.
Results: The in vivo neutralizing assay showed that c-1F2C2 was able to protect mice against tetanus toxin with an estimated potency of 100 IU/mg for c-1F2C2 compared to 19 IU/mg for human anti-toxin PAb. The MAb recognizes fragment C of the toxin, which is responsible for binding of the toxin to its receptor on neuronal cells. Accordingly, c-1F2C2 partially interfered with the toxin binding to its receptors on PC12 cells (37% inhibition of the toxin binding).
Conclusion: The chimeric MAb showed similar structural and functional activities to that of its murine counterpart. This chimeric MAb could be considered as an alternative to the commercially available human anti-toxin PAb for the passive immunotherapy of tetanus.
Keywords: Chimeric antibody, Monoclonal antibody, Polyclonal antibody, Tetanus toxin, Toxin neutralization

(18692)

Identification of fully human single chain Fragment variable Antibody against Interleukin-6 using Phage Display

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Background: Immunotherapy is one of the newest therapies in which immunological tools such as monoclonal antibodies, vaccines and immune cells are used. In the field of treatment, monoclonal antibodies are widely used to treat various types of cancers, inflammatory diseases, infectious diseases, and other disorders. Regarding the role of interleukin-6 in the onset and exacerbation of the symptoms of many cancers, inflammatory diseases and autoimmune diseases, the interleukin-6 inhibitors are a novel therapeutic strategy for these diseases.

Methods: In this study, the phage display method was used to identify the best phage clone against recombinant protein interleukin-6. Polyclonal phage ELISA, monoclonal phage ELISA, monoclonal antibody ELISA and electrophoresis of polyacrylamide gel were also used to determine the binding of selected phage clones and antibodies to the desired protein.

Results: Upon completion of each round of biopanning process and titration, titer reduction and the removal of non-specific phages indicated the accuracy of the panning process. The results showed that the phages obtained from the fourth round of panning had the highest absorbance compared to negative control. Of the 30 clones evaluated in the monoclonal phage ELISA, clones number 5 and 6 showed the highest absorption compared to bovine serum albumin (negative control) and were evaluated in monoclonal antibody ELISA.

Conclusion: Eventually, the band of single-chain Fragment variable antibodies from the selected clones in the region of 27 kDa was observed on the gel. After confirmation of in vitro and in vivo complementary tests, the selected antibodies have the potential to enter the field of treatment, become a commercial product and enjoy mass production in the country.

Keywords: Immunotherapy, Monoclonal antibodies, Interlukine-6, Phage display, Biopanning

(16711)

Design and optimization of a chimeric single-chain fragment variable (scFv) antibody against IL2Rα (CD25)

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Background: The IL-2Rα plays a critical role in maintaining immune function. However, expression and secretion of CD25 in the various malignant disorders and autoimmune diseases are now well established. Thus, CD25 is considered as an important target candidate for antibody-based therapy. The aim of this study was to design and optimization of a functional single-chain fragment variable (scFv) against IL2Rα (CD25) derived from the FDA-approved Daclizumab antibody and its production in a bacterial expression system.

Materials and Methods: Here, the anti-CD25 scFv with (Gly4Ser) 3 linker were constructed and cloned into pET-22b (+). Then, recombinant plasmids were transformed into *Escherichia coli* Bl21 (DE3) for expression using IPTG and Lactose as the inducers. Anti-CD25 scFv was purified from the periplasm, and detected by SDS-PAGE and Western blot. Afterwards, functionality was evaluated using ELISA.

Result: The results of SDS-PAGE, Western blot, and ELISA confirmed the accuracy of anti-CD25 scFv production and its ability to bind to the human CD25.

Conclusion: Conclusively, our work provides an experimental basis for production of an anti-CD25 scFv, which may be applied for various malignant disorders and autoimmune diseases.

Keywords: Single-chain variable fragment (scFv); CD25; IL-2Rα; Linker peptide, Daclizumab.

(18591)

Quantum Dot-labeled Tags Improve Minimal Detection Limit of CA125 in Ovarian Cancer Cells and Tissues

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Background: Most ovarian cancers (OC) are diagnosed in advanced stages, while early detection have increase survival rate of over 90%. The aim of this study was introduction of a more sensitive diagnostic technique of CA 125, as well-known tumor markers of OC, based on quantum dot (QD) nanoparticles, as fluorescent sensors and study of potential capacity of this probe in early diagnosis of OC.

Methods: Using a homemade anti-CA125 mAb and QD525- or FITC-labeled probes, immunofluorescent staining of CA125 biomarker was performed in an ovarian cancer cell line and cancer tissues. Samples are illuminated with excitation filters 460-495nm/330-360nm and 460-495nm for QD525 and FITC, respectively. Fluorescent signals were inspected with an emission filter of 525 nm. Exposure time for each excitation/emission filter set was optimized in reference to negative control slides of the same staining procedure. Digital images for each fluorophore were captured at and analyzed by Image J software. The optical properties of fluorophores were compared qualitatively and quantitatively.

Results: Our results showed that besides lower background and exceptionally higher photobleaching resistance, QD525 exhibited higher fluorescent intensity for both ovarian cancer cell and tissues at different exposure times ($p<0.0001$) and excitation filter sets ($p<0.0001$) exemplified by significantly higher staining index ($p<0.016$). More importantly, the FITC-labeled probe detected antigen-antibody complex at minimum concentration of 0.3µg/mL of anti-CA125, while reactivity limit decreased to 0.078µg/mL of anti-CA125 when QD525-labeled probe was applied showing four times higher reactivity level of QD525 probe compared to the same probe labeled with FITC.

Conclusion: QD-based detection systems possess undeniable superiority over wavelength-matched conventional dyes. It seems that QDs are inimitable tags for sensitive detection and quantitatively and qualitatively improve detection of CA125 expression in both ovarian cancer cells and tissues.

Keywords: Carcinoma antigen 125; Minimal reactivity limit; Neoplasm micrometastasis; Ovarian neoplasms; Quantum dots; Sensitivity

(16792)

Protection against *Acinetobacter baumannii* infection by novel anti outer membrane protein A (Omp A) monoclonal antibody (MAb)

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Background: *Acinetobacter baumannii* is renowned for an escalating global health threat in emerging epidemics because of its propensity to develop resistance against antimicrobial agents. This opportunistic bacterium can live on the skin or respiratory mucosa and is a type of nosocomial pathogens, so its prevention and control has become a sensitive issue. Outer membrane protein A (Omp A) has multiple roles in interacting with the host during infection, and thus represents an attractive target for the development of novel antibacterial therapies. Producing high affinity monoclonal antibody (MAb) against Omp A provides a powerful tool to monitor and tracing different models of *A. baumannii* in natural systemic infections.

Objectives: In this study we aimed to produce a novel murine MAb with the ability of specific recognition of the OmpA-peptide arm of *A. baumannii.*

Methods: Mice were immunized with a synthetic peptide corresponding to the outside surface of β-barrel Omp A conjugated with a carrier protein. Antibody-producing cells were produced by a standard protocol and screened for positive reactivity by enzyme-linked immunosorbent assay. Reactivity of selected mAb was then assessed by Western blotting, indirect immunofluorescence assay, flow cytometry, and opsonophagocytic killing assay.

Results: Produced MAb showed specific reactivity with the peptide in ELISA and native OmpA in immunofluorescence assay and flow cytometry. No reactivity was observed with other Gram-negative bacteria like *Escherichia coli.* The purified mAb enhanced opsonophagocytic killing of the *A. baumannii* especially accompany with complement system.

Conclusion: The results of experiment showed that the native OmpA located on surface of *A. baumannii* can be detected with our produced MAb. This novel anti-OmpA MAb can be used for tracing of OmpA in mentioned laboratory techniques and has potential for investigating the multiple roles of OmpA in *A. baumannii* pathogenesis.

Keywords: *Acinetobacter baumannii*, monoclonal antibody, outer membrane protein A, ELISA, flow cytometry, in immunofluorescence assay, opsonophagocytic killing

(18586)

Production and immunohistochemical characterization of mouse monoclonal antibodies specific for the human tumor-associated antigen Ki67

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Background: Identification of tumor-associated antigens is considered as an important tool for cancer diagnosis.*Ki67* is a nuclear protein which is closely linked to the active phases of cell cycle. Expression of Ki67 is strongly associated with tumor growth and cell proliferation and is commonly used as a proliferation marker in routine pathological investigations. This study describes the generation and characterization of mouse monoclonal antibodies (MAbs) against the human Ki67 protein.
Methods: Peptides from certain sequences of the protein were designed, synthesized and coupled tothe carrier KLH protein. Spleen cells from peptide immunized BALB/c mice were fused with a mouse myeloma cell line and hybrid cells were selected on HAT selective medium. Stable hybridoma cells were screened by ELISA using BSA-conjugated peptides and subsequently cloned. Hybridoma clones were cultured and MAbs were purified by affinity chromatography and their isotype was determined by ELISA.The specificity and reactivity of these MAbs was assessed by immunohistochemistry (IHC).
Results: Thirteen productive hybridoma colons were established of which five MAbs were able to detect the target antigen by IHC. These MAbs were further tested on paraffin-embedded tissue sections from different patients with breast cancer as well as normal tonsil to approve their specificity and IHC applicability.
Conclusion: Our findings indicate that these novelKi67 specific MAbs which have been established for the first time in Iran may serve as suitable diagnostic tool for cancer diagnosis.
Keywords: Monoclonal antibody, Ki67, Immunohistochemistry, Cancer diagnosis

(18144)

Evaluation of two genomic DNA extraction method from fecal samples of patients with colorectal cancer

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Background: Stool DNA evaluation is one of the most successful non-invasive strategies for screening for gastrointestinal diseases, especially colorectal cancer (CRC) in people at moderate risk. In this process, without the need to take a biopsy sample from the organism, the DNA of epithelial cells isolated from the gastrointestinal tract is extracted and the mutated genes involved in causing the disease are easily evaluated using molecular methods. Non-invasive, high sensitivity and cost-effectiveness are the advantages of this methods. In this research, fecal samples of CRC patients were investigated manually and using a commercial Stool DNA isolation mini kit to compare the consistency of the extracted DNA.

Materials and Methods: About 2-3 grams of feces were collected to obtain the necessary DNA from every 10 volunteers with colorectal cancer. Spectrophotometric methods were used for analysis after DNA extraction and inspection of the samples in terms of DNA purity and ensuring non-contamination. Then using ARMS-PCR, the samples were analyzed for mutations in the K-RAS gene.

Results: ARMS-PCR results showed that there was no substantial difference in the consistency and quantity of amplification of the fragments of the K-RAS gene in the two manual extraction and commercial kit methods. **Conclusion:** Considering the effectiveness of genomic DNA extraction method from patients' fecal samples manually and quickly, as well as its low cost, it can be concluded that if DNA extraction kits are not available, low-cost manual methods can be used.

Keywords: Stool, K-Ras, CRC, DNA extraction

(18334)

Construction of eukaryotic expression vector harboring HIV-1 Nef linked to the C-terminal of heat shock protein 70

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Background: Development of a potent HIV-1 vaccine is a main priority for improving human health worldwide. The HIV-1 Nef protein was known as an attractive antigenic candidate in vaccine development. The Nef protein is thought to increase viral replication and infection through a combination of various functions. Recent reports have shown that heat shock proteins (HSPs) interact with viral particles. HSPs are generated in response to stress and act to help protein folding so-called as chaperones. In this study, a eukaryotic expression vector harboring HIV-1 Nef linked to the C-terminal of heat shock protein 70 was constructed using molecular cloning.

Methods: At first, the cloning of the C-terminal of *hsp70* gene (*C-hsp70*) was done in pET-*nef* prokaryotic vector. The process included primer design, PCR, digestion with restriction enzymes, ligation between linear pET-*nef* and *C-hsp70* gene, transformation and confirmation. After preparation of pET-*C-hsp70-nef*, the *C-hsp70-nef* gene was inserted into the linearized pcDNA3.1 through subcloning method. The pcDNA-*C-hsp70-nef* vector was detected by agarose gel electrophoresis. The confirmation of pcDNA-*C-hsp70-nef* was performed by digestion, PCR and sequencing.

Results: The pcDNA-*C-hsp70-nef* was confirmed by PCR and digestion as a clear band of ~ 1048 bp related to *C-hsp70-nef* gene on agarose gel.

Conclusion: Generally, the *C-hsp70-nef* DNA fusion was successfully cloned in pcDNA3.1 vector for development of DNA vaccine candidate.

Keywords: HIV-1, Nef, Heat shock protein, pcDNA3.1 eukaryotic vector, cloning

(18135)

Expression of two Long non-coding RNAs (LncRNA), PWRN1 and TTTY14 as prognostic markers in colorectal cancer

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Abstract:
Colorectal cancer is the most common cancer of the digestive tract and is the common cause of death from gastrointestinal cancer worldwide. This cancer is in women in 3th position in ranking after lung and breast cancer, and in men after lung and prostate cancer. Despite the improvements in treatment such as radiation therapy and chemotherapy, these patients are still facing a major challenge to improve survival and quality of life. Today, one of the important factors in the study of cancers is genetic factors in both aspects of prognosis and treatment, and among them, LncRNAs are in the focus of researchers in recent years.
The impress of LncRNAs as tumor suppressors or oncogenes has been demonstrated in several types of cancers. Recent researches have disclosed that LncRNAs transcripts play a pivotal role in the tumorigenesis. Many LncRNA are tissue and cancer-type specific and have already revealed to useful as prognostic.
In this review, we focus on recent finding concerning aberrant expression of two LncRNAs (PWRN1 and TTTY14) in CRC tumors and emphasize their prognostic potential in CRC. Bioinformatics studies show that these two LncRNAs are involved in gastric and prostate cancers, and they are also involved in colorectal cancer, both of which are involved in the PTEN / Akt / MDM2 / p53 pathway. The results showed that these two LncRNAs (PWRN1 and TTTY14) could be novel prognostic markers for colorectal carcinoma and the present study aimed to provide novel insight into the diagnosis and treatment of colorectal cancer.
Keywords: colorectal cancer, long non-coding RNA, LncRNA, PWRN1, TTTY14

(18136)

Bioinformatics analysis of gene signaling pathways of CASP3 with respect to SNP (rs1049216) in targeting miRNA (hsa-miR-4760-3p) related to colon cancer.

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Background: Considering the limitations of the common diagnostic test for colon cancer, the introduction of higher-specific biomarkers for a more accurate and timely diagnosis of colon cancer is desired. Identification of meaningful microRNA (miRNA) or representative biomarkers related to the pathological stage of colon cancer helps to predict prognosis and reveal the mechanisms behind cancer progression. Bioinformatic methods could identify a set of SNPs within miRNA binding sites of inflammatory genes, and provide data and direction for subsequent functional verification research. In this study, we aimed to investigate the SNP (rs1049216) of gene (CASP3) with miRNA (hsa-miR-4760-3p) and the target genes using bioinformatics prediction tools in order to propose potential diagnostic biomarkers for colon cancer.

Methods: In this theoretical study, based on bioinformatics study of micro RNA, miRNA target prediction databases (MirSNP, miRNASNP 2.0, Mirwalk and Mirbase) were used to predict miRNA target sites.

In addition, using the DAVID software, cellular signaling pathways were Identified in KEGG.

Results: In this study, the hsa-miR-4760-3p is predicted to have a higher binding capacity to the rs1049216 mutant (A) allele than to the dominant (G) allele of this SNP and may therefore be a risky mutant allele and cause cancer. The results showed that hsa-miR-4760-3p plays an important role in pathways like colon cancer and apoptosis.

Conclusion: These findings help to advance the understanding of apoptosis in the progression of colon cancer and provide prognostic biomarkers as well as therapeutic targets.

Keywords: colon cancer, CASP3, miRNA, hsa-miR-4760-3p, rs1049216

(16905)

Bioinformatics approach via effect of rs8063 on UBE2I gene, hsa-miR-1237 in Hepatocellular carcinoma (HCC)

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Background: Hepatocellular carcinoma is one of the most lethal malignant tumors worldwide and one of the most common cancers in men.
Surgery is the only treatment available for it; however, it can be performed only in 10-15% of patients. The development and progression of Liver cancer are primarily the results of uncontrolled regeneration of liver cells.
Today, bioinformatics is used to analyze biological problems to increase our understanding of biological processes through mathematical and statistical algorithms.
MicroRNAs are a small group of non-coding RNAs, ranging from 18 to 25 nucleotides in length, which can suppress the translation of proteins. Besides, SNPs are the simplest and most widely used method for determining markers in genetic studies.
Methods: This study aimed to analyze genetic factors associated with liver cancer, including the interaction between mRNA-miR-LncRNA and SNP related to this network. GEO analysis identified 250 differentially expressed genes involved in the signaling pathway of RNA transport.
Results: The findings revealed that Hsa-miR-1237 suppresses the UBE2I gene, and their interactions were affected by rs8063. However, this miR competes for adhesion to chr22-38_28785274-29006793.1 and KCNQ1OT1. Finally, these findings can lead to the development of an effective biomarker or diagnostic model in the diagnosis and treatment of HCC.
Conclusion: The present study examines the UBE2I gene as one of the most critical genes in the development of HCC.
Keywords: Hepatocellular carcinoma , Liver , Liver cancer , HCC , UBE2I , GEO , mRNA , miR , LncRNA , SNP

(18751)

Optimization of an in-House Elisa for detection of mouse ovalbumin specific IgG

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Background: Allergic diseases are one of the most critical health issues in the world. Allergen-specific antibodies are considered a prognostic factor. IgG-blocking antibodies can modulate allergic inflammation, and assessment of these antibodies is essential to enlighten disease pathogenesis. Ovalbumin induced mouse model of allergy is a current model for investigational purposes. This study aimed to develop an Elisa method for the detection of mouse OVA-specific IgG.

Methods: In the process of ELISA optimization, optimal dilutions of ovalbumin coated on plate, serum, anti-mouse IgG conjugated with HRP along with a selection of efficient blocking buffer and washing steps of microtiter plates were studied. Female Balb/c mice were sensitized by intraperitoneal injection of ovalbumin. Induction of immune response confirmed by OVA-specific IgE Eliza kit and allergic symptoms. Sera were collected from the healthy and sensitized mice then used as negative and positive samples, respectively.

Results: The optimal condition of the experiment was chosen based on signal to noise ratio. In summary, the optical density of the negative sample and blank wells showed OD 450 < 0.2 in the optimized method. Three µg/well showed the best results among the ovalbumin amounts, and 1% BSA buffer clearly blocked the plate. The best incubating condition was overnight at four °C and 120 min for blocking at room temperature. Moreover, the optical density (OD) values of serial dilution of positive samples correlated with their titers significantly.

Conclusion: This optimized in-house Eliza kit for detection of OVA-specific IgG showed reliable results and can be used as a cost-effective substitute for the commercial kit.

Keywords: Ovalbumin, Elisa

(18354)

Design of a prokaryotic expression vector harboring HIV-1 *nef* gene fused to the N-terminal of heat shock protein 70

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Background: Human immunodeficiency virus (HIV) causes the potentially life-threatening and chronic disease called as acquired immune deficiency syndrome (AIDS). Nef protein plays a role in the early stages of virus replication and the progression of AIDS. On the other hand, extracellular heat-shock proteins (HSPs) interact with the immune system in a very complex manner. The N-terminal ATPase domain of HSP70 made it important as an effective adjuvant. HSPs are significant modulators of antigen presentation, cytokine production, T-lymphocyte activation, and NK cell killing in response to both intracellular and extracellular physiological stress.
Methods: In this study, the *hsp70* gene was synthesized in pUC57 vector. The N-terminal of *hsp70* gene (*N-hsp70*) was amplified by PCR with specific primers. The PCR product was digested by *Nde*I/*Eco*RI enzymes and cloned in the linearized pET23a-*nef*. The recombinant pET-*N-hsp70-nef* was confirmed by PCR, digestion and sequencing. The purification and concentration of the recombinant vector was determined by NanoDrop spectrophotometry.
Results: The pET-*N-hsp70-nef* was confirmed by PCR and digestion as a clear band of ~1808 bp related to *N-hsp70-nef* gene on agarose gel. The concentration of purified plasmid was about 250 ng/µL.
Conclusion: Briefly, the *N-hsp70-nef* DNA fusion was successfully cloned in pET23a vector for generation of the recombinant fusion protein.
Keywords: HIV-1, Nef, Heat shock protein, prokaryotic expression vector

(18028)

Immunotherapy with Indoleamine 2, 3-dioxygenase (IDO) inhibitor nanoliposomes improves the tumor microenvironment and enhances anti-tumor immunity

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Background: The catabolism of tryptophan by indolamine-2, 3-dioxygenase (IDO) is one of the major metabolic pathways in cancer progression that leads to suppression and induces tolerance of the immune system. Inhibition of IDO has been considered in the treatment of many cancers, including colorectal cancer (CRC). Epacadostat is a potent and selective inhibitor of IDO1 enzyme. In the present study, to improve the pharmacokinetics of Epacadostat and subsequently reduce the dose, side effects, and treatment costs, a nanoliposomal form of Epacadostat was prepared and its effect on CRC was evaluated.

Methods: Liposomes were synthesized and using the remote loading method, Epacadostat loaded on the liposomes. Physicochemical properties of liposomes include morphology, size, surface charge or zeta potential, total phospholipid content of nanoliposomes, and intra-liposomal concentration of the drug were evaluated. For in vivo experiments, after induction of colorectal cancer in mice, they were treated with the free or liposomal forms of Epacadostat and monitored for tumor size and survival. To evaluating immune responses, immune cells including T helper, Cytotoxic T lymphocytes (CTLs), and regulatory T cells were analyzed using flow cytometry. Also, IFN-γ production was assessed using IFN-γ ELISpot assay.

Results: Both the TCD8 + and TCD4 + lymphocyte populations isolated from the spleen and tumor of mice receiving liposomal Epacadostat produced higher levels of IFN-γ compared to the other groups ($P < 0.05$). However, the population of Treg cells in this group decreases. In addition, in mice treated with liposomal Epacadostat, tumor growth was reduced ($P_{value} < 0.05$) and survival was significantly increased ($P_{value} < 0.05$) compared with controls.

Conclusions

Compared to free Epacadostat, nano-liposomal Epacadostat improves the immune response, IFN.λ production and increased survival in the colorectal model.

Keywords: Colorectal cancer (CRC), indoleamin-2, 3-dioxygenase (IDO), Nanoliposome, Epacadostat

(18491)

Chitosan as an efficient non-viral transfection vehicle for miR-155 delivery

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Background: MiR-155 plays a crucial role in the regulation of development and effector functions of B and T cells. Its upregulation can convert M2 macrophages with anti-inflammatory and pro-tumorigenic activities into pro-inflamatory, anti-tumor M1 macrophages. In order to access their target sites/cells, miRNAs should overcome several challenges including nuclease degradation, phagocytosis by immune cells as well as renal clearance. Additionally, efficient cellular uptake is also of great importance. Chitosan's capability of spontaneously forming stable complexes with genetic materials as a consequence of cooperative electrostatic interactions between its positive amino groups and the negative phosphate groups of DNA and RNA, has made this polymer an appropriate candidate for vehicle-mediated immunomodulatory applications.

Methods: In this study, we examined the potential of chitosan nanoparticles (CNPs) in the delivery of a miR-155-encoding plasmid DNA (pDNA). CNPs were prepared by ionic gelation and coacervation methods. Then, these CNPs were characterized for size, morphology and surface charge. Their pDNA loading capacity and ability to protect pDNA against degradation by DNaseI (as a nuclease) as well as transfection efficiency in RAW 264.7 macrophages were assessed.

Results: Our results indicated the high capability of CNPs to protect the pDNA from DNaseI degradation. We observed that with the increase in the N/P ratio, CNPs size decreased while CNPs zeta potential increased. Besides, these CNPs showed an appropriate transfection efficiency in Raw 264.7 macrophages.

Conclusion: It is concluded that CNPs prepared using the coacervation method can efficiently incorporate and protect pDNA from degradation. These nanoparticles are suggested to serve as proper vehicles for miR-155 delivery to modulate immune responses.

Key words: Chitosan, Coacervation, Ionic gelation, CNP

(16578)

Effects of nano-resveratrol on mesenchymal stem cells from multiple sclerosis patients: proliferative and anti-apoptotic activities

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Background: Multiple sclerosis (MS) is a disabling disease of the brain and spinal cord that the immune system attacks the sheath (myelin) covering nerve fibers. There is no effective cure for stopping progression of MS. Mesenchymal stem cells (MSCs), as immunomodulatory agent, attracted worldwide attention for the neurologic disease. In the last decades, resveratrol (*trans*-3, 4', 5 tryhidrostilbene), a natural polyphenolic phytoalexin from fruits and vegetables with multiple health benefits has received considerable attention, especially for its neuroprotective and anti-cancer and anti-inflammatory activities. However, poor systemic bioavailability and insolubility of resveratrol limited its clinical use while, the nano-formulations of resveratrol removed these shortcomings. In the present study, we identified comparative proliferation and anti-apoptotic effects of nano-resveratrol and free resveratrol on adipose-derived MSCs (AT-MSCs).

Methods: AT-MSCs was isolated form MS patient and characterized (immunophenotyping and conderogenetic and adipogenetic potential). Moreover, gold nanoparticles were synthesized and characterized. The effects of nano-resveratrol and free resveratrol were evaluated by MTT and flow cytometry assays to evaluate the percentage of proliferation and apoptotic death of MSCs.

Results: According to the data, low concentrations of both nano-resveratrol (1.25, 2.5, 5µM) remarkably enhanced MSCs viability. They also protected ATMSCs against apoptosis at concentrations of 2.5 and 5 µM.

Conclusion: Our findings demonstrated efficacy of resveratrol and the nano-formulation on AT-MSCs with a better effect toward nano-resveratrol. We concluded that nano-resveratrol may considerate as complementary treatments for the MS patients who have received MSCs.

Keywords: Adipose-derived mesenchymal stem cells, Multiple sclerosis, Nano-resveratrol

(18788)

Preparation and *in-vitro* evaluation of pH-responsive cationic cyclodextrin coated magnetic nanoparticles for delivery of methotrexate to the Saos-2 bone cancer cells

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Background: Osteosarcoma, as a common malignant neoplasm in children and adolescents, still remains a challenge for conventional therapeutic regimens. In the meantime advent of innovative and revolutionary techniques such as drug delivery systems and smart nano-biomaterials seems promising in tackling these complications.
Methods: In this study, we designed a smart nano-system consisting of a magnetic inner core and polymeric outer shell with cationic moieties for targeted delivery and enhanced uptake of methotrexate anticancer agent for Saos-2 cell line. The designed nano-formulation was characterized and its drug loading capacity and drug release profile were studied as well that about 60% of methotrexate was released in the first 12 h. The efficacy of the nano-formulation in killing cancer cells was assessed using MTT, cellular uptake, and uptake flow-cytometry.
Results: Our *in-vitro* results confirmed the prepared nano-system has a potential for delivery of anticancer drugs against the Saos-2 cell line and suggests more investigations such as *in-vivo* tests to be implemented.
Conclusion: All results persuaded us to suggest this biocompatible nano-system for therapeutic biomedical applications.
Keywords: Cationic nanoparticles, Drug delivery systems, Osteosarcoma, Methotrexate

(18619)

Effects of silver and zinc oxide nanoparticles against drug-resistant Mycobacterium tuberculosis

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Background: Tuberculosis (TB) is among the top three fatal infectious diseases and is considered as a significant global health threat. Emergence of 457 000 new cases with multidrug-resistant TB (MDR-TB) in the year 2017 worldwide, shows that drug-resistant TB is still a main challenge for treatment of TB. The goal of current study was to determine the antimicrobial effects of silver and zinc oxide nanoparticles against drug-resistant Mycobacterium tuberculosis (MTB).

Methods: In current study, silver and zinc oxide nanoparticles were synthesized by the chemical reduction and chemical deposition methods. By broth microdilution and agar microdilution methods, we determined minimum inhibitory concentration and minimum bactericidal concentration of silver and zinc oxide nanoparticles on MTB isolates.

Results: Activity of several concentrations of silver and zinc oxide nanoparticles against MTB isolates were evaluated. The results of MIC demonstrated that 1 µg/mL of both silver and zinc oxide nanoparticles can inhibit growth of XDR-MTB. Moreover, the concentrations of 4 µg/mL silver nanoparticles had inhibitory effect on MDR-MTB. Unfortunately, silver and zinc oxide nanoparticles could not kill MDR-MTB and/or XDR-MTB.

Conclusion: Our study is one the few investigations which carried out during recent years on effects of silver and zinc oxide nanoparticles against MDR and XDR MTB isolates. Due to in current survey silver and zinc oxide nanoparticles had bacteriostatic effects against drug-resistant MTB isolates, they may be considered as promising antibacterial agents. Although, more investigations should be done to affirm the bactericidal effects of them on TB.

Keywords: Tuberculosis, silver, zinc oxide, nanoparticles

(18477)

In vitro functional evaluation of single-chain recombinant antibodies against dimerization domain of EGFR

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Background: Coexpression of EGFR and HER2, belonging to the ErbB family of receptors, has been observed in many cancers, in which EGFR appears to compensate for the HER2 signaling pathway that causes resistance to therapeutic antibodies, such as Herceptin. We previously produced a recombinant single-chain variable fragment (scFv) antibody against the EGFR dimerization domain. Here, we evaluated the functions of the produced scFv.

Methods: A recombinant scFv was generated using a prokaryotic system and purified by affinity chromatography. Cell-ELISA was used to evaluate the binding of the purified antibodies to the receptors and confirmed by in silico methods. MTT assay was used to show the effect of the scFv in the killing of normal and cancerous cells. Moreover, the effect of the scFv on STAT3 phosphorylation, as a part of the EGFR signaling pathway, and the expression of apoptotic-related genes were evaluated using immunoblotting and qRT-PCR, respectively. Finally, inhibition of EGFR and HER2 dimerization by the produced scFv was evaluated, using the dimerization inhibition test.

Results: The scFv was able to significantly reduce the proliferation and survival of MCF7, MDA-MB-468, and SKOV3 cancer lines, while it did not affect the normal VERO line. Moreover, it was able to inhibit STAT3 phosphorylation, and also reduce the expression of anti-apoptotic genes, such as Bcl2 and increased pro-apoptotic genes, such as Bax. Finally, the dimerization inhibition test confirmed the capacity of the scFvs to inhibit EGFR and HER2 dimerization.

Conclusions: Considering the importance of simultaneous targeting of the ErbB family of receptors, recombinant antibodies against the dimerization domain of the EGFR could be considered as useful tools in the treatment of breast cancer as well as other cancers expressing EGFR.

Keywords: EGFR, HER1, HER2, scFv

(17983)

Single-Chain Variable Fragment-Based Bispecific Antibodies: Hitting Two Targets with One Sophisticated Arrow

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Despite the success of monoclonal antibodies (mAbs) to treat some disorders, the monospecific molecular entity of mAbs as well as the presence of multiple factors and pathways involved in the pathogenesis of disorders, such as various malignancies, infectious diseases, and autoimmune disorders, and resistance to therapy have restricted the therapeutic efficacy of mAbs in clinical use. Bispecific antibodies (bsAbs), by concurrently recognizing two targets, can partly circumvent these problems. Serial killing of tumor cells by bsAb-redirected T cells, simultaneous blocking of two antigens involved in the HIV-1 infection, and concurrent targeting of the activating and inhibitory receptors on B cells to modulate autoimmunity are part of the capabilities of bsAbs. After designing and developing a large number of bsAbs for years, catumaxomab, a full-length bsAb targeting EpCAM and CD3, was approved in 2009 to treat EpCAM-positive carcinomas besides blinatumomab, a bispecific T cell engager antibody targeting CD19 and CD3, which was approved in 2014 to treat relapsed or refractory acute lymphoblastic leukemia. Furthermore, approximately 60 bsAbs are under investigation in clinical trials. The current review aims at portraying different formats of the single-chain variable fragment (scFv)-based bsAbs and shedding light on the scFv-based bsAbs in preclinical development, different phases of clinical trials, and the market.

Keywords: monoclonal antibody, single-chain variable fragment, bispecific antibody, cancer, HIV-1, bacteria, ESKAPE, autoimmune diseases

(16718)

Isolation and evaluation of single chain variable fragment of antibody (scFv) against receptor 2 vascular endothelial growth factor from phage human antibody library

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Background: 1- Can a single-chain phage antibody (scFv) be isolated from the Tomlinson I library in terms of specific antibody against ocular vein (VEGFR-2)
2- Are the isolated antibody clones of the required diversity?
3- Can the isolated antibodies be obtained with the right purity and amount in the bacterial host?
4- Is the recombinant scFv antibodies isolated ability to detect differential expression of VEGFR2 cells from cells lacking it will have.
5- Is recombinant antibodies capable of inhibiting angiogenesis will be isolated
Methods: Solution phage bio-panning and screening was performed in order to isolate scFv against two conserved of VEGF. Characterization of scFv are carried out by immunoblotting and SDS-PAGE.
Results: After four stages of planning and selection, phage enrichment during polyclonal ELISA significantly increased the amount of optical absorption in the fourth step of Panning compared to the first, second and third phases. Seven of the 10 clones were confirmed by PCR screening and subsequent steps, including expression, purification, were successfully performed.
Conclusion: The project produced recombinant phages capable of delivering antibodies to their surface. Based on the findings, this antibody can potentially be used in treatment, diagnosis, targeted pharmacy as well as laboratory diagnostic tests
Keywords: Scfv, Paninng, VEGFR2, Selection
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(18773)

Study serum levels of interleukin 17 in type 2 diabetic patients by type of treatment

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Introduction: Diabetes is the most common metabolic disorder that increases the morbidity and mortality in patients. Therefore, identifying the effective factors for finding effective treatment is essential. These factors include cytokines.

Objective: The aim of this study was to evaluate serum levels of interleukin-17 in type 2 diabetic patients by treatment.

Methods: This study was performed on 80 diabetic patients. After obtaining patient consent and demographic data, serum IL-17 level was also recorded. Chi-square and Mann-Whitney tests were used to compare the data.

Results: The results of our study showed that the mean serum level of interleukin 17 in patients with FBS more than 125 was significantly higher than in individuals with FBS less than 125 and the mean serum level of interleukin 17 in patients without medication was significantly higher than A person was on medication, which was significant in women after grouping patients by age and sex. Finally, there was a significant positive correlation between interleukin-17 and fasting blood sugar levels

Conclusion: Based on the findings of the present study, it can be concluded that IL-17 is involved in the physiopathology of diabetes and may be a therapeutic target.

Keywords: Diabetes, IL-17, Treatment

(18701)

Evaluation of pleural fluid T helper cells subtypes and Adenosine deaminase for tuberculous pleural effusion

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Background: Tuberculous pleural effusion (TPE) is one of the most common forms of extrapulmonary tuberculosis. Patients with tuberculous or malignant pleural effusions (MPE) frequently have similar pleural fluid profiles. **Objective**: We aimed to determine the diagnostic value of T helper (Th) subtypes in the PE as markers for differential diagnosis of TPE.

Methods: 30 patients with TPE, 30 patients with MPE, 14 patients with empyema (EMP) and 14 patients with parapneumonic effusion (PPE) were enrolled between Dec 2018-2019 at referral center of Masih Daneshvari Hospital, Tehran, Iran. The frequency of CD4+IL-9+, CD4+IL-22+, CD+IL-17+ and CD4+CD25+FOXP3+ T cells were determined by flowcytometry. Besides, the level of Adenosine deaminase (ADA) was measured in pleural fluids.

Results: We found TPE character with CD4+CD25+FOXP3+ T cells (optimal cut-off value =13.6 (%), sensitivity 90%, specificity 75.86%). However, in compared to ADA (cut off value 27.5 (IU/L), sensitivity 90%, specificity 96.5%), these cells had less specificity. A high frequency of CD4+IL-9+ (cut off value= 12.35, sensitivity 90%, specificity 55.17%), CD4+IL-22+ (cut off value= 35.6 (%), sensitivity 90%, specificity 27.59%) and CD+IL-17+ (cut off value= 8.55 (%) sensitivity 56.67%, specificity 65.52%) were also predictive of TPE. **Conclusion**: The current data suggests that high CD4+CD25+FOXP3+ T cells subtype able to differentiate between TPE and non-TPE. Further studies with multicenter with high participants need to be addressed.

Keywords: Tuberculous pleural effusion, T helper, ADA

(18689)

Circulating tumor DNA (ctDNA); a potential marker in colorectal cancer early detection, screening and monitoring: A systematic review

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Background: Colorectal cancer (CRC) is the third most prevalent cancer and fourth cause of cancer-related deaths worldwide. Early detection enhances cancer prognosis and treatment outcome and survival rate. Circulating tumor DNA (ctDNA) is a subset of cell-free DNA (cfDNA) originated from tumor cells, which is able to function as a marker for specific and early detection of malignancies. Moreover, ctDNA could be utilized in screening, staging, and monitoring response to therapy. Previous investigations have detected ctDNA in different body fluids, such as serum, plasma, urine and stool, which provides a cost-effective and non-invasive detection. Detected genetic alterations are valuable sources for determining tumor features such as stage, prognosis and predict the tumor resistance or response to therapies. The collected data from ctDNA, are essential in selecting the efficient treatment in targeted therapy. KRAS and BRAF mutations are the most studied gene mutations in CRC liquid biopsy. For instance, KRAS mutation is detected in 40% of CRC cases, which also indicates the tumor resistance to anti-EGFR antibody therapy. ctDNA analysis by polymerase chain reaction (PCR) is cost-effective, accurate and rapid. Various sensitivity and specificity of ctDNA analyzes are reported based on samples, analyzing technique, and analyzed genes. The sensitivity and specificity could be elevated to an appropriate level in different methods and samples.
Methods This review article uses articles from PubMed, Google Scholar, and Scopus from 2007 to 2020. The primitive number of related articles was 46 from which 27 articles were reviewed.
Conclusion: ctDNA is a potential marker that provides specific, cost-effective and early detections in malignancies, especially in CRC. Indeed, it provides valuable information about cancer prognosis, treatment and survival rate. These data are helpful in determining the efficient treatment option. Taken together, ctDNA can be a novel promising marker for CRC early detection and screening programs.
Keywords: circulating tumor DNA, colorectal cancer, cancer screening, early detection

(18636)

Use of MiRNA to Diagnose Systemic Lupus Erythematosus (SLE)

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Background: Systemic lupus erythematosus is an autoimmune disorder that is more common in women and has different symptoms, the most severe of which is lupus nephritis.
The gold standard for diagnosis is renal biopsy, which is invasive and non-functional.
The use of miRNAs, which are small, non-encoding chains involved in regulating gene expression, is appropriate for the diagnosis of SLE as a complement.
Methods: This review provides an overview of several articles on websites such as PubMed about Systemic Lupus Erythematosus.
Results: In a study of 78 people, 22 had lupus with nephritis. 15 miRNAs were selected and the RT-q PCR technique was used. Finally, three miRNAs named miR-221-3p, miR125a-5p and miR-146a-5p showed the difference between lupus with nephritis and lupus without nephritis.
MiR-146a-5p is a specific marker for the diagnosis of lupus nephritis even before examining the albumin and protein to creatinine ratio.
In SLE patients, the production of IL-21 by $CD4^+$ T cells is increased, leading to the expression of miR-155.
Conclusion: Studies show that miRNAs expression level can be used to differentiate sick people from healthy people and is not just about a specific disease.
As a complementary role along with other indicators with 97% sensitivity and 70% specificity for the diagnosis of SLE can be used.

Keywords: miRNA, nephritis, MiR-146a-5p, IL-21

(18560)

Circulating tumor DNA (ctDNA); a potential marker in colorectal cancer early detection, screening and monitoring: A systematic review

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Background: Colorectal cancer (CRC) is the third most prevalent cancer and fourth cause of cancer-related deaths worldwide. Early detection enhances cancer prognosis and treatment outcome and survival rate. Circulating tumor DNA (ctDNA) is a subset of cell-free DNA (cfDNA) originated from tumor cells, which is able to function as a marker for specific and early detection of malignancies. Moreover, ctDNA could be utilized in screening, staging, and monitoring response to therapy. Previous investigations have detected ctDNA in different body fluids, such as serum, plasma, urine and stool, which provides a cost-effective and non-invasive detection. Detected genetic alterations are valuable sources for determining tumor features such as stage, prognosis and predict the tumor resistance or response to therapies. The collected data from ctDNA, are essential in selecting the efficient treatment in targeted therapy. KRAS and BRAF mutations are the most studied gene mutations in CRC liquid biopsy. For instance, KRAS mutation is detected in 40% of CRC cases, which also indicates the tumor resistance to anti-EGFR antibody therapy. ctDNA analysis by polymerase chain reaction (PCR) is cost-effective, accurate and rapid. Various sensitivity and specificity of ctDNA analyzes are reported based on samples, analyzing technique, and analyzed genes. The sensitivity and specificity could be elevated to an appropriate level in different methods and samples.

Conclusion: ctDNA is a potential marker that provides specific, cost-effective and early detections in malignancies, especially in CRC. Indeed, it provides valuable information about cancer prognosis, treatment and survival rate. These data are helpful in determining the efficient treatment option. Taken together, ctDNA can be a novel promising marker for CRC early detection and screening programs. Further studies should be done to extend findings and validate ctDNA as laboratory marker and improve the analyzes.

Keywords: circulating tumor DNA, colorectal cancer, cancer screening, early detection

(18542)

Cloning, expression and purification of recombinant N protein to design ELISA kit for the detection of COVID- 19

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Background: SARS-CoV-2 sparked attention in December 2019, by identifying a cluster of patients with unrecognized pneumonia symptoms who all associated to a seafood market in Wuhan, china. High-speed transmission of this infection, which was named Coronavirus Disease 2019 (COVID-2019), from person to person cause rapidly spreading of this coronavirus disease globally. Given the high prevalence and epidemic of the disease and the lack of vaccines or definitive treatments for the virus, it seems that accurate and early diagnosis is important and may lead to better treatment management and prevent the transmission of the disease to other people. The structural proteins of SARS-CoV-2 are the surface spike (S) glycoprotein, the small membrane (M) protein, the envelope (E) glycoprotein, and the nucleocapsid (N) protein. This study aimed to development of a high-quality ELISA Method based on antigen of N protein for antibodies detection of this disease. The N protein is considered most antigenic and thereby can evoke immune responses and generate neutralizing antibodies that can block the virus attachment to the host cells.

Methods: The synthesized N gene was sub-cloned into pET28a (+) plasmid. XhoI and NcoI restriction enzymes were used to confirm the recombinant plasmid extraction. Colony PCR, and digestion enzymes methods verified cloning. To express N protein, a strain of Escherichia coli BL21 (DE3) was induced with IPTG. A Ni-NTA column was used for purification, and SDS-PAGE as well as western blotting analyzed the expressed protein. ELISA test was used to identify the antigenicity of produced protein.

Results: The presence of N gene fragment in the recombinant plasmid was confirmed. SDS-PAGE showed that the BL21 (DE3) strain had the highest level of expression and a protein band of 42 kDa was observed in induced bacteria. Western blotting approved the purity of N protein, and ELISA test measured sensitivity and specificity as 93% and 95.5%, respectively.

Conclusion: These results confirm the reproducibility of high-quality N recombinant antigen as a reliable candidate in serological test.

Keywords: ELISA**,** Diagnosis, COVID-19, N protein

(18533)

A Review Study of Prognostication of chronic lymphocytic leukemia (CLL)

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Background & Aim: Chronic lymphocytic leukemia (CLL) is the most common leukemia in western countries. Knowing the prognosis helps determine whether it makes more sense to attempt specific treatments or withhold them, thus playing an essential role in end-of-life decisions. Novel prognostic markers in CLL may be helpful to clinicians for predicting results and in clinical decision-making. This study aimed to Know the relevant prognostic factors for predicting individual prognosis of CLL.
Methods: This study is a review study by analyzing articles from databases, including ScienceDirect, PubMed, and google scholar. This research has been done with keywords "prognosis CLL" and "Chronic lymphocytic leukemia" from 2012 to 2020.
Results: With recent developments, flow cytometry, immunophenotypic markers, molecular and genomic traits have been used to identify various prognostic indicators. Flow cytometry-based predictors, such as overexpression of CD38, ZAP-70, and CD49d, are associated with an unfavorable prognosis. Harmful chromosomal abnormalities analyzed by fluorescence in situ hybridization consist of deleting the long arm of chromosome 11 (del11q) and the short arm of chromosome 17 (del17p). Patients who carry these deletions have an aggressive clinical course and worse consequences than those who have trisomy 12, del13q, or no abnormalities on fluorescence in situ hybridization.
Conclusion: With a great extent of information on these prognostic markers, it may become challenging to make useful advice. Also, the cause of CLL's clinical heterogeneity, not all patients with harmful prognostic factors will have active disease requiring remedy. An international consortium of study groups created a novel prognostic score to dominate this challenge, including biochemical, genetic, and clinical parameters: the CLL-International Prognostic Index (CLL-IPI).
Keywords: Chronic Lymphocytic Leukemia, prognosis CLL, CLL-International Prognostic Index (CLL-IPI).

(18345)

Is it possible to detect Protein kinases related Immunodeficiency disorders by Biosensors? A *Suggestion* for future perspectives

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Protein kinases act as a trigger for regulating a wide range of cellular processes including development, survival, apoptosis, control of metabolism, transcription signals and so on. These molecules play a vital role in the appropriate immune responses so that the different immunodeficiency disorders happen due to the protein kinases deficiency. As recently the significant advances have been made in the biomolecular detection methods, particularly in biosensors technology, the protein kinases related to the immunodeficiency disorders seems to be an attractive area for detection by biosensors. This review offers suggestions based on which the fast and real-time identification of immunodeficiency disorders related to the protein kinases will be possible in the future. We briefly refer to the important protein kinases involved in the immunodeficiency conditions in order to emphasize their pivotal roles, while sensors are designed for them have not been regarded compared to the other protein kinases already detected by the different biosensors until now. It is anticipated that a bright and promising future will happen for detection of the related anomalies by biosensors.

Keywords: Protein kinase, Immunodeficiency disorders, Biosensors, Diagnosis

(18133)

Immunosensors for detection of viruses

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Abstract: Immunosensors are kind of affinity biosensor with high selectivity and sensitivity because of specific interactions between an antigen and specific antigen immobilized on a transducer surface. Immunosensors can be designed for cancer biomarkers, autoimmune diseases, infectious diseases, etc. The threat to global health from viral infections, such as COVID-19, HIV, influenza, hepatitis, Ebola, etc., emphases the requirement for prompt, sensitive and selective detection of viral pathogens in addition to post-infection antibodies. The immunosensor could be considered as a hopeful alternative method to RT-PCR for virus detection. Immunosensors have revealed promise in rapid diagnosis of influenza subtypes. Electrochemical biosensing platform are more complex developing novel nanomaterials to attain highly selective and sensitive detection and quantification of viruses. The benefits of each biosensor for COVID-19 detection are emphasized. Gold nanoparticles and gold nanoislands, were used for the development of an immunosensor and a DNA-sensor for MERS and COVID-19, respectively, with detection limits in the fempto-pico molar range. Immunosensor has also the ability to detect spike (S) protein or nucleocapsid (N) protein in untreated saliva along with SARS-CoV-2 in saliva clinical samples and cultured SARS-CoV-2, without any cross-reactivity with pH1N1 influenza pandemic. A lot of efforts are essential to be advanced in future studies for the development of Internet of Things (IoT) wearable nanobiosensors, which includes medical devices and software applications connected to the Internet, present wide-ranging healthcare services, for COVID-19 detection, to perform rapid, precise and early diagnosis and, therefore, to inhibiting further pandemic outbreaks.

Keywords: Immunosensor, Viruses, COVID-19.

(18055)

Utilizing localized surface plasmon resonance for viral detection

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During the COVID-19 pandemic, the value of cheap and reliable testing methods in viral diseases became more noticeable. There are various methods of testing for infectious diseases like using polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay (ELISA). However, there is a need for other testing platforms to complement affirmation platforms. Localized surface plasmon resonance (LSPR) biosensors can provide the required virus monitoring method while keeping the cost low and being reliable for even a small amount of samples down to the range of zeptomole. This method has been devised for the detection of Dengue, Avian Influenza, Porcine Circovirus 2 (PCV-2), Zika, hepatitis B, HIV-1, and many more viruses. Here we will compare the recent developments in designing biosensors for virus detection with a particular focus on the biomarker or antibody that they used in the chip. It will also compare the limit of detection and specificity of the different sensors.
Keywords: Biosensors, LSPR, Viral infections, Virus detection

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

(18014)

Early stage evaluation of colon cancer using tungsten disulfide quantum dots and bacteriophage nano-biocomposite as an efficient electrochemical platform

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Abstract: Recently, biosensors have become popular analytical tools for small analytes due to their high sensitivity and wide analytical range. In the present work, development of a novel biosensing method based on tungsten disulfide quantum dots (WS_2 QDs)-Au for rapidly and selectively detecting c-Met protein is introduced. As a proof of concept, M13 bacteriophage-based biosensors were used for the electrochemical detection of c-Met protein as a colon cancer biomarker. The M13 bacteriophage (virus), as the bio-recognition element, was immobilized on glassy carbon electrodes which were modified by WS_2 QDs-functionalized gold nanoparticles. The stepwise presence of the WS_2 QDs, gold nanoparticles, and immobilized phage on glassy carbon electrodes were confirmed by scanning electron microscope (SEM) and square wave voltammetry (SWV) technique. The designed biosensor was applied to measure the amount of c-Met protein in standard solutions, and consequently the desirable detection limit of 1 pg was obtained. Finally, as a proof of concept, the developed platform was used for the evaluation of c-Met protein in serum samples of colon cancer-suffering patients and the results were compared with the results of the common Elisa kit. As an interesting part of this study, some concentrations of the c-Met protein in colon cancer serum samples which could not be determined by Elisa, were easily analyzed by the developed bioassay system.

Keywords: Electrochemical; Biosensor; Cancer marker; Phage, Gold nano-layer; WS_2 QDs.

(17957)

Does neutrophil phenotype predict the survival of trauma patients?

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According to the World Health Organization (WHO), trauma is responsible for 10% of deaths and 16% of disabilities worldwide. This is considerably higher than those for malaria, tuberculosis, and HIV/AIDS combined. While the human suffering and death caused by injury is well-recognized, injury has a significant medical care cost. Better prediction of the state of trauma patients in the days immediately after trauma may reduce costs. Traumatic injuries to multiple organs can cause dysfunction in all systems of the body especially the immune system placing patients at high risk of infections and inflammatory complications which are often fatal. Neutrophils are the most abundant leukocyte in the human circulation and are crucial for the prevention of microbial disease. Significant changes in neutrophil functions such as enhanced chemotaxis, Neutrophil extracellular trap (NET)-induced cell death (NETosis), and phagocytosis occur early after injury followed by prolonged functional defects such as phagocytosis, killing mechanisms, and receptor expression. Analysis of these changes may improve the prediction of the patient's condition over time. We provide a comprehensive and up-to-date review of the literature investigating the effect of trauma on neutrophil phenotype with an underlying goal of using this knowledge to examine the predictive potential of neutrophil alterations on secondary complications in patients with traumatic injuries. We conclude that alterations in neutrophil surface markers and functions may be potential biomarkers that predict the outcome of trauma patients.

Keywords: trauma, neutrophil subtype, injury, survival, neutrophils

Congress Abstracts

Stem Cell & Immune Cell Therapy

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

15497

The Impacts of Lupus Mice MSC on Healthy and Lupus Balb/c Mice Model

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Background: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease affecting roughly several organs. Autoreactive T cells and autoantibodies are highly produced, which lead to damage in lupus patients. Genetic susceptibility along with environmental factors are to blame for disease sign as well. On the one hand, mesenchymal stem cells (MSCs), isolated from bone marrow and other sites exhibit specific immunomodulatory in addition to anti-inflammatory properties which can be beneficial as ideal tool for treatment, on the other hand, defect of MSCs could induce SLE. The aim of current research is to evaluate different effects of lupus MSCs on the frequency of inflammatory and regulatory T cells as well as their cytokines.

Methods: Female Balb/c mice (3-4 weeks) purchased and divided in different groups. First, lupus group mice are prepared and injected with 0.5cc pristane (intraperitoneally) in order to induce SLE in 6 months. Then, the dsDNA level and proteinuria of these mice are checked to make sure of proper disease progress. After 6 months, induced lupus mice are scarified and lupus MSCs are harvested in cell culture medium under standard conditions. Next, lupus MSCs are counted and injected into two healthy and lupus mice group for two month. After two month, the clinical manifestations of mice are recorded. Then the mice are killed and different subtype of T cells are isolated by ficoll gradient density. Finally, Flow cytometry assay is performed to evaluate the frequency Th17 and Treg cells. Moreover, the expression levels of IL-10, TGF-β, FOXP3, IL-17 and IDO are evaluated by Real-Time PCR methods.

Results: The study is in process and the data will be presented in the congress.

Conclusion: Upon the defect of lupus MSCs function, we expect that this cells cannot show a proper anti-inflammatory or immunoregulatory response. Therefore, we anticipate that injection of lupus MSCs in healthy mice can induce SLE and also in SLE mice group probably helps SLE progression. Overall, this study provided a comprehensive information for a better understanding of MSCs properties as well as new ways to prevent and treat SLE disease.

Keywords: Systemic Lupus Erythematosus, Mesenchymal Stem Cell, Lupus Mice, T cells, Cytokine

16571

Assessment of proliferativeand anti-apoptotic and immunomodulatory activity of crocin and crocetin on adipose-derived mesenchymal stem cells from multiple sclerosis patients

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Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) with extensive socioeconomic burdens. Mesenchymal stem cells (MSCs) are unlimited sources, have spectrum of beneficial properties such as neuroprotective, and immunomodulatory traits, and as novel therapeutic tools in regenerative medicine and curing neurodegenerative diseases, including MS. Saffron (Crocus sativus L) is a well-known spice with pharmacologically active components including crocin, crocetin. In current study, we compared the effects of crocin and crocetin on beneficial functions of MSCs.

Methods: After isolating AT-MSCs from MS patients, and cultured with of crocin and crocetin concentrations, used MTT assay to evaluate MSC proliferation, flowcytometry assay to measure the percentage of apoptotic MSCs and Tregs population.

Results: Our finding indicated crocin and crocetin at low concentrations (2.5, 5µM) exhibited significant effects on increasing MSCs viability and protecting them against apoptosis-induced death. Furthermore, crocin and crocetin at low concentrations (2.5, 5µM) could increase Tregs proportion significantly.

Discussion: Altogether, both crocin and crocetin at lower concentrations exhibited more efficacy on AT-MSCs with a better effect toward crocin. We concluded that crocin and crocetin can considraate as complementary treatments for the patients who have received MSCs.

Key words: Mesenchymal stem cells, T regulatory cells, Proliferative, Crocin and Crocetin

18002

Immunomodulatory functions of Mesenchymal Stem Cells treated with Tretinoin altered the Clinical and Histopathological Aspects in Experimental Rheumatoid Arthritis

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Abstract

Background: Multipotent mesenchymal stem cells (MSCs) are employed in autoimmune problems due to their regenerative and immunomodulatory features. This research aims at evaluating the impact of Tretinoin-treated mesenchymal stem cells on the histopathological and clinical aspects of experimental Rheumatoid arthritis.

Methods: The experiment was carried out on male Wistar rats (n= 40) in 4 groups with equal members, which included Positive Control (Rheumatoid Arthritis model), Tretinoin-treated MSCs and untreated MSCs (intravenous injection of one million cells), and Negative Control (healthy). The total duration of all treatments was 30 consecutive days. Afterward, we evaluated the phagocytosis ability, spleen cell production of respiratory burst, and nitric oxide production.

Results: According to the research findings, the phagocytosis ability, nitric oxide production in the spleen immune cells and respiratory burst in MSCs group treated with Tretinoin were significantly lower compared to the untreated MSCs group.

Conclusion: Tretinoin-treated MSCs led to an increase in regulatory function in the Rheumatoid Arthritis model in comparison with mesenchymal stem cells without treatment.

Key words: mesenchymal stem cells, Tretinoin, inflammation, Rheumatoid Arthritis

18101

Intranasal administration of mesenchymal stem cells derived exosomes reduced the disease severity of experimental autoimmune encephalomyelitis in a mouse model

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Background: The Mesenchymal stem cells (MSCs) implement a range of their effects including anti-inflammatory and neurotrophic effects through cell-contact independent secretory mechanisms which to a large extent are dependent on secreted exosomes (MSC-EXO). These nanometer-sized vesicles can easily pass through the blood-brain barrier, which made them good candidates for therapy of neurological diseases.
Methods: The MSC-EXO was isolated from MSCs derived from C57BL/6 mice abdominal adipose tissue. Afterward, the therapeutic effects of intranasal administration of both MSC and MSC-EXO on the experimental autoimmune encephalomyelitis (EAE) mice model were evaluated. To achieve this goal, the clinical sign of the disease progression and histological evaluation of the spinal cord was used. In addition, the cytokine production assay and gene expression analysis were performed.
Results: In vivo treatment of EAE mice by both MSC-EXO and MSC effectively reduced the clinical score and also induced Treg responses that were significantly higher than the PBS group (8.28±0.87 and 7.73±0.55 vs. 2.95±0.45, p=0.007 and p=0.009, respectively). Furthermore, the TGF-β level was increased by both treatments (1004±54 and 948±82 vs. 642±70, p=0.009, and p=0.040, respectively). However, IL-10 level was increased only in the group received MSC treatment (95.5±14 vs. 42±3.1, p=0.033). Although these immunomodulatory responses were accompanied the reduced clinical symptoms; however, the MSC-EXO was more efficient in alleviating clinical score compared to MSC (0.88±0.08 and 1.27±0.14 vs. 1.97±0.01, p<0.001 and p=0.001, respectively) through prominent histological lesion resolving by MSC-EXO treatment (2.9%±0.29 vs. 5%±0.32).
Conclusion: Administration of MSC-EXO via nasal rout demonstrated in vivo immunomodulatory effects. Due to the limited homing of MSCs to the CNS and the short half-life of MSCs in the body following in vivo administration, they cannot implement their neurotrophic effects. Therefore, MSC-EXO which can effectively pass the BBB following intranasal administration has a higher efficiency in the regeneration and repair of damaged CNS.
Keywords: Mesenchymal stem cell, exosome, experimental autoimmune encephalomyelitis

18112

Impact of IFN-β and LIF overexpression in human adipose-derived stem cells (hADSCs) properties

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Abstract

Adipose-derived stem cells (ADSCs) are a subset of MSCs that their therapeutic effects in various diseases make them an interesting tool in cell therapy. In the current study, we aimed to overexpress IFN-β and LIF cytokines in human ADSCs to evaluate the impact of this overexpression on human ADSCs properties. Here, we designed a construct containing IFN-β and LIF and then, transduced hADSCs by this construct via a lentiviral vector (PCDH-513B). We assessed the ability of long-term expression of the transgene in transduced cells by western blotting and ELISA techniques on days 15, 45 and 75 after transduction. For evaluation of stem cell properties, flow cytometry and differentiation assays were performed. Finally, the MTT assay was done to assess the proliferation of transduced cells compares with controls. Our results showed high-efficiency transduction with highest expression rates on day 75 after transduction which were 70 pg/ml for IFN-β, and 77.9 pg/ml for LIF in comparison with 25.60 pg/ml, and 27.63 pg/ml, respectively in un-transducted cells (p=0.0001). Also, transduced cells expressed a high level of ADSCs surface markers and successfully differentiated into adipocytes, chondrocytes, neural cells and osteocytes besides the preservation rate of proliferation near untreated cells (p=0.88). All in all, we successfully constructed a hADSC population stably overexpressed IFN-β and LIF cytokines. Considering the IFN-β and LIF anti-inflammatory and neuroprotective effects as well as immune-regulatory properties of hADSCs, the obtained cells of this study could be subjected for further evaluations in EAE mice model.

Key words: Adipose-derived stem cells (ADSCs); Lentiviral vector; Overexpression; Interferon-beta (IFN-β); Leukemia Inhibitory Factor (LIF)

18211

Hepatic differentiation of human bone marrow mesenchymal stem cells is associated with changes in selected cellular cytokines

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Background: Hepatic differentiation of mesenchymal stem cells (MSCs), are well known for their immunomodulatory functions. Likewise, the hepatocytes perform a number of immunological roles in addition to their essential metabolic functions. The immunological and inflammatory reactions are mainly regulated by cytokines as the cell signaling factors.
Aims: The determine the levels of selected anti- and pro-inflammatory cytokines in undifferentiated MSCs and their possible changes during hepatic differentiation of the MSCs
Methods: Bone marrow biopsies from young healthy donors were used for isolation of MSCs. Briefly, mononuclear cells were isolated and seeded into culture plates containing DMEM-low glucose containing 15% FBS, 2 mM glutamine, 100 mg/ml streptomycin and 100 U/ml penicillin. The culture was incubated at 37°C in a humidified 5% CO2 incubator. The adherent cell population that were growing as fibroblastic cells were maintained to obtain 70-90% confluency. The cells were harvested and plated in 25-cm^2 flasks. Hepatic differentiation was carried out in DMEM-low glucose medium containing 15% FBS, HGF, DEX as well as OSM. At time intervals; 2, 7 and 14 days the cells were recovered for determination of cytokines. TNF-α, IL- 6, IL- 8 and IL- 10 were determined by ELISA. The results obtained from the hepatocytes were compared with undifferentiated MSCs.
Results: Cellular level of pro-inflammatory factors; IL-6, TNF-α showed a substantial increase during hepatic differentiation of MSC. Time-course analysis showed that there was about 3-fold increase in IL-6 and TNF- α. The level of IL-10 showed relatively lesser increase in hepatocytes recovered on day 14 of differentiation. IL-8 was also initially depleted (day 7) but remained constant in cells collected on day 14.
Conclusion: Differentiation-dependent changes in the cytokines may suggest their role in regulation of hepatic differentiation and protection of hepatocytes during differentiation.
Keywords: Stem cells, Hepatocytes, Differentiation, Cytokines

18634

Manufacturing Process of Chimeric Antigen Receptor T Cells Disposes Them to Expression of A2a Receptor, an Inhibitory Molecule

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Background: Various immunotherapy methods such as TIL Therapy and recently CAR T cell therapy have been developed to overcome cancers. Although, CAR T cell therapy has shown significant results in the treatment of blood malignancies and with less success in solid tumors, in some patients these cells do not show strong anti-tumor activity. In this study, to better understand the mechanisms involved in CAR T cell function and Optimizing CAR-T Cell Manufacturing Processes, we investigated the expression of A2a receptor as an inhibitory molecule on lymphocytes at different stages of CAR T cell production process.

Methods: To produce CAR T cells, primary T cells from 6 donors were activated with anti CD3/CD28 beads first, and then transduced with viral particles containing the CAR construct. The expression of CAR was assayed using Anti ScFv antibody. A2aR levels were analyzed in different stage of CAR T cell production, including fresh Primary lymphocyte, anti-CD3/CD28 activated T cells, and T cells expressing transduced CARs. To control for this, we did have a mock-transfected group of T cells that were prepared similar to CAR T cells but were transduced with viral particles containing an empty vector (instead of the vector expressing the CAR construct). Statistical analyses were performed Prism 7 software.

Results: A2aR levels were low in un-activated primary T cells, but the levels increased significantly after stimulation with anti CD3/CD28 beads and viral transduction. Also, the mock-transfected T cells showed enhanced A2aR expression similar to CAR T cells, which indicated that enhanced expression was likely due to activation and possibly transduction, but not CAR expression.

Conclusion: Activation and viral transduction might enhance the expression of inhibitory receptors on T cells and make the CAR T cells prone to exhaustion before tumor stimulation. This finding can be used to optimize the CAR T cell manufacturing protocols in order to produce stronger CAR T cells.

Keywords: Manufacture, Adenosine 2a-receptor, Viral Transductions, chimeric antigen receptor (CAR) T cells.

18681

Highly Efficient and Selective CAR-gene Transfer Using CD4- and CD8-Targeted Lentiviral Vectors

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Background: CAR-modified T cells have revealed promising results in cancer treatment but still, have various hurdles. Receptor-targeted lentiviral vectors delivering genes selectively to T cell subtypes may facilitate and improve CAR T cell generation but still resulted in low gene delivery. To overcome this limitation, we studied the effect of transduction enhancer Vectofusin-1 on gene delivery to human T cells with CD4- and CD8-targeted LVs, encoding a second-generation CD19-CAR linked to ΔLNGFR. Vectofusin-1 significantly enhanced gene delivery of CD4- and CD8-LVs, with retaining target cell selectivity and killing capability of the generated CAR-T cells.

Methods: Vector particles were generated by transient transfection of HEK-293T cells using polyethyleneimine, second-generation packaging plasmids, and applied to transduced activated PBMC with Vectofusin-1. Transgene expression was determined by flow cytometry 7-13 days post-transduction. Cytotoxic activity of transduced cells was analyzed in a CFSE-based cytotoxicity assay. The presence of ΔLNGFR on the surface of LV particles was investigated applying binding assay and ELISA.

Results: The number of CD4-positive cells transduced by CD4-LV was enhanced 2-fold from 22% to 57%. The pronounced effect of Vectofusin-1 for CD8-LV observed and the transduction rate of CD8-positive cells increased from 32% to 87%. Importantly, receptor-specificity was retained for retargeted vectors. Both CAR T cell products showed significantly higher killing activity compared to untransduced cells. With Vectofusin-1 treatment, particle binding to, and thus ΔLNGFR detection on, PBMCs enhanced for all vector types, without preference for cell subtypes.

Conclusion: CD8- and CD4-targeted LVs may facilitate and improve the generation of CAR T cells in the future since only the desired cell population of choice will be transduced. T cell purification steps for the manufacturing process of CAR T cells may then become obsolete. Moreover, other therapeutic applications in the genetic modification of lymphocytes may profit from targeted gene delivery to lymphocyte subtypes.

Keywords: transduction enhancer, Vectofusin-1, receptor targeted viral vectors, LV, LNGFR, protein transfer

14384

Effect of pomegranate extract in mesenchymal stem cells by modulation of microRNA-155, microRNA-21, microRNA-23b, microRNA-126a and PI3K\AKT1\NFKB expression

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Abstract

Aims: Today, mesenchymal stem cells (MSCs) are candidates for various autoimmune disease treatments due to immunomodulatory activity in these cells. Much research has recently been done to improve the immunomodulatory activity of MSCs. Genetic variation is one of these methods.

MicroRNAs (miRNAs) are small non-coding RNAs that control most of the cell's biological activities. Recent studies have shown that miRNAs play a significant role in the regulation of MSC immunomodulatory activity. Pomegranate is a fruit that has antioxidant, anti-inflammatory and anti-cancer properties and has been used for many years for therapeutic purposes.

The objective of this research is to evaluate the immunoregulatory related miRNAs level of Ad-MSCs obtained from adipose tissue in the presence or lack of pomegranate (Punica granatum) extract (PGE).

Results: Our results showed that miRNA-23 and miRNA-126 up-regulated by PGE treatment in MSCs and the other hand miRNA-21 and miRNA-155 down-regulated by PGE treatment in MSCs. In addition this research show that PGE can down regulation the expression of PI3K/Akt/NFKB in Ad-MSCs. Our bioinformatics data have shown that the target of these 4 miRNAs and the signaling pathways in which these targets are involved can play an important role in regulating the immunomodulation function of stem cells.

Conclusions: In conclusion, PGE can inhibit the expression of PI3K / Akt / NFKB genes involved in inflammatory pathways via miRNA-23 and miRNA-126 **over expression or** miRNA-21 and miRNA-155 **down regulation that play a role in the pathways of immune modulation in Ad-MSCs.** These results may provide insight into the mechanism underlying the regulation of the immunomodulatory activity of Ad-MSCs by PGE.

Keyword: mesenchymal stem cell (MSCs); micro-RNA (miRNAs); immunoregulatory or immunomodulatory; pomegranate (Punica granatum)

15499

The role of Armored T Cells in tumor inhibition by disrupting the Tumor microenvironment (TME)

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Background: Tumor microenvironment (TME) is the environment around the tumor. This microenvironment is composed of different cellular and molecular components that reduce the strength of the immune system against the tumor and also affect the activity of Car T Cells. Tumor-suppressing cytokines, such as β-TGF and IL-10, are secreted from both tumor cell and immune-suppressing cells from the microenvironment around the tumor and can divert the immune system and prevent a strong immune response. To overcome this action, special T lymphocytes such as Armored T Cells or TRUCKs are used in the microenvironment around the tumor. These Car T Cells are designed to secrete proinflammatory cytokines that cause tumors to regress due to the disruption of the microenvironment around the tumor.

Methods: In this review study, searches were conducted in the electronic and scientific databases of PubMed, Medline, Google Scholar, Scopus, and ISI, and valid articles related to the subject were searched using the keywords tumor microenvironment and Car T Cells.

Results: The use of armored T cells can be explained as a new treatment method in the discussion of immunotherapy.

Conclusion: Considering the role of armored T cells in microenvironmental disorders, it can be used in the treatment of other tumors, autoimmune diseases, and new infectious diseases by further studying the morphology and physiology of their function.

Keywords: Tumor microenvironment (TME), armored T cells, immunotherapy, proinflammatory cytokines

16539

Immunomodulatory Effects of Mesenchymal Stem Cells on Different Cytokines of SLE in Patients and Animal Models

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Abstract

Systemic lupus erythematosus (SLE) is a chronic heterogeneous autoimmune disorder. Autoantibodies, inflammatory T cells responses and distinct cytokines are extremely produced in lupus patients, affecting diverse organs. The etiology is largely unknown; however, it is generally accepted that genetic predisposition in combination with environmental factors trigger immune responses that lead to disease progression. Clinically periods of remission and relapse occur and diagnosis is attained via clinical findings along with laboratory examinations. Current SLE treatments comprise application of immunosuppressive agents which are not efficiently curative. Mesenchymal stem cells (MSC) are multipotent stem cells with low immunogenicity that can differentiate into different kinds of cells. Recently, Immunomodulatory functions of MSCs bring them as potential candidate for treating SLE. It has also been recorded that MSCs down-regulate Th17 cells and upregulate Treg proportion through the regulation of TGF-β as well as PGE2 in lupus patients. In addition, Reduction of Th1-cytokines (IFN-γ, IL-2) and proinflammatory cytokines (TNF-α, IL-6 and IL-12) beside Th2 cytokines (IL-4, IL-10) has been seen through immunotherapy with MSCs. The aim of this study is to review the immunomodulatory impact of MSCs on the expression level of cytokines in both innate and adaptive immunity that is assessed in either animal models or SLE patients.

Key words: Systemic lupus erythematosus, Mesenchymal stem cells, Cytokine, Animal model, SLE patient

16593

Immunomodulatory effects of mesenchymal stem cells on cells as well as innate and adaptive mediators expression in multiple sclerosis

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Abstract

Multiple sclerosis is a chronic autoimmune disease targeting central nervous system (CNS) which distinguished by demyelination, neurological degeneration and dysfunction leading to progressive disability. The disease-modifying treatments (DMTs) like immunosuppressive and immune modulating agents are the common therapy for MS that can control the inflammation but they are not curative. Recently, Stem cell therapy is considered as a parallel treatment for MS. Mesenchymal stem cells (MSC) are a class of stem cells, which produced in bone marrow like hematopoietic stem cells. According to different studies, MSCs have exhibited immunomodulatory and immunosuppressive properties such as suppression of T and B cell proliferation, inhibition of pro-inflammatory cytokines, balance of Th1/Th2 ratio, adjustment of Treg's function, regulation of antibody production and activation of DCs and NK cells. Regard to mentioned information and the potential ability of MSCs to repair CNS lesions and neural damage, MSCs are considered as a candidate cells for MS treatment. The aim of this study is to review the all aspect of MSCs effect in treatment of MS regarding innate and adaptive immune system and their mediators.

Key words: Multiple sclerosis, Mesenchymal stem cell, Cell based therapy, Innate immunity, Adaptive immunity.

16895

Mesenchymal Stem Cell-Derived Exosomes: A cell-free therapy in different inflammatory diseases

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Mesenchymal stem cells (MSCs) have been widely used in clinical trials and different animal models. The therapeutic effects of MSCs also have been demonstrated in immune and non-immune diseases. But always in cell therapy, there are few concerns about immune rejection, genetic disability, and malignancies. In comparison to MSC therapy, exosome therapy (cell-free) improves treatment outcomes. They are also naturally secreted and widely distributed in body fluids, thereby will be well tolerated by the body. Their storage is safe and provides cell-free therapeutic applications avoiding the risk of immunological rejection, malignant transformation, and obstruction of small vessels associated with cell therapy. Giving to this, MSC-Exosome looks to be a novel and interesting approach to be studied in clinical trials of different inflammatory diseases, such as acute and chronic liver diseases, cardiovascular diseases, kidney disease, neurological disease, and autoimmune diseases. However, the role of MSC-exosomes in tumors is controversial and requires further studies. Since exosomes are used as ideal vehicles for gene therapy, we hypothesize that exosomes from modified or manipulated MSCs could be a new therapeutic approach for different diseases. With all that, there is still a long road ahead for the probable use of MSC-exosome in the clinic and lots of questions about the exosomes should be answered, such as the best route of administration, the protocol of isolation, and the number of doses.

Keywords: Mesenchymal stem cells, cell therapy, exosome

16898

Exosomes of Mesenchymal Stem cells Reduces Hepatic Fibrogenesis by Inhibiting TGF-β/Smad3 Signaling Pathway in cholesterol-treated LX2 cell line

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Background: Hepatic fibrosis is considered integral to the progression of chronic liver diseases. Activation of hepatic stellate cells (HSCs) is the dominant event in hepatic fibrogenesis. We investigated the accumulation of free cholesterol in HSCs, which accelerates experimental liver fibrosis. TGF-β is a major profibrotic cytokine in the liver that activates HSCs and converts them to myofibroblasts, which increases αSMA expression and high extracellular matrix accumulation and conditions are provided for the development and progression of hepatic fibrosis. In fact, TGF-β can be considered the starting point of fibrosis and is a very important factor in liver fibrosis. We investigated the accumulation of free cholesterol could lead to increased TGF-β, followed by activation of stellate cells and increased expression of α-SMA gene.

Methods: Human hepatic stellate cells (HSCs) were cultured to reach 80% confluency then cells were seeded into well plates and allowed to attach for 24 hours. Then the medium was changed to different concentrations of Cholesterol, 25, 50, 75 and 100µM for 24h. Total RNAs were extracted and Quantitative Real-time PCR (qRT-PCR) was performed.

Results: After treated with 100µM Cholesterol, the expressions of TGF-β and αSMA genes were significantly increased. Then after treated with 20µM exosomes the expressions of TGF-β and αSMA genes were significantly reduces ($P< 0.05$).

Conclusion: In this experiment, it was shown that increased Cholesterol in (HSCs) can increase markers of hepatic. Exosomes reduced the expression of genes involved in the progression of liver fibrosis including TGF-β, α-SMA

Keywords: Liver fibrosis, Cholesterol, TGF-β, HSCs, Exosomes

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

16899

Fibroblast growth factor 21 Reduces Hepatic Fibrogenesis by Inhibiting TGF-β/Smad3 Signaling Pathway in LX2 Cell Line

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Background: Hepatic fibrosis is a very important stage in the development of liver diseases from the onset of fatty liver to cirrhosis and liver failure. Activation of hepatic stellate cells (HSCs) is a significant phase in hepatic fibrogenesis. FGF21 has strong anti-inflammatory capacities, but its ability to prevent liver fibrosis is not yet known. In this study, we demonstrated that FGF21 reduces the expression of TGF-β/Smad3, αSMA and collagen-1 in activated HSCs using Cholesterol-induced human HSCs LX2 cell line.

Methods: Human hepatic stellate cells were seeded into well plates for 24 hours. Then the medium was changed to concentrations of FGF21, 1µM for 24h. For Cholesterol stimulations, LX2 cells were activated with 100µM in DMEM supplemented with 1% FBS for 24h.

Results: The real-time-PCR analysis showed that Cholesterol markedly increased the mRNA levels of TGF-β and α-smooth muscle actin (α-SMA), and collagen-1 (COL1A1) which are representative markers of HSC activation that almost completely reversed by FGF21 treatment

Conclusion: in this study, we observed that FGF21 reduced the expression of genes involved in the progression of liver fibrosis including TGF-β, α-SMA, and COL1A1 and disrupted the SMAD3 signaling pathway in activated human HSCs LX2. Inhibition of TGF-β signaling In many studies that have been done so far suggested as a potential mechanism to reduce fibrogenesis

Keywords: liver fibrosis, hepatic stellate cells, FGF21, transforming growth factor-beta, Smad3

17967

Evaluation of the effect of tolereogenic probiotics on the maturation of healthy dendritic cells versus immature dendritic cells

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Abstract

Background: Dendritic cells as the main cells of the innate immune system are responsible for initiating, developing, and control of acquired immune responses. Myeloid dendritic cells can use as a vaccine in several autoimmune and tomural diseases. Tolerogenic probiotics with regulatory properties can affect the maturation and development of immature dendritic cells (IDC) into mature DCs and can induce certain modulatory properties in these cells.

Methods: In this project, the IDCs were derived from healthy donors in GM-CSF and IL-4 medium. Mature DCs (MDC) were produced in the presence of LPS, *L. delbrueckii* and *L. rhamnosus* from *the* IDCs. Flow cytometry and Real-Time PCR were used to determine the expression level of DC markers and IDO, IL10, and IL12, respectively.

Results: Probiotic-derived DCs showed a significant reduction in the expression of HLA-DR, CD86, CD80, CD83 and CD1a. In addition, the expression of IDO and IL10 were increased in these cells while IL12 expression was decreased.

Conclusion: Our findings revealed that tolerogenic probiotics could induce regulatory DCs through reduction of co-stimulatory molecules along with increasing the expression of IDO and IL10 during the differentiation process. These inhibitory cells of healthy individuals can used in the treatment of various inflammatory diseases.

Keywords: Probiotics, Lactobacillus delbrueckii, Lactobacillus rhamnosus, Tolerogenic Dendritic Cell, Immature Dendritic Cell

18009

Cell therapy in female infertility-related diseases: Emphasis on recurrent miscarriage and repeated implantation failure

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Abstract

About 17% of couples suffer from infertility conditions, worldwide. The most common reasons for female infertility are ovulation disorders, fallopian-related disorders, RM, RIF, endometriosis, and unexplained infertility. Despite advances in Assisted Reproductive Technologies, infertility has remained a serious problem. In recent years, a considerable progress in cell therapy as an emerging approach for the treatment infertility has been made. Cell therapy involves utilizing lymphocytes, platelet -rich plasma, PBMCs and different types of stem cells as therapeuticagents. Stem cells are usually multipotent cells existed in embryos, fetuses, and adults that proliferate and differentiate into different cell types under certain circumstances. The main types of stem cells are embryonic stem cells, decidual stromal cells, MSCs, human amniotic epithelial cells, and induced pluripotent- stem cells each functioning in a different way. The advantages of using stem cells as therapeutic agents are convenient sampling, abundant sources, and avoidable ethical issues. Lymphocyte immunotherapy, a simple and cost effectivemethod, can be safe and useful approach if performed with proper dose of fresh lymphocytesintradermally before and during pregnancy. Overall, cell therapy mechanism of actions are inducing the production of cytokines ,blocking antibodies and growth factors , proliferation of B10 cells, reducing the activity of NK cells, increasingTh2 and Treg cells and decreasing Th1 and Th17 cells. Cell therapy can be an effective strategy as it provides an interactive, dynamic, specific and individualized treatment. Although cell therapy is a promising approach, it still needs more investigation in order to improve and make it safer.

Keywords: Cell Therapy, Infertility, Recurrent Miscarriage (RM), Recurrent Implantation Loss (RIF)

18096

Cancer Stem Cell associated miRNAs: An overview

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Background: Cancer Stem Cells (CSCs) reside in dedicated niches in many cancers. CSCs are products of combinational genetic and epigenetic changes in normal stem cells. Cancer is a complex disease caused by genetic abnormalities, which ranks as the second leading cause of death worldwide. Micro RNAs (miRNAs), belong to small noncoding RNAs Which are about 20-22 long nucleotides. Over 60 percent of genes in mammals are regulated by different miRNAs. Different groups of miRNAs are expressed in order to regulate specific sets of proteins in various cells and tissues according to their specificity. Growing evidence demonstrated that miRs have critical role in tumor relapse, proliferation, apoptosis and metastasis. Accordingly, miRs regulate many properties of CSCs. In this review, we provide an update on CSCs related miRNAs.

Methods: Electronic databases (PubMed, Scopus, Google Scholar) and Persian language databases (Magiran, Scientific Information Database [SID]) were searched.

Results: Several studies have demonstrated that miRNAs regulate various protein levels which involved in cancer progression. Accordingly, overexpression or downregulation of specific miRNAs can be involved in tumor relapse, proliferation, apoptosis and metastasis. Studies showed that miR-451, miR-486, miR425, miR-16, miR-107, miR-185 in glioblastomas CSCs, miR-29 in breast cancer which is regulated by the female hormone progesteron, miR-143, miR-145 in colorectal tumor cells and miR-124 in both glioma tissues and cell lines are downregulated and inhibits cell proliferation, invasion and metastasis. Also it was shown that miR-10b is increased in glioblastoma tissue and CSCs.

Conclusion: miRNAs may have a prognostic/diagnostic value in different types of cancers. Overexpression or downregulation of different miRNAs contribute to cancer development in several ways. These abnormal expressions might regulate CSC proliferation and metastasis to facilitate cancer development.

Keywords: Cancer, miRNA, miR, stem cell, caner stem cell, CSC

18176

Green Tea Epigallocatechin Gallate Enhances in Vitro Immunomodulatory and Beta Cell Protective Functions in Streptozotocin-Induced Diabetic Mice Model with Bone-marrow-Derived Mesenchymal Stem Cells

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Background: Mesenchymal stem cells (MSC) are judged by their ability as an immunomodulator and their potential to regenerate the insulin secreting cells in type 1 diabetes (T1D). However, some experimental results indicate that the high glucose concentration or diabetic environment suppresses some crucial proteins and increases senescence in stem cells. Regarding antioxidative and immunosuppression characteristics of epigallocatechin-3-gallate (EGCG), the present study investigated the feasibility of using EGCG, along with MSCs, to improve regeneration in pancreatic beta cell line (bTC3) and modulation in immune responses.

Methods: MSCs were extracted from bone marrow of normal mice and cultured. Diabetes was induced in the mice by administration of multiple low-doses of streptozotocin. Splenocytes were prepared from normal and diabetic mice. Proliferation, cytokine production and insulin secretion assays were performed in coculture experiments.

Results: Comparing with other groups, significant improvement in viability as well as insulin secretion of treated bTC3 cells was observed in the MSC+ EGCG group. The EGCG and MSCs treatment more efficiently inhibited splenocyte proliferative response to specific (islet lysate) and nonspecific (PHA) triggers. Decreased production of IFN-γ *as a* proinflammatory cytokine and increased secretion of IL-4 as a regulatory cytokine by stimulated splenocytes were also shown in response to islet lysate or PHA stimulants

Conclusion: Overall, it seems that natural anti-inflammatory products and stem cell treatment cross-effect may provide a new horizon for T1D cell therapy and islet transplantation in the future.

Keywords: Mesenchymal Stem Cell, Epigallocatechin gallate, Type 1 diabetes

18239

Therapeutic and Immunomodulatory Effects of Mesenchymal Stem Cell (MSC) Therapy on Ulcerative Colitis

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Background: Ulcerative colitis (UC) is a progressive and disabling autoimmune disease. UC symptoms vary depending on the severity of the inflammation and may include rectal bleeding, abdominal and rectal pain, diarrhea, fever, fatigue and weight loss. The disease stays throughout life and there is no definitive cure for it at the moment. Newly emerging therapies, in particular MSC therapy are currently being investigated in regenerative medicine and autoimmune disorders as a potential treatment strategy, due to their immunomodulatory effects. In this study, we investigated the efficacy of MSC-therapy on UC.

Methods: The review article was performed within articles published at Google Scholar, PubMed and ScienceDirect from 2016-2020, with keywords mesenchymal stem cell and ulcerative colitis. By searching these databases, 314 articles were found, of which 271 articles were removed after reading the titles or abstracts. Review articles were also excluded. Forty-three articles were selected under the inclusion criteria.

Results: Of the 43 studies, all reported improvement in symptoms, immunomodulation and a significant reduction of disease activity, ulcer size, inflammation and colorectal mucosal degeneration. Studies reported a decrease in Th17 cells and pro-inflammatory cytokines (IL-6, IL-12, IL-17A, IL-1β, TNF-α, IFN-γ and MCP-1) and increase in Treg cells and anti-inflammatory cytokine (IL-10 and TGF-β) expression. MSC also reduced dendritic cell levels, macrophages and macrophage inflammatory proteins. Studies reported no adverse effects and the most effective routes of administration were intraperitoneal (IP) and subcutaneous (SC) injections.

Conclusion: MSC cell therapy regulates the immune system, promotes tissue repair and regeneration, and seems to be a promising treatment strategy for UC and other autoimmune diseases.

Keywords: Ulcerative colitis, Mesenchymal stem cells, Autoimmune, Cell therapy

18244

Assessing immunomodulatory effects of Olfactory ecto-mesenchymal stem cells and their comparison with Adipose tissue-derived mesenchymal stem cells.

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Abstract

Background: Mesenchymal stromal cells (MSCs) have potent immunomodulatory abilities to regulate most of immune cells. Not only the tissue origin of MSCs can affect their functions, their microenvironment can also strongly affect their biology, particularly through TLR detection. In the present study, we compared MSCs derived from two different sources, i.e. human olfactory ecto-mesenchymal stromal cells (OE-MSCs) and adipose tissue (AT-MSCs), in terms of their immunosuppressive effects before and after TLR3 and TLR4 stimulation through low-level and short-term TLR-priming protocol.

Methods: After isolation and characterization of OE-MSCs (N=10) and AT-MSCs (N=10), flowcytometry analysis was used to assess the expression of TLR3, TLR4 by MSCs. Secretion levels of immune-related genes were analyzed using ELISA technique. Then, the effect of MSCs in both before and after LPS, PIC or IFN-γ treatment on the proliferation inhibition and on differentiation (into Th1, Th2, Th17 and Treg cells) of naïve T cells that stimulated by Anti-Human-CD3 and Anti-Human-CD28, in co-culture was evaluated by flowcytometry.

Results: Based on the results, the gene expression and also protein levels of both TLR3 and TLR4 were significantly higher in OE-MSCs, compared to AT-MSCs. Among the examined cytokines and chemokines, OE-MSCs exhibited significantly higher levels of CCL5, IL-8, and TGF-β production, in comparison with AT-MSCs. Whereas, treatment of MSCs with LPS and PIC had little effect on the pattern of cytokine secretion but increased the inhibitory capability of MSCs on proliferation of naïve T cells. In addition, AT-MSC and OE-MSC were able to enhance the differentiation of naïve T cells into Treg cells.

Conclusion: According to the obtained data, OE-MSCs had stronger immunomodulatory effects, compared to AT-MSCs. Before and after LPS or PIC treatment, OE-MSCs secreted greater amounts of chemokines and TGF-β and thus had a higher ability to inhibit proliferation of naïve T cells and to differentiate naïve T cell into Treg. According to our results, it seems that OE-MSCs are able to attract immune cells by chemokine secretion and then inhibit them by TGF-β secretion.

Keywords: Mesenchymal stromal cells; Toll-like receptors; human olfactory mucosa; adipose tissue; Immunomodulation.

18337

Over-expression of MARCH-1 in U937 cell line promotes alternative features (M2) of macrophage

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Background: Functional plasticity of macrophages have been concerned in various disease conditions. Two macrophage subsets (M1 and M2) have been identified. M1 (classical) and M2 (alternative) macrophages are functionally antagonistic to one another. During the initial of inflammation, M1 macrophages dominate the site of infection with anti-microbial activity, however M2 macrophages release anti-inflammatory cytokines such as IL-10, which negatively regulate M1 activity and secrete products concerned in wound healing.

The membrane-associated RING-CH (MARCH) proteins are part of a family of RING type E3 ubiquitin ligases containing 11 known members, some of which target important players of the immune response. MARCH1 is mainly found in secondary lymphoid organs, more specifically in the endocytic pathway of dendritic cells (DCs) and B cells. MARCH1 reduces the half-life of peptide/MHC II complexes by causing their redistribution from recycling endosomes to lysosomes. MARCH1 is highly expressed in conventional immature DCs, and its downregulation by LPS stabilizes cell surface peptide. In this study, we investigated the possible role of MARCH-1 over expression in U937 differenciated macrophage plasticity.

Methods: 2 groups of cells, 1- MARCH-1 expression +PMA. 2-NO-MARCH-1 expression +PMA (control) were planned. $5*10^5$ cells of U937 cell line were transduced with lentviral vector expressing MARCH-1. After 72 hrs of transduction, cell were treated by 50 ng/ml PMA for more 3 days for differentiation to macrophage. Cell morphology was seen by light microscopy. The concentration of IL-10, TNF-α, IL-6 were studied by ELISA. The expression of CD14, CD163 were studied by flowcytometry.

Results: Data showed that the concentration of IL-6, TNF-α in MARCH-1 expressing cells were higher than control group. The concentration of IL-10 in MARCH-1, PMA treated was 2 folds rising compared to control group(p value < 0.05). cell surface expression of CD163 was higher than control group but not significant. The viability of PMA treated cell was less than control group.

Conclusion: in conclusion, our data showed that over expression of MARCH-1 promotes anti-inflammatory features of macrophage in u937 differenciated cell line.

Keywords: MARCH-1, U937, macrophage, PMA

18378

Comparison of the amount of exosomes isolated from the supernatants of AD-MSCs and HepG2 cell culturs by BCA and Bradford protein assays

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Background: Exosomes are 30-100 nm endosome-derived vesicles that secrets from all cell kinds to the environment. These Nano-vesicles carry cellular lipids, proteins, mRNA, and non-coding RNA and delivered their contents to the target cells in a receptor-mediated manner or by membrane fusion. Recently, exosomes have been considered as drug delivery systems for immunotherapy. Since the amount of exosomes is estimated based on the amount of protein, it is important to choose an efficient protein measurement method. In the present study, two protein assay methods were compared.

Materials and Methods: For this purpose, human Adipose mesenchymal stem cells (AD-MSCs) and HEPG2 cell lines were cultured in T75 culture dishes to reach 80% confluency. Then the cells were washed with PBS and cultured with FBS-free DMEM-media for 5 days. Every 24 hours, supernatants were collected and stored at -20°C. Finally, the exosome was isolated using the precipitation method. Size and morphology of exosomes determined by DLS and SEM analysis. BCA and Bradford assay estimated the exosome protein content of collected samples.

Results: Based on electron microscopy and DLS analysis, the exosomes' normal morphology and size in the range of 30-100 nm were confirmed. According to protein estimation results, the amount of protein in the BCA method was significantly ($p \leq 0.05$) higher than the Bradford method at all times. The maximum production in AD-MSC and Hep-G2 based on BCA and Bradford method was reported in the 72-hour post starvation at 1562.77973 and 1157.624633 mg/ml respectively for AD-MSC and 1471.9531 and 1206.01173 mg/ml respectively for Hep-G2.

Conclusion: Since the peptide bonds and aromatic amino acids react with the BCA and Bradford reagents, respectively, it is expected that the estimated amount of protein in the BCA method will be closer to reality. But there is no difference in determining the peak time of exosome production between these two methods.

Keywords: BCA, Bradford, exosome, Hep-G2, AD-MSCs

18386

Human placenta-derived mesenchymal stem cell therapy in patients with COVID-19

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Background: SARS-CoV-2 that causes COVID-19 disease, a genus of the β-lineage Coronaviridae family, is RNA enveloped virus that emerged for the first time in Wuhan, China December 2019. COVID-19 host immune response depends on ACE2 and Spike proteins that are implicated in inflammatory responses. COVID-19 has no effective treatment, and order is mostly based on symptoms and antiviruses. MSCs transplantation from several sources as a major anti-inflammation has been suggested to treat inflammatory diseases treatment. Mesenchymal stem cell therapy in COVID-19 patients may be characterized as a crucial therapeutic mediator too. This systematic review will provide an overview of the Human placenta-derived-MSC therapy related to SARS-CoV-2 infection treatment.

Methods: This systematic review study was performed to identify studies using 5 key words Stem Cell, Immune Modulator, Human placenta, Coronavirus, COVID-19, published in Scopus, Pubmed, Google Scholar databases in 2019-2020 Time interval. From initially 25 identified 20 articles, **were selected after** scanning**.**

Results: The COVID-19 stimulates inflammatory condition and suppress the respiratory system. ACE2 is a host cell receptor for SARS-COV-2 inflammatory function. Cell-based therapy of COVID-19 characterized as potent immune-modulatory properties among these Human placenta-derived-MSCs are superior due to having almost 100% genetic information, stem properties, differentiation sensitivity, ease of genetic manipulation, highest cell proliferative capacity, low level of ACE2, anti-inflammatory signature, and renewal. They migrate to the lung after systemic injection. Their low immunogenicity profile protects them from rapid immune destruction and dampens on local activation of immunity. All of those previously mentioned advantages make Human placenta-derived-MSCs perfect immunotherapeutic purposes of COVID-19.

Conclusion: In the context of COVID-19 immunopathogenesis and inflammation, the Human placenta-derived-MSC transplantation is considered a convincing event. These attempts urge clinicians to utilize anti-inflammatory therapeutic strategies using human placenta derived-MSC, targeting inflammatory system regulation in COVID-19 patients.

Keywords: Human placenta-derived- MSC, COVID-19, SARS-COV-2, Immunity.

18413

The effects of mesenchymal stromal cells on neutrophils isolated from severe congenital neutropenia patients

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Background: Neutrophils are the most abundant, yet with the shortest lifespan among the circulating leukocytes. These cells are produced in the bone marrow during granulopoiesis process. Severe congenital neutropenia (SCN) is a hematological disorder with disturbance in granulopoiesis process, in which the neutrophils apoptosis rate is escalated. Previous reports indicated that mesenchymal stem cells (MSCs), as an immunomodulator cell, could increase neutrophil lifespan in addition to the supportive effects on cardiomyocytes or the neuroprotective effects. So, we examined the effects of MSCs on function and survival of SCN neutrophils.
Methods: In this study, MSCs were co-cultured with neutrophils isolated from SCN patients. Then, we evaluated the MSC co-culture effects on neutrophils survival (annexin V/PI assay), reactive oxygen species (ROS) production (colorimetric NBT assay), and phagocytic activity (Giemsa staining after exposure to yeasts).
Results: It was demonstrated that MSC co-culture could increase neutrophil lifespan and phagocytic activity of the neutrophils isolated from SCN patients.
Conclusion: It could be concluded that MSCs could be considered as novel candidates for treatment of SCN patients.
Keywords: Mesenchymal Stem Cell, Neutrophil, Apoptosis, Severe congenital neutropenia.

18456

The Effect of Different Culture Media on Phenotype and Growth of Amniotic Epithelial Cells

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Abstract:

Background: Human amniotic epithelial cells (hAECs) have properties of stem cells with unique immunomodulatory characteristics. To evaluate the potential immunomodulatory effects of these cells, we can co-culture them with other cells, especially immune cells. Also, the culture media has important impacts on these cells behavior. In the present study, we investigated the effect of some common culture media for immune cells culture on the growth and phenotype of hAECs.

Methods: Freshly isolated hAECs from three amniotic membranes were cultured in optimum cell culture conditions including 37 °C, 5% CO2 and >80% humidity in T25 flasks. Three types of culture media, including RPMI-1640, DMEM-High Glucose, and DMEM/F12 were used as complete media.

Results: The cells adhered and they had epithelial phenotype after 24 hours in all types of media. However, cultured cells in RPMI-1640 were survived for three days, but we did not find significant proliferation and adhesion. AECs cultured in DMEM-HG media were stable up to 14 days with an acceptable viability and phenotype, but their proliferation was steadily limited. Moreover, in DMEM / F12 media, hAECs had viability and logarithmic growth phase up to 21 days with increased cell adhesion capacity.

Conclusion: According to our findings the optimum culture medium to keep the stem cell characteristics of hAECs is DMEM/F12. However, DMEM-HG medium is recommended to induce differentiation or co-culture with a controlled and steady cell number.

Keywords: amniotic epithelial cells, culture medium, phenotype

18499

Wharton's Jelly Mesenchymal Stromal Cells Conditioned Media and Exosomes Augmented Neutrophil Lifespan and Phagocytosis Capacity

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Background: Neutrophils are the first cells involved in inflammation and pathogen elimination, but they have a short lifespan. So, strategies for enhancing neutrophil lifespan and activities can be useful in many situations such as patients with immunodeficiencies. Previous researches demonstrated that mesenchymal stem cell (MSC) has anti-apoptotic effects on neutrophils. These multipotent cells can be isolated from different tissues. MSCs isolated from Wharton's jelly (WJ-MSCs), may be better candidates than MSCs obtained from bone marrow or adipose tissues. Cell to cell contact or secretion of soluble factors and exosomes are the main approaches of MSCs in applying their effects.
Methods: Exosomes and conditioned media (CM) were prepared from WJ-MSCs. Then, neutrophils were isolated and cultured with medium, CM, or exosomes. Then, neutrophil respiratory burst, apoptosis, and phagocytosis capacity were assessed by NBT assay, Annexin V-PI method, and Giemsa staining, respectively.
Results: It was recognized that both treatments improved neutrophil lifespan and phagocytosis. Only MSC-CM could enhance neutrophil respiratory burst.
Conclusion: This research demonstrated that MSC-exosomes and CM have protective effects on neutrophil function and lifespan. MSC mediators can be responsible factors for protective functions of MSCs on neutrophils.
Keywords: Mesenchymal Stem Cell, Neutrophil, Exosome, Conditioned Media

18585

The effect of Conditioned medium of Mesenchymal stem cells treated with nicotine on Concanavalin A induced Autoimmune hepatitis induced in C57BL/6 mice

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Background: Autoimmune hepatitis (AIH) is an autoinflammatory and chronic liver disease. Stem cells are undifferentiated cells with capability of self-renewal and differentiation through replication. Results from clinical studies show therapeutic potential of stem cell based therapy in the treatment of autoimmune diseases. Nicotine appears to be an important immunomodulatory molecule that inhibits the expression of inflammatory cytokines and is able to alter cell morphology. In this study, nicotine-treated mesenchymal stem cell supernatant was used to treat acute autoimmune hepatitis.
Methods: C57bl6 mouse mesenchymal stem cells were isolated and cultured in flasks. These flasks were exposed to 0, 0.1, 0.5 and 1 µM nicotine for choosing the best concentration of nicotine.
In the in vivo phase, 75 C57bl6 mice were divided into 9 groups. Mice in different groups were injected with Con A to induce acute hepatitis. Mesenchymal stem cell supernatant was used to treat these mice and prednisolone was used to determine the effect of treatment. Sampling was performed 8 hours after injection of 20 mg / kg.
Results: The results of mesenchymal stem cell culture tests with different amounts of nicotine showed that the supernatant of nicotine-treated stem cells has immunomodulatory properties and can be used to treat acute autoimmune hepatitis. The results of treatment with the prednisolone-treated group are comparable
Conclusion: The obtained data can offer a new insight into the potential mechanisms, underlying the immunomodulatory effects of nicotine.
Keywords: Conditioned medium of Mesenchymal stem cells, Nicotine, Concanavaline A.

18633

Investigating the development of Iranian branding in stem cell therapies

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Introduction : Patients' knowledge and need for new therapies during the last decade in Iran has been the focus of researchers and the country's treatment system and supported by extensive research activities and projects in the field of stem cells, medical biotechnology, nanotechnology and pharmaceutical fields. a great deal has also been achieved. centers active in this field have started working with strategic plans and long-term approaches in order to evaluate great and innovative ideas in recognizing the disease and treating patients in the country, and it promises a great revolution in the treatment of the country. On the other hand, the market for such services requires new strategies to meet the growing needs of patients.

Methods : In this study, by reviewing the data obtained from the development of stem cell-based therapies and reconstructive medicine in Iran, we present branding development strategies with the aim of providing models for attracting international patients and improving the quality of services and foreign exchange earnings.

Results : The study of stem cells in Iran began in 1992 and achieved significant progress over a period of 20 years; to the extent that the Islamic Republic of Iran is currently the third country in the world in the practical use of this knowledge. the formation of a human starts from 16 stem cells, and therefore the importance of stem cells is that they have the ability to form a complete human; The discovery of stem cells, like the discovery of genes or DNA, has revolutionized the world, and today many diseases of the liver, heart, and especially blood diseases can only be treated with stem cells. The results of the scientists' research have led them to say that in the next 20 years, about 80% of diseases will be treated through stem cell transplantation, and therefore it is necessary to pay attention to stem cells in the country. Iran is the third country to extract stem cells from the pulp of deciduous teeth, and this is only done in countries such as the United States and Japan. Iran is also one of the one percent of countries in the world that has the ability to transplant hematopoietic stem cells.

Conclusion : Iran has now made good progress in research and treatment in the field of stem cells, one of the most important steps that can be taken in Iran to take advantage of this strategic potential of Iranian researchers and physicians is to expand the admission of international patients in cell therapy centers and hospitals providing stem cell therapy services throughout the country. It should be noted that stem cell-based therapies in Iran can have a significant annual contribution in attracting international patients and health tourists to the country, which among the issues that should be addressed can be the establishment of representation in target countries, effective advertising Through international media and the production of content in foreign languages, he mentioned the establishment of facilitators and as a key and important step to improve the quality of clinical services.

Keywords : stem cell, health tourism, Iran

18654

Mesenchymal stem cells ameliorate sulfur mustard-induced pulmonary complications

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Background:
Sulfur mustard (SM), as a chemical agent, causes major long-term pulmonary complications. Due to the poor understanding of SM immmunopathogenesis mechanisms, there is a lack of effective medical care for the victims. Prolonged activation and the imbalance between two alveolar macrophage phenotypes (AM) (M1 vs M2) are known to be the main culprits of SM toxicity. We tried to investigate the effectiveness of the therapeutic effect of adipose-derived mesenchymal stem cells (AD-MSC) and MSC-derived conditioned medium (CM-MSC) on long-term pulmonary injury induced by CEES, an SM analog, in an animal model.
Methods:
C57Bl/6 mice initially received CEES and were then treated with either AD-MSCs or CM-MSC. The immunophenotypical analysis of surface markers of AMs and regulatory T-cells was carried out by flow cytometry and the concentration of cytokines were also determined by ELISA. The functional changes in the lungs were also checked using SPECT and histopathology.
Results:
AD-MSC or CM-MSC injection following CEES administration, reduced histopathologic changes in the lung that were also confirmed by SPECT imaging. Both treatments reduced the levels of pro-inflammatory cytokines and induced modulating effects on T-regs in the lymph nodes after CEES exposure. M1 and M2 macrophage accumulation (CD86 and CD206-expressing macrophages respectively) in response to CEES exposure, was reduced after AD-MSC and CM-MSC administration and this modulating effect in the M1 subset was much more pronounced, compared to the M2 subset.
Conclusion:
The therapeutic effect of MSCs in CEES pulmonary-long term complications were due to restoring the balance between M1/M2 alveoal macrophage populations and may represent an effective approach to protect lung injury induced by mustards.
Keywords: Sulfur mustard, Alveolar macrophage, Inflammation.

18708

Histopathologicul study of effect of human Wharton's jelly mesenchimal stem cells extract on skin wound healing in rat

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Abstract

Background: Wound a disruption in its natural form and function of skin with underlying texture. To keep the integrity of skin to protect against bleeding, dehydration, prevention of microorganisms to the body its safety is vital. It's been analyzing since years ago by scientists and researchers to heal wounds in shortest time with least side effects. The use of stem cells is one of the methods to accelerate the process of healing wound. Mast cells are extraordinary to the capability of rebuilding and reproduction of the. Most of The exerted researches try to make use of the cell extract as the product of stem cells.

Methods: The study was performed on 28 Wistar rats divided randomly into four equal groups. A skin wound was created sharply. The first group was injected 1 cc of PBS Intradermal around the wound. In the second group, the human Wharton's jelly mesenchymal stem cells extract with concentration of 5%, third group with 10% and the fourth group with 20% was injected 1 cc Intradermal around the wound. After 48 hours, the next injection conducted in the same way. On days of 7th, 14th, 21st after injection, a particle of healthy and injured tissue was sampled into Formalin 10% and coloured sections (H&E) were examined.

Results: In Histopathological study, the re-epithelialization in the 5% group was complete, and with increase of cell extract concentration, the re-epithelialization was decreased. The healing tissue was acanthotic and there was no sign of acute, chronic or plural inflammation. The wound healing was also significantly faster in-group 5%, in comparison with the control group but the wound healing was not significantly faster in groups 10% and 20%, in comparison with the control group.

Conclusion: The results showed that the human Wharton's jelly mesenchymal stem cells extract with concentration of 5% has a significant effect on skin wound healing.

Keywords: Histopathology, Wound healing, Stem cell, Skin

18733

Characterization of manipulated human mesenchymal stem cells with lentiviral vector.

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Background: Gene therapy could be a potential approach for treatment of many diseases. Viral vectors are tools which are used to insert genes into stem cells genome until they deliver genes or proteins into targeted organs or tissues. Since critical parameters can be used for the detection and isolation of manipulated stem cells from forming cells of targeted issues, the present study aimed to examine the effects of lentiviral vectors on identity features of stem cells.

Methods: Three lentiviral vectors, i.e., psPAX2, PMD2, and PCDH, were added on the HEK-293T cell line by using the calcium phosphate method. Viral supernatant was collected, centrifuged, and then added to the human adipose-derived mesenchymal stem cells (hASCs). on the sixth day, transduced hASCs were analyzed and compared to untransduced hASC in terms of critical parameters such as morphology, adhesion intensity, differentiation capacity to adipocyte and osteocyte lineages as well as the expression level of differentiation markers.

Results: The microscopic examination of transduced and untransduced mesenchymal stem cells by inverted microspore showed fibroblast like cells in both groups. By using alizarin red and oil red, the differentiation ability into osteogenic and adipogenic lineages were approved in both test and control groups. The expression of markers CD34 and CD166 did not indicate any significant differences between the test and control groups in flow cytometry technique.

Conclusion: The present study indicated that lentiviral vectors had no adverse effect on the identity features of stem cells. Therefore, stem cell characteristics can be used for the identification of the manipulated stem cells from other cells in inflammatory areas.

Key words: Manipulated mesenchymal stem cell, Lentiviral vector, Flow cytometry

18722

Evaluation the therapeutic effects of rat bone marrow-derived mesenchymal stem cells (BM-MSCs) in Glycerol-induced Acute Kidney Injury (AKI) and their effects on the types of T helper cells in the kidney of diseased rats

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Background: AKI, as a serious and abrupt kidney disturbance, is accompanied with infiltration of immune cells to affected kidneys. However, the changes of immune factors in affected kidneys have not been compared between the two well-known models of AKI (Glycerol-induced and Ischemia-Reperfusion-mediated AKI). On the other hand, MSC-based therapy is emerging as a novel approach to accelerate the kidney recovery and alleviation of the established inflammation in AKI. Therefore, the aim of this study was to compare the expression of T helper cells-dependent cytokines and transcription factors in the two models of AKI and the effect of MSC therapy on the expression of T helper cells-dependent cytokines and transcription factors in glycerol-induced AKI was also investigated.
Method: After uniformizing of disease severity in two models of AKI, the expression of Th-dependent cytokines and transcription factors in kidneys were compared by quantitative real-time PCR (RT-PCR). In addition, 4×10^6 and 8×10^6 cells rat bone marrow-derived MSCs were administered intraperitoneally to study their effects in glycerol-induced AKI model. The expression of genes-related to T helper cells in affected kidneys was also evaluated through RT-PCR. Pathological changes were also studied microscopically after H&E staining of affected kidneys.
Results: The expression of Th-dependent genes and histopathological changes were almost similar in two models of AKI. Moreover, IP injection of BM-MSCs an hour after rhabdomyolysis reduced the ratio of expression of inflammatory/anti-inflammatory-related genes in the kidneys of inflicted rats. In addition, by increasing the number of injected cells (8×10^6 cells/rat), the recovery of renal function in rats suffering from AKI was facilitated.
Conclusion: The immunological changes in two models of AKI are similar and the results of studies that use each of these two models can be generalized to each other. In addition, we found that MSCs therapy would ameliorate the pathological complications of the disease.
Keywords: AKI; BM-MSC

18792

Investigation the effect of Toll like receptor 3 stimulation on the expression of galectins in exosomes isolated from human Wharton's jelly mesenchymal stem cells

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Background: The regenerative and immunomodulatory properties of mesenchymal stem cells (MSCs) make them potential cellular candidates for the treatment of variety of immune-related diseases. Due to the limitations of cell therapy in the treatment of diseases, exosomes secreted by MSCs are increasingly being considered as prospective non-cellular therapeutics through paracrine effects. Immunomodulatory activities and the contents of exosomes derived from MSCs can change under inflammatory conditions such as TLR-agonist engagement which could further affect their therapeutic potential. Galectins play an immunosuppressive role in MSCs. The aim of this study was to investigate the expression of galectins gene in exosomes isolated from human Wharton's jelly mesenchymal stem cells (hWJ-MSCs) after stimulation with Poly (I:C).

Methods We isolated hWJ-MSCs based on explant culture. HWJ-MSCs were treated with Poly(I: C) for 12, 24 and 48 hours. Then, exosomes were isolated from the culture supernatants. The size and morphology of the exosomes were analyzed by DLS and SEM. At each period, 12 ,24 and 48 hours after treatment the gene expression of galectin 3, 9 were examined by Real-Time PCR.

Results: Our results showed that after stimulation with Poly (I:C) after 12h, the expression of galectin 9 gene significantly increased compared to the control group ($P<0.05$) and after 24 and 48h, the expression of galectin 9,3 genes significantly increased compared to the control group ($p<0.01$, $p<0.05$).

Conclusion: TLR3 stimulation can improved the immunosuppressive abilities of exosoms derived from hWJ-MSCs via increase the expression of galectins gene.

Keywords: Exosome, Galectin3, Galectin9, TLR3, Mesenchymal Stem Cells

Congress Abstracts

Tolerance & Autoimmunity

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

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Evaluation of SOCS1 methylation in patients with Behcet's disease.

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Introduction: Epigenetic discusses to inherited changes in mitosis and meiosis in the gene expression pattern which is independent of primary DNA sequence. Since, SOCS1 hyper-methylation can activate JAK / STAT signaling pathway and activation of this pathway can directly affect the impact of different cytokines on cell function and subsequently lead to pathophysiology of diseases, in particular autoimmune diseases that interact directly with the amount of cytokines and due to the fact that the cause and pathology of Behcet's disease (BD) have not ever been completely determined. So, the purpose of this study was to evaluate the methylation pattern of SOCS1 gene in patients with BD and compare them with healthy group. **Methodology**: This study was a case-control study in which 50 patients with BD and 60 subjects as healthy group participated. Blood samples were collected from all participants and then Peripheral Blood Mononuclear Cells (PBMCs) were isolated through Ficoll method. After extraction of DNA by Salting out method and its analysis with Nano-drop, the methylation level of SOCS1 was examined using qMS-PCR technique. **Results**: Findings about methylation and gene expression in SOCS1 gene showed that the level of SOCS1 methylation was increased in patient groups compared with healthy subjects (control group) which the increase was statistically significant (p-value<0.05). Also, the results of gene expression revealed that the fold change of SOCS1 gene expression was decreased in patient group compared with healthy subjects which the decrease was statistically significant (p-value<0.05). **Discussion And Conclusion:** According to the results of this study, it can be suggested that the DNA methylation of SOCS1 gene is likely to affect the gene expression and thereby contribute to the pathogenesis of Behcet's disease.

Keywords :Behcet's disease SOCS1 methylation

18601

Differential expression of miR-27a and miR-138a in patients with systemic sclerosis

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Background: Systemic sclerosis (SSc) is a chronic disease affecting connective tissue, which is characterized by skin thickening and visceral involvement due to fibrosis, vascular damage, and autoimmunity. Due to their potent regulatory roles in molecular pathways, microRNAs are extensively being studied to be utilized for diagnosis and treatment of various diseases such as SSc. MiR-27a and miR-138a are well known for their roles in fibrosis and cancer; hence we hypothesized that their expression could be dysregulated in the blood of SSc patients.

Methods: Blood was collected from 60 SSc patients (30 limited and 30 diffused) diagnosed by rheumatologists according to ACR/AULAR criteria; following RNA isolation and cDNA synthesis, real-time qPCR was performed on the samples using Taq-Man probes. Besides, sensitivity and specificity of the relative expression of these two microRNAs were assessed using ROC analysis.

Results: After data analysis, it was revealed that miR-27a was significantly down-regulated, while miR-138a was significantly upregulated in whole blood of the SSc patients compared to healthy individuals as the control group.

Conclusion: It seems that miR-27a and miR-138 both play a role in SSc pathogenesis, and their aberrant expression could result in the disease onset or progression. It is speculated that miR-27a likely targets some anti-SSc factors that are elevated upon downregulation or absence of miR-27a. Since no difference was observed between limited and diffused patient groups, it is unlikely that miR-27a has a role in disease progression. But, because miR-138a was only significantly upregulated in diffused SSc patients, it may has a role in disease progression; the differential expression of miR-138a could be employed in diagnosis of diffused form of SSc too. According to ROC analysis of qPCR data, the results implicate that miR-27a expression shows high sensitivity and specificity; thus it can be used as a diagnostic biomarker in systemic sclerosis.

Keywords: systemic sclerosis, SSc, scleroderma, miR-27a, miR-138a, miRNA, gene expression, microRNA

18257

Effect of Platelet Rich Plasma and Autologous Conditioned Serum on Knee Osteoarthritis: A Randomized Clinical Trial

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Introduction: Knee osteoarthritis (OA) is one of the common degenerative articular disorder that is associated with decreased quality of life. Currently novel biologic therapeutic approaches are introduced in literature for OA management. In this study, clinical efficacy of platelet-rich plasma (PRP) and Autologous Conditioned Serum (ACS) injection on the level of pain and function in Knee OA were compared.

Methods: A randomized clinical trial was conducted on 62 knee OA patients. Patients were randomly divided into two groups: 30 received autologous PRP for 2 time with 7 days interval, and in the remaining 32 patients 2ml of ACS were injected 2 times every 7 days. Study participants were assessed through the Western Ontario and McMaster Universities (WOMAC) score, the Visual Analogue Scale (VAS), at baseline, 1 and 6 months post intervention.

Results: Both ACS and PRP treated patients showed amelioration in pain intensity and knee function during 1 and 6 months pursue; however, this progress was more significant in ACS group.

Conclusions: Treatment of Knee OA with ACS and PRP injections are associated with pain reduction and knee function improvement. Not only, ACS therapy is more effective than that of PRP, but also due to its less variation in processing and less reported side effects, it could be considered as a safe and effective non-surgical alternative for OA management.

Key words: Knee Osteoarthritis; Autologous Conditioned Serum; Platelet-Rich Plasma

18152

Effect of hydroalcoholic extract of *Ferula assa-foetida L.* resin on rheumatoid arthritis symptoms in the collagen-induced animal model

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Background: : Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease that affects synovial tissue in multiple joints. According to potential side effects of current treatments, interest in using complementary and alternative medicine(CAM) has reappeared.The purpose of this study was to evaluate the effect of extract of Ferula assa-foetida L. resin on the severity of rheumatoid arthritis symptoms which is caused by collagen.

Methods: In this experimental study, 30 female Wistar rats were randomly divided into 6 groups: healthy control, CIA, Dexamethasone receiving group to amount 1 mg/kg, receiving group to 100 mg/kg concentration of extract of asafoetida resin, receiving group to 300 mg/kg concentration of extract of asafoetida resin and receiving group to 100 mg/kg extract and dexamethasone (mixed group). Rheumatoid arthritis was induced by the administration of collagen type 2 and adjuvant. The clinical evaluation started and the severity of the symptoms of rheumatoid arthritis, by examination and standard scoring was performed.

Results: From the thirteenth day, Symptoms of the disease appeared and from the fourteenth day, there was a significant difference between the control and CIA groups in the clinical symptom score of arthritis. Among intervention groups, receiving group to 100 mg/kg concentration of extract earlier and more cause to decreased severity of symptoms. So on the 28th day, disease severity in the control group was 13.4 and in the treatment group with a concentration of 100 mg/kg extracts of Ferula assa-foetida L. resin was 9.6

Conclusion: Hydroalcoholic extract of asafoetida resin, its could reduce the severity of symptoms of ankle RA and in the dose of 100 mg/kg cause to mitigate the symptoms of apparent swelling and inflammation

Keywords: Arthritis Animal Model ;Ferula assa-Foetida L; Rheumatoid Arthritis

16754

investigation of Lactobacillus rhamnosus and Lactobacillus delbrueckii effects on differentiation of macrophages produced from monocytes to M1 and M2 subtypes in patients with rheumatoid arthritis.

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Background: RA is a systemic, chronic, inflammatory disease that affect 0.5 to1 percentage of population. lead to progressive destruction of joints and bones, poly arthritis and if left untreated, result in extra-articular complications, as vasculitis, neurological, pulmonary and cardiac symptoms. gastrointestinal microbiota affects this disease by pathogenic bacteria restriction, determining M1 or M2 deviation of macrophages. macrophages play important role in RA. osteoclast, M1 and M2 are macrophages determine RA fate. M1 macrophages involved in antigen presentation and production of TNF, IL1 and IL6 that result in activation and proliferation of osteoclasts and fibroblast synovial cells (source of RANKL and MCSF) .M1 also can produce CCL2, IL8 ,IL12 and IL23 which responsible for neutrophil attraction, differentiation to TH1 and TH17 respectively .on the other hand M2 macrophage by IL10 and TGFβ result in immune system suppression and repair damages . in this study we investigate invitro effects of this bacteria in macrophage polarization that show conflict results in similar studies.

Methods: in this study we cultured lactobacillus and gained PBMC from buffy coat of RA patients by ficoll-hypaque preparation then isolated monocytes by cell adhesion method in RPMI medium and convert theme to macrophages. then co-cultured bacteria and macrophages and check marker and gene expression by PCR and flow cytometry respectively to find out M1 or M2 deviation

result: tolerogenic lactobacillus are expected to reduce local and systemic inflammation by increase of M2/M1 ratio this finding can approve by checking CD206, CD86 and CD80 cell markers with flowcytometry and reducing the expression of IL1, IL12, TNF and increase of INOS IL10 by PCR

conclusion: rheumatoid arthritis is a debilitating and painful disease that require high cost medical treatment. this medication can have side effects and sometimes may not be effective. lactobacillus have few side effects and can regulate immune system instead of suppression and affect disease condition.

key words: rheumatoid arthritis, probiotics, inflammation, macrophage

16743

Beneficial effects s of combined prednisolone and theophylline in improving experimental rheumatoid arthritis

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Background: Rheumatoid arthritis (RA) is an inflammatory and autoimmune disease known as synovial inflammation and joint damage in several joints. Immunomodulatory effects of theophylline and prednisolone were documented in previous surveys. This study was designed to evaluate the combined effects of theophylline and prednisolone in an experimental model of RA.
Methods: Fifty male Wistar rats were divided into equal five groups: normal group, RA group, RA rats treated with theophylline (20 mg/kg orally), RA rats treated with prednisolone (2mg/kg orally), and RA rats received combined theophylline and prednisolone. All protocols were started at day seven p.i. when all animals had a clinical score of ≥1. Clinical signs were monitored every other day until day 23 p.i.

Results: Combination therapy ameliorated the severity of the signs and improved weight-gaining more impressive than each treatment alone. Moreover, combination treatment promoted a significant detraction in some sera parameters pf RA, like Myeloperoxidase, C-RP, and Nitric oxide more pronounced than each therapy alone. Also, RT-PCR results showed that combination therapy has more beneficial effects in the reduction of TNF-α in articular tissues of RA rats compared to monotherapy.
Conclusion: Combined prednisolone and theophylline is a promising strategy to reduce the inflammation in a rat model of RA.

Keywords: Rheumatoid arthritis, Prednisolone, Theophylline, Wistar rat.

16576

Effects Of β-D-mannuronic Acid On TLR2 And TLR4 Expression And Downstream Signalling In Monocyte Derived Macrophages In Ankylosing Spondylitis Patients

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Objective; The β-D-mannuronic Acid (M2000) is a new non-steroidal anti-inflammatory drug (NSAID). We have previously shown that expression level of genes associated with TLR/NF-kB Signaling Pathway are reduced in PBMC (Peripheral blood mononuclear cells) of treated Ankylosing Spondylitis (AS) patients with M2000 under in vivo condition. Here, we aimed to determine the effect of M2000 on TLR2 and 4 expression and their downstream signaling in monocyte derived macrophages in AS patients under in vitro condition.

Methods; The blood samples were used for isolating PBMCs and then using Magnetic Activated Cell Sorted (MACS) method, monocytes were isolated and differentiated to macrophages for evaluating TLR2 and TLR4 expression by flow cytometry and Myd88, MAPK14, NF-KB (p65 subunit) and IkB-α gene expression by Real time PCR. Cell culture supernatants were collected and the concentrations of TNF-α and IL-6 cytokines were performed by enzyme-linked immunosorbent assay (ELISA).

Results; The gene expression of NF-κB and MAPK14 was significantly increased in the monocyte derived macrophages from AS patients in comparison with that of healthy subjects. Furthermore, Our results showed that M2000 alone and in combination with TLR2/4 agonists (LTA/ LPS) significantly suppress the TLR2,4 expression and downstream signaling pathway in monocyte derived macrophages. Also, the production of TNF-α and IL-6 was decreased in M2000-treated monocyte derived macrophages.

Discussion; It should be noted that the inflammation triggered through TLR2,4 is important in the pathogenesis of AS. Therefore, M2000 might be recommended as a therapeutic option by modulating TLR2 and TLR4 expression in AS patients.

Key words: β-D-mannuronic acid, TLR, Ankylosing spondylitis, NF-kB, MAPK14, Myd88, IKB- α

(18743)

Reduction of circulating CD19 / CD24hi / CD38hi Breg cells could result in Psoriasis pathogenesis

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Introduction: Psoriasis (Ps) is the most common, chronic, heterogeneous immune-mediated inflammatory form of dermatological diseases that a detailed interaction of environmental factors with genetic background and immunologic elements might play an implicated role in the pathophysiology of psoriasis. We aimed to design this work to determine the frequency and essential function of blood Breg, which bears specific CD19+CD24hiCD38hi markers in individuals with psoriasis compared to healthy control persons with taking together the susceptibility of different risk factors contributing to the immunopathology of psoriasis.

Material and Methods: From January 2018 to March 2019 a total of 28 psoriasis patients and 23 healthy individuals, presenting to the dermatology ward and clinic of the Imam Khomeini hospital affiliated to Jundishpur University of Medical Sciences, Ahvaz, Iran, were enrolled in this case-control study for monitoring concurrent frequency discovery of peripheral blood regulatory B (Breg) cells using multi-color flow cytometry method. Two-tailed t-test and the non-parametric chi-square, Fisher's exact and Mann-Whitney U tests, and the bivariate Pearson correlation test were used to evaluate significant differences and the linear canonical relationship between two ordinal independent variables. The $p<0.05$ criterion was set as the threshold of significance.

Results: Our data showed that circulating CD19 / CD24hi / CD38hi Breg cells with regulatory capacity was significantly reduced in patients with psoriasis, unlike healthy B cells from healthy individuals ($p<0.001$).

Conclusion: We integrated our findings into a model of active psoriatic skin lesions versus normal skin that confirmed prominent modulatory and disturbance effects of the remarkable reduction of Breg cells, resulting in the promotion of distinct adaptive immunity resistance and Ps pathogenesis.

Keywords: Psoriasis, regulatory B cells, flow cytometry, PGA, PASI Score.

(18663)

Evaluation of TLR2, TLR4, TLR9 expression with Angiopoietin 4 proteins affection on mono nuclear cells in MS patients

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Background: MS is an inflammatory disease in which the myelin sheaths of nerve cells in the brain and spinal cord are damaged. This injury can impair the ability of the parts of the nervous system that are responsible for communication and cause many physical signs and symptoms. TLRs are also present in the brain in addition to blood cells and tissue epithelial and endothelial cells. The reason for choosing TLR2, TLR4 is due to the great importance of these two receptors in transmitting messages at the cell surface and membrane surface.

Methods: 30 MS patients referred to Imam Reza MS clinic with mild to moderate stages were selected and blood samples were taken from patients and monocytes were isolated from PBMC by MACS method. Monocytes were evaluated by purity percentage by flow cytometry with CD14 antibody. Monocyte cells were then cultured and stimulated with angiopoietin 4 proteins at a time, zero, six, twelve, and twenty-four and forty-eight hours. After stimulation, the cells were collected and the expression levels of TLR2 and TLR4 were evaluated by Real-Time PCR.

Results: The expression level of TLR2 and TLR4 receptors decreased significantly with a time course of stimulation time, which reached its lowest value in 12 hours after stimulation. Compared to TLR2 and TLR4, the reduction rate was the same. The performance of angiopoietin 4 was evaluated as a time course.

Conclusion: The results of real-time PCR showed that angiopoietin 4 significantly reduced the expression of innate immune receptors such as TLR2 and TLR4. This decrease was in surface receptors such as TLR2 and TLR4.

Keywords: Angiopoietin 44, TLR2, TLR4, Multiple Sclerosis

(18593)

Therapeutic treatment with Curcumin decreases the severity of experimental autoimmune encephalomyelitis in animal model of Multiple sclerosis

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Background: Multiple sclerosis (MS) is the most frequent chronic inflammatory demyelinating autoimmune disorder of the central nervous system (CNS) causing a physical disorder and paralysis. Experimental autoimmune encephalomyelitis (EAE) is employed as an animal model for this disease. Curcumin is a natural product that is identified with its anti-oxidant and anti-inflammatory characterizes. This study was designed to reveal the immune responses that determine the effect of curcumin on EAE alleviation.

Methods: A total of 24 Female C57BL/6 mice were divided into three groups: Control group (receiving PBS), Low-dose treatment group (100 mg/kg curcumin) and High-dose treatment group (200 mg/kg curcumin). EAE was induced by myelin oligodendrocyte glycoprotein (MOG) emulsified in complete Freund's adjuvant and intraperitoneally injection of pertussis toxin. Clinical and weight parameters were monitored until day 25. Brain sections were stained with Hematoxylin and Eosin (H&E) and Luxol fast blue. The profile of proinflammatory and anti-inflammatory cytokines and transcription factors determined by ELISA and real-time PCR. Brdu assay was used for splenocytes proliferation.

Results: Histological studies revealed lower lymphocytic infiltration and demyelination in treated group. Mean Weight showed a significant increase in treatment group comparing with control group; development of the disease had an observable decrease in treated group in comparison to the control group. The secretion of inflammatory cytokines from inflammatory T cells decreased significantly in the treated groups. However, the secretion of anti-inflammatory cytokines in these groups has increased significantly compared to the control group.The proliferation of MOG-sensitive T lymphocytes was significantly reduced in the treated groups compared to the control group. Expression of transcription factor and cytokines related to Treg and Th2 showed significant increase in treated group in comparison to control group.

Conclusion: Under our results, Curcumin alleviated clinical symptoms in EAE induced mice , reduced CNS demyelination and cell infiltration, suppressed spleen T cell proliferation and raised production of anti-inflammatory cytokine in splenocytes including TGF-1, IL-4 and IL-10. Besides, the results of real-time PCR in CNS showed enhanced expression levels of Th2 and Treg transcription factors and related cytokines, including IL-13, IL-27, IL-33, IL-35, Foxp3, CTLA-4, GATA3 and STAT6 in the treatment groups. It seems that curcumin has a protective effect on EAE progression and shifts the immune responses toward Treg and Th2 cell expansion.

Keywords: Multiple sclerosis, Experimental autoimmune encephalomyelitis, Myelin oligodendrocyte Glycoprotein, Curcumin

(18488)

The expression analyses of RMRP, and RORC in RRMS patients treated with different drugs versus naïve patients and healthy controls

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Background: Since T helper 17 (Th17) lymphocytes defend mucosal barriers against infections, they have been involved in multiple sclerosis progression (MS). RORC can control the differentiation of Th17 and the development of MS. Since RMRP can interact with RORC as a long non-coding RNA (lncRNA), this lncRNA can be involved in the development of MS. This study examined RORC and RMRP expression levels in patients with treatment-naïve multiple sclerosis, relapsing-remitting multiple sclerosis (RRMS), healthy controls, and RRMS patients treated with IFNβ-1, dimethyl fumarate (DMF), fingolimod, or glatiramer acetate acetate (GA).

Methods: Samples were obtained from 83 MS patients and 44 healthy controls. Total RNA was isolated, and expression analysis of RORC, and RMRP were performed.

Results: In treatment-naïve RRMS patients, there was significant up-regulation in the expression of RORC and RMRP relative to healthy controls. Among the comparisons of their expressions with treatment-naïve patients in various groups of treated patients, only down-regulation of the level of RMRP expression was significant in patients treated with IFNβ-1. Even in female patient groups, these changes were more pronounced.

Conclusion: The high diagnostic utility of RORC and RMRP in treatment-naïve patients with RRMS has been highlighted in our analyses. In addition, RMRP in treated RRMS patients has shown moderate positive associations with RORC expression.

Keywords: Multiple sclerosis, Th17, Gene expression, autoimmune disease

(18387)

The ex vivo effects of Lactobacillus delbrueckii and Lactobacillus rhamnosus on inflammatory and anti-inflammatory cytokines and their related molecules on PBMCs of SLE patients

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by production of autoantibodies, imbalance in inflammatory and anti-inflammatory cytokines and deposit of immune complexes in organ and tissue. Studies showed that tolerogenic probiotics can develop immune responses and reduce inflammation in the immune system and can control the autoimmune disease. This study tried to assess the impact of Lactobacillus delbrueckii and Lactobacillus rhamnosus on inflammatory and anti-inflammatory cytokines and their related molecules on the PBMCs of SLE patients.

Methods: In this study, a total number of 20 newly diagnosed SLE patients were registered. Peripheral blood mononuclear cells (PBMCs) were isolated from the whole blood and treated with L. delbrueckii (10^5 Bac/ml), L. rhamnosus (10^7 Bac/ml), and the mix of both probiotics cultured in RPMI 1460 for 48h. Then, total RNA was extracted and cDNA was synthesized. Gene expression of forkhead box P3 (Foxp3), transforming growth factor β, interleukin 6(IL-6), IL-10 and IL-2 was evaluated by quantitative real-time PCR method.

Results: The results showed that expression levels of Foxp3, TGF-β, IL-10 and IL-2 increased in probiotics receiving groups while the level of IL-6 decreased compared with untreated groups.

Conclusion: L. delbrueckii and L. rhamnosus could increase the expression of Tregs related molecules such as Foxp3 and IL-2 and also could increase the expression of IL-10. These probiotics also decreased the expression of pro-inflammatory cytokines, IL-6, in the PBMCs of the SLE patients.

Keywords: Lactobacillus delbrueckii, Lactobacillus rhamnosus, PBMCs, Systemic lupus Erythematosus

(18288)

Assessment of expression profile of microRNAs in multiple sclerosis patients treated with fingolimod

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Abstract: Fingolimod is an immunotherapeutic drug approved in certain countries as first-line therapy for relapsing–remitting multiple sclerosis (RRMS). The drug has been shown to alter the expression of several coding and non-coding genes. In the current study, we assessed the expression of miR-506-3p, miR-217, miR-381-3p, miR-1827, miR-449a and miR-655-3p in peripheral blood of patients with RRMS undergoing treatment with fingolimod compared with healthy controls. We also compared the expression of these miRNAs between fingolimod responders and non-responders to determine their relevance with regard to response to fingolimod. Expression of miR-381-3p was significantly higher in responders than in controls (RE difference = 3.903, P =0.005), while expression of miR-655-3p was significantly lower in both responders and non-responders compared with controls (RE difference = −1.03, P = 0.014; RE difference = −1.41, P < 0.0001, respectively). No difference was found in the expression of other miRNAs between study subgroups. In addition, there was no significant difference in the expression of any miRNA between responders and non-responders. Although there were significant pairwise correlations between expression levels of all of the assessed miRNAs in controls, MS patients exhibited differences in correlation patterns. Expression of miR-381-3p was correlated with age in responders. However, expression of other miRNAs did not correlate with age in any study subgroup. The current study indicates a possible role for miR-655-3p and miR-381-3p in the pathogenesis of MS or possible effects of fingolimod on the expression of these miRNAs. Future studies are needed to verify these results in larger patient populations.

Keywords: Fingolimod, multiple sclerosis, miRNA expression

(18114)

Redox imbalance in CD4$^+$ T cells of relapsing-remitting multiple sclerosis patients

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Background: As a prevalent autoimmune disease of the central nervous system in young adults, multiple sclerosis (MS) is mediated by T cells, particularly CD4$^+$ subsets. Given the evidence that the occurrence of perturbation in reactive oxygen species (ROS) production has a pivotal role in the onset and progression of MS, its regulation through the anti-oxidants molecules is really important. Here, we investigated the level of the redox system components in lymphocytes and CD4$^+$ T cells of MS patients.

Methods: The study was performed on relapsing-remitting MS (RRMS) patients (n=29) and age- and sex-matched healthy controls (n=15). Peripheral blood mononuclear cells (PBMCs) were cultured and stimulated by anti-CD3/CD28. The level of ROS, anion superoxide ($O2^-$), and GSH were measured by flow cytometry in lymphocytes/CD4$^+$ T cells. Using Real-time PCR, the gene expression level of gp-91 phox, catalase, SOD1/2, and Nrf-2 were also investigated.

Results: we found that lymphocytes/CD4$^+$ T of RRMS patients at relapse phase significantly produced higher levels of ROS and $O2^-$ compared to patients at remission phase (*P*-value <0.001) and healthy controls (*P*-value < 0.001 and *P*-value <0.05, respectively). Interestingly, the gene expression level of gp-91 phox, known as the catalytic subunit of the NADPH oxidase, significantly increased in MS patients at relapse phase as well (*P*-value < 0.05). Furthermore, the catalase expression was augmented in patients at acute phase (*P*-value < 0.05) while, an increased expression of SOD1 and Nrf-2 were found in RRMS patients at relapse and remission phase (*P*-value <0.05).

Conclusion: The increased production of ROS in CD4$^+$ T cells RRMS patients highlights the importance of amplifying anti-oxidants components as an efficient approach to ameliorate disease activity in MS patients.

Keywords: Redox, multiple sclerosis, autoimmune disease, reactive oxygen species

(18090)

Alteration of Sema3A, Sema7A and their receptors gene expression in treated multiple sclerosis patients

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Background: Recently, members of the semaphorin family have received major attention in various medical fields, especially autoimmunity. In this study, we selected semaphorin-3A (Sema3A), semaphorin-7A (Sema7A), and their receptors to determine the possible relationship between these molecules and multiple sclerosis (MS).

Methods: We measured the gene expression of Sema3A, Sema7A, neuropilin-1 (NP-1), plexin-C1, and β1 integrin in the blood samples of relapsing-remitting multiple sclerosis (RRMS) patients, treated with high-dose interferon-β1a (IFN-β1a), low-dose IFN-β1a, IFN-β1b, and glatiramer acetate (GA) via quantitative real-time polymerase chain reaction (qRT-PCR) assay, and then, compared the results of these groups and treatment-naive patients with the healthy controls.

Results: The gene expression of Sema3A ($P=0.02$), NP-1 ($P<0.001$), and plexin-C1 ($P<0.01$) significantly decreased in the treatment-naive group, compared to the healthy controls. Sema3A significantly increased in all treated patients, compared to the treatment-naive patients ($P<0.001$). However, expression of NP-1 ($P<0.001$), plexin-C1 ($P<0.001$), and β1 integrin ($P<0.05$) only increased in patients receiving high-dose IFN-β1a, IFN-β1b, and GA. Expression of Sema7A increased in only two groups of patients treated with IFN-β1b ($P<0.001$) and GA ($P=0.018$), without any significant decrease in the treatment-naive group, compared to the healthy controls ($P>0.05$).

Conclusion: Our findings confirm that the presence of Sema3A, Sema7A, and their receptors can play critical roles in the treatment of MS patients. Therefore, they can be potential target molecules for MS treatment in the future.

Keywords: Multiple sclerosis, Interferon-β, Glatiramer acetate, Semaphorin

(17963)

Inhibitory effects of tolerogenic probiotics on migratory potential of lupus patients – derived DCs

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Aims: The present in-vitro study aimed to evaluate whether Lactobacillus delbrueckii and Lactobacillus rhamnosus treatments can induce regulatory phenotype, together with modulating the expression of chemokine receptors (CRs), during the generation of lupus dendritic cells (DCs).

Methods and Results: In brief, monocytes of patients with systemic lupus erythematosus (SLE) and healthy donors were isolated and differentiated to regulatory or inflammatory mature DCs through treatment with Lactobacillus delbrueckii, Lactobacillus rhamnosus, mixed probiotics, and LPS. FACScan analysis showed that the expression of chemokine receptors, including CXCR3, CCR5, CCR4, and CCR3, was significantly reduced in all of probiotic-treated groups of SLE and healthy (control) donors, when compared with LPS treated group.

Conclusions: The results demonstrated that tolerogenic probiotics could prevent or decrease the expression of inflammatory chemokine receptors on the surface of tolerogenic DCs during the maturation process.

Significance and Impact of Study: The chemokine receptors of DCs have been found to involve in the pathogenesis of SLE disease through directing recruitment and migration of immune cells.

Keywords: Systemic Lupus Erythematosus; Chemokine Receptor; Dendritic Cell; Lactobacillus Delbrueckii; Lactobacillus Rhamnosus

(16592)

Generation of lupus M1 and M2 macrophages differentiated by tolerogenic probiotics

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Background: Systemic lupus erythematosus is an autoimmune disease. The etiology is not clear but it occurs when the immune system attacks to auto-antigens by self-reactive T cells and autoantibodies, causing immune complex deposition and inflammation in affected tissues. Self-tolerance breakdown is the main cause of SLE pathogenesis that innate immunity is considered to collaborate with adaptive immune cells. Macrophages are responsible in pathogenesis through defective phagocytosis of dead cells and aberrant activation and M1/M2 imbalance. According to various studies, Immunomodulatory effects of lactobacillus delbrueckii and lactobacillus rhamnosus are proven. Studies have shown that lactobacillus delbrueckii can increase macrophage function in animal models and in vitro, lactobacillus rhamnosus can induce M2 phenotype in vitro and both of them can induce tolerogenic DCs in vitro. The aim of study is to investigate the effect of lactobacillus delbrueckii and lactobacillus rhamnosus on differentiation of M1 and M2 macrophages in lupus patients.

Methods: At first, lactobacillus delbrueckii and lactobacillus rhamnosus probiotics cultured in MRS mediums. Second, isolation of lupus patient's PBMCs using ficoll method. Third, monocytes obtained from PBMCs by cell adhesion method in RPMI medium and transformed to macrophages in combination with our probiotics. Finally, generated macrophages surface markers and gene expression were investigated by flowcytometry and PCR to distinguish M1 and M2 macrophages.

Result: the study is in process and the data will be presented in congress.

Conclusion: According to the anti-inflammatory effects of mentioned probiotics, it is expected that the M2/M1 ratio can be increased by our probiotics and be a good option to use as a complement drug.

Keywords: systemic lupus erythematosus, macrophage, lactobacillus delbrueckii, lactobacillus rhamnosus, tolerogenic probiotic

(18810)

Serum cytokine level in patients with Graves' disease

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Background: Recent studies showed that cytokines play an important role in Graves' disease pathogenesis and development. Interleukin-27 is a cytokine that has been newly discovered. This cytokine has both inflammatory and anti-inflammatory functions. The aim of the present study was to examine the changes in the serum level of this cytokine in GD patients in comparison to healthy controls.
Methods: In this study, serum level of IL-27 was determined by an ELISA method; anti TPO and anti Tg were measured by an RIA method in 40 new cases of Graves's disease. The findings were compared with 40 healthy controls.
Results: The serum level of IL-27 in patients' group was significantly lower than control group (P value = 0.0001). Anti TPO and anti Tg serum levels in patients' group were also significantly different from control group (P value = 0.001).
Conclusion: The reduction in the serum levels of IL-27 in GD patients compared to normal subjects suggests the possible anti-inflammatory role of this cytokine in GD.
Keywords: Graves' disease, IL-27

(18675)

Evaluation of the frequency of CD4$^+$ T cells in women with Hashimoto's thyroiditis

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Background: Hashimoto's thyroiditis (HT) is the most prevalent autoimmune illness and there is no definitive treatment available for this disease. In order to find the appropriate therapeutic approach it is necessary to undrestand the mechanism of the disease. To achieve this purpose the frequency of CD4$^+$ T cells was evaluated in HT patients and compared to that in healthy indivduals.

Method: Twenty-six female patients with HT, aged 20-45 years were enrolled in this study. Patients were divided into two groups. In group 1 (n=13) the serum level of anti-thyroid peroxidase antibody (anti-TPO) was above 100 IU/ml; whereas, in group 2 (n=13) the serum levels of both anti-TPO and anti-thyroglobulin antibody (anti-TG) were above 100 IU/ml. Eleven healthy women were considered as control group, group 3. After blood collection, the frequency of CD4$^+$T cells T helper1 (Th1), T helper2 (Th2), T helper17 (Th17), T regulatory type 1 (Tr1) and IL-17–producing TH2 cells and mean fluorescent intensity (MFI) of their related cytokines were evaluated using flow cytometry.

Result: The frequency of Th2 cells in groups 1 and 2 were more than, group 3, the healthy control group .However, only the difference between groups 2 ans 3 was obtained significant (P= 0.022) The frequency of IL-17–producing TH2 cells in group 1 was significantly higer than group 3 (P=0.027) and the population of these cells in group 2 was more than group 3; However, this increase was not significant (P=0.126).

The expression of interferon gamma (IFN-γ) in groups 1 (P= 0.001) and 2 (P= 0.001) were significantly higher than group 3. The frequency of Th17, Th1 and Tr1 cells, and MFI of IL-17 and IL-10 were not significantly different between study groups.

Conclusion: Since the Th2 cells frequency and the expression of IFN-γ were increased in women with HT, if these results will confirm in other studies, effort to restore them to the normal levels may be effective in control of the disease progression in these patients.

Keywords: Hashimoto's thyroiditis; CD4$^+$ T cells, Th17, Tr1, Th1, Th2, IL-17–producing TH2

(18598)

Investigating the Interferon regulatory factor 3(IRF3) expression in multiple sclerosis patients in comparison with control group in the Iranian population

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Background: Relapsing-remitting (RRMS) is the most common course of multiple sclerosis. Interferon Regulatory Factor 3 (IRF3) as a key regulator of immune system genes plays an important role in activating type I interferon promoters, especially the IFNβ promoter. We therefore aimed to evaluate the expression level of IRF3 in RRMS patients undergoing different types of IFNβ treatment.
Methods: We collected 100 venous blood sample from normal and patients. We grouped samples in 4 separately groups by their illness status. To evaluate the expression of IRF3 the Real-Time PCR method using SYBR Green dye was done. The level of gene expression was measured by a comparative threshold cycle formula.
Results: In the study we compared the IRF3 mRNA expression of all subjects in association with gender, which no significant difference was seen ($P > 0.05$). Also assessment of the gene mRNA level in study groups revealed that the B1b, B1a and new case group had the lowest expression respectively. Moreover, comparison of the mRNA level between new case and B1b groups showed remarkable difference ($P < 0.05$). According to age and sex factors, no remarkable differences between study groups were seen ($P > 0.05$).
Conclusion: Perhaps the IFNβ recombinants decreases the IRF3 expression as a negative feedback mechanism. Overall the data reported here, supports the previous studies in important role of IRF3 in autoimmune inflammatory disease of CNS and Multiple Sclerosis.
Keywords: multiple sclerosis, IRF3, IFNβ

(18582)

Relationship between serum levels of complement proteins and clinical manifestations of SLE disease

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Background: Systemic lupus erythematosus is a chronic multifactorial autoimmune disease that affects various organs of the body. Different serological biomarkers including autoantibodies and complement proteins have been identified in this disease. The aim of this study was to determine the relationship between serum C2, C3, C4 and C1q levels and the pattern of clinical manifestations in SLE patients.

Methods: In this cross sectional study, 127 patients with systemic lupus erythematosus were studied. Serum levels of C2, C3, C4, C1q and Anti-dsDNA in these patients were measured by nephlometric method, and the results of the serological assessments were analyzed in relation to clinical presentations.

Results: In this study, we observed the higher significant serum levels of C3 was observed in patients with lupus nephritis (P=0.02). Correlation between serum levels of C2 and articular symptoms, lupus nephritis and cutaneous involvement were observed. Increased levels of C4 levels was shown in patients with pulmonary (P=0.02) and cardiovascular (P=0.01) involvements. Serum level of C1q didn't show statistical differences in terms of different clinical manifestations.

Conclusion: Our findings indicate that serum levels of complement proteins (C2, C3 and C4), can be considered as potential prognostic markers for development of various clinical presentations in SLE disease.

Keywords: Systemic Lupus Erythematosus; Complement; C2; C3; C4; C1q; Clinical manifestations

(18509)

A Review Targeting myeloid-derived suppressor cells in the immunological thrombocytopenia purpura: current state and future prospect

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Abstract: Thrombocytopenic purpura is an autoimmune disease that natural platelet injury and prohibiting platelet production occur by the immune system and consequence to hemorrhagic symptoms. The cells constitute a heterogeneous population of naïve myeloid cells that modulate adaptive immunity. Myeloid-derived suppressor cells have been identified via CD11b+CD33+ HLA-DR^{low} markers and represent in both of the peripheral blood and the spleen with a low number and abnormal function. Autoimmune disorders will happen in the absence of these cells that are mediated by regulatory T and B cell reduction. It is pointed to the role of myeloid-derived suppressor cells in immunological thrombocytopenia purpura in several studies. Evidence demonstrates that the myeloid-derived suppressor cells' number and function increased when the immunological thrombocytopenic purpura patients received high dose dexamethasone and intravenous immunoglobulin. Also, in vitro cell culture with high dose dexamethasone has been shown it could cause elevating in the interleukin-10 and transforming growth factor-B serum level and CD11b+CD33+ HLA-DR ^{low} cell population. Besides, diminish in CD4+ T helper cell proliferation and platelet degradation by cytotoxic T cells reduction have been observed in patients treated by the cells. The present study reviews the mechanisms that myeloid-derived suppressor cells play a role in the immunological thrombocytopenic purpura patient improvement. Overall, myeloid-derived suppressor cell is a pivotal regulator in the immunological thrombocytopenia purpura pathogenesis, and interventions that restore these cells function could be fruitful in diminishing autoimmune disorders and particularly immunological thrombocytopenia purpura, however, it is required more investigation.

Keywords: MDSCs, Thrombocytopenia, Immunological, Purpura

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

(18489)

Inhibition of cGAS -STING signaling pathway: a novel paradigm in targeted therapy of Systemic Lupus Erythematosus

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Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that causes inflammation and damage in various organs. The pathogenesis of SLE is related to the production of autoantibodies directly against nucleic acid, accumulation of immune complexes, and loss of self-tolerance. Common therapeutic strategies to cure SLE is limited to immune regulator drugs and glucocorticoid. Cytosolic DNA sensing using cyclic GMP-AMP Synthase (cGAS) activates signaling through STimulator of INterferon Genes (STING) or Transmembrane protein 173(TMEM173) as the most important cytoplasmic adaptor protein in mammalian cells and thereby leads proinflammatory responses. Despite the critical role of aberrant cytosolic DNA sensing in the pathogenesis of SLE, most parts of the cGAS-STING pathway have been discovered in recent years so our current knowledge related to the role of the pathway in SLE is limited. The aim of this review is to present a current understanding of the contribution of this pathway in the molecular pathogenesis of SLE, with a focus on the emerging strategies for targeted treatment of this clinically heterogeneous disease.
Methods: A systematic search was performed in different databases including Scopus, PubMed and Google Scholar, to find review and original articles from 2013 using different keywords such as Systemic Lupus Erythematosus, STING, cGAS, targeted therapy, TMEM173. Finally, 20 articles were selected for this study.
Results: One of the early hallmark features and diagnostic criteria in SLE, is an increase in serum anti-DNA antibody level. Recent reports have shown that dysregulated DNA sensing as an initiator for the cGAS-STING pathway can incite autoimmunity and inflammation. Moreover, it has been proved that the accumulation of foreign nucleic acids from invading pathogens in the cytosol of cells with defective DNA sensing can also lead to the trigger of this pathway. In the other word, this pathway through production of IFN 1 and activation of NF-κB -dependent proinflammatory response, play a vital role in the pathogenesis of SLE. Emerging evidence also revealed that, dysregulated STING signaling pathway promotes autophagy, apoptosis, and necroptosis and thereby increases the severity of SLE. Thus, blockade of the cGAS-STING axis using inhibiting factors such as TRIM29, NRLX, NLRC3 and Cia-cGAS have shown great therapeutic value for SLE treatment.
Conclusion: The recent progress in understating the mechanisms underlying autoimmunity such as dysregulated cGAS–STING pathway have provided new opportunities for targeted therapy in complex inflammatory diseases such as SLE, and lupus-like disease. The continued scrutiny in the cGAS–STING axis, due to strong evidence for its central role in the pathogenesis of SLE, will open a new avenue in finding better candidates in the management of SLE and other autoimmune diseases.
Keywords: Systemic Lupus Erythematosus, STING, targeted therapy, transmembrane protein 173, TMEM173

(18453)

Escape from X chromosome inactivation and female bias of autoimmune diseases

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Background and Aims: Generally, autoimmune diseases are more prevalent in females than males. Various predisposing factors, including female sex hormones, X chromosome genes, and the microbiome have been implicated in the female bias of autoimmune diseases. During embryogenesis, one of the X chromosomes in the females is transcriptionally inactivated, in a process called X chromosome inactivation (XCI). This equalizes the impact of two X chromosomes in the females. However, some genes escape from XCI, providing a basis for the dual expression dosage of the given gene in the females. The current literature provides evidence in the contribution of a number of the escape genes, including CD40L, CD99, LAMP-2, IRAK-1, TLR7, USP27X, DDX3X, CXORF21 and XIAP, in the autoimmunity. Current literature also confirms contribution of some escapes genes including CD40L, IRAK-1, TLR7, CXORF21 and XIAP to the female bias of autoimmune diseases especially SLE disease. Herein, the contribution of these escape genes to the female bias of autoimmune diseases was discussed.

Keywords: Autoimmune disease, Escape genes, Female bias, X-chromosome inactivation.

(18410)

A Maternal death due to the intracerebral hemorrhage caused by antiphospholipid syndrome: A case report

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Background: antiphospholipid Syndrome (APS) is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies in patients with arterial or venous thrombosis or pregnancy complications.

Methods: this paper reports a case of a 31-year-old woman who died after she underwent C-section for intra uterine fetal death (IUFD) at the 25th week of gestation.

Results: the patient was complaining of pelvic pressure, swelling in the lower limbs, and pain in the groin, one big toe, and both wrists. She had low platelet count, liver abnormalities, and proteinuria. After IUFD, she complained of flank pain and headache. After discharge from the hospital, the patient had constant headaches and 5 days later woke up with hemiplegia. CT scan showed cerebral hemorrhage in the right hemisphere and thrombosis in the left hemisphere. The LA and APS tests were positive. The main cause of death was hemorrhage and infarction in the brain.

Conclusion: considering the potential complications of APS, physicians should take great care to diagnose this condition as soon as possible to allow for early treatment. In the case of pregnant women, physicians should strongly insist on the appropriate treatment to protect the mother as well as the baby and provide cautionary suggestions and consider the right time to terminate the pregnancy.

Keywords: Antiphospholipid Syndrome - Lupus Anticoagulant - Beta-2-Glycoprotein I - Intracerebral Hemorrhage

(18392)

A review on the role of parasite infection in multiple sclerosis and recommendation of Olibanum as a new herbal treatment

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Background: Multiple sclerosis is a common neurological disease of humans especially women. Helminths have been shown to augment immunoregulation so it can be used to MS treatment such as recent researches with *Trichuris suis* eggs in MS revealed good tolerance and surprising clinical effects. It can be used to Olibanum as one herbal treatment, orally beside parasite treatment, too.
Materials and Methods: In this study, which is a systematic review study, all papers presented on this subject were evaluated at the databases, SID, Google Scholar, PubMed, Scopus, and others. In the last 50 years, environmental factors such as helminth infections have been proposed to explain why autoimmunity is less prevalent in the developing world; this proposal has been termed the hygiene or old friend's hypothesis.
Results and conclusion: It is widely accepted that the Th2 and Treg cell responses which develop in helminth infections can suppress autoimmune disease such as MS. Recent researches with *Trichuris suis* eggs in MS revealed good tolerance and surprising clinical effects. The mechanism of protection is manifold and included; the increasing activity of T reg cell, activated macrophage, inducing Th2 related cytokines with antiinflammatory qualities and more recently, IL-10 producing regulatory B cells. *Trichuris suis* has the potential as an effective, safe and orally available treatment option in MS. Also, MS disease is a type of autoimmune disease in which the immune system considered the spinal cord myelin as a foreign agent and destroys it, and on the other hand, given the growing global acceptance of the use of medical plants, which is due to the modification of the immune system of the person on one side, as well as the ability to decontaminate bacterial and viral causes. With this herbal treatment, we can be hoped that MS will be eradicated forever soon, as we are currently researching mouse as a laboratory model for humans, which will be published, as soon as possible.
Keywords: Parasite infection, MS, Olibanum, Herbal treatment.

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

(18366)

Association between percentage of Tr1 cells and osteopontin in patients with RRMS

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Background: MS is triggered by an inflammatory attack on the myelin of neurons in the CNS by myelin-specific T cells. MS has three clinically defined forms. Relapsing-remitting MS (RRMS) is the most common primary presentation of MS that if untreated, approximately 50% of these patients develop into secondary progressive MS (SPMS) and primary-progressive MS (PPMS). The growing sensitivity of the magnetic resonance imaging (MRI) technique has made it a key tool in the diagnosis and monitoring of MS based on McDonald's criteria. However, there are still cases of MS that do not meet McDonald's standards. Furthermore, MRI-based prognosis is difficult; for this purpose, molecular biomarkers can be helpful. Myelin-specific T cells stimulate an inflammatory response, eventually damaging the myelin sheath. Tr1 cells are a subset of Treg cells that suppress inflammation by secreting IL-10 and TGF-β. Osteopontin cytokine stimulates T cell proliferation and also reduces the production of IL-10 from Tr1 cells in a CD44-dependent pathway. In the present study, we investigate the association between the percentage of Tr1 cells and osteopontin in patients with RRMS.

Methods: PBMCs were isolated from the blood of RRMS patients and healthy controls (N=30 for each group). The percentage of Tr1 cells was measured using flow cytometry. Plasma levels of osteopontin were tested by ELISA.

Results: The Tr1 cells' percentage was significantly decreased in the RRMS patients compared to the healthy controls ($P < 0.05$). Plasma levels of osteopontin were significantly increased in the RRMS patients compared to the HCs ($P < 0.05$). Moreover, there was a strong negative association between Tr1 percentage and plasma- OPN in the RRMS patients (($P=0.002$), 95% confidence interval (CI) = -0.7578 to -0.2324) while this association was not observed in healthy groups.

Conclusion: In summary, it may be possible to use these biomarkers as important factors in the diagnosis and prognosis of RRMS disease.

Keywords: Multiple sclerosis, Tr1, Osteopontin

(18308)

Prevalence of HLA- B27 and HLA- B5 in the group of patients referred to Noor Pathobiology Laboratory

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Background: The HLA region encodes several molecules that play important roles in the immune system. Intense association between the HLA region and autoimmune disease has been previously reported. HLA-B27 and HLA-B5 genotyping is commonly used to provision a diagnosis of ankylosing spondylitis (AS) and Behcet's syndrome respectively. The purpose of this study was to determine the prevalence of HLA- B27 and HLA- B5 in the patients referred to Noor Pathobiology Laboratory, Sanandaj, Iran.

Methods: DNA was extracted from blood samples of 762 patients with suspected clinical Symptoms of ankylosing spondylitis and Behcet's disease. Frequency of HLA-B27 and HLA-B5 genotype was evaluated by Real Time PCR in the population of suspected patients.

Results: A total of 762 patients for HLA-B27 and HLA-B5 have been studied. These results demonstrate that the alleleas and genotype frequencies of the HLA-B 27 and B5 in the patients with symptom (Suspect to AS and Behcet's) were found as 7.6 % and 32.9% respectively.

Conclusion: determination of HLA- B27 and HLA- B5 prevalence can be used as important data for public health management and may help physicians in choosing the best treatment strategy.

Keywords: HLA-B27, HLA-B5, Prevalence, Autoimmune.

(18224)

Assessment of IL-38 levels in patients with acquired immune-mediated polyneuropathies

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Abstract: Acute and chronic inflammatory demyelinating polyneuropathy (AIDP and CIDP) are two types of immune-mediated neuropathies in which abnormal cellular or humoral immune responses have been observed. Although dysregulation of several cytokines has been detected in these disorders, expression of interleukin 38 (IL-38) has not yet been assessed in AIDP and CIDP. In the current study, we evaluated serum concentrations of this member of the IL-1 family of cytokines in 24 patients with CIDP, 13 patients with AIDP and 27 healthy subjects. We detected higher levels of IL-38 in CIDP patients compared with controls. When assessing study subgroups based on gender, there were no significant differences in IL-38 levels among the three female subgroups (P= 0.14). However, the difference among male subgroups was significant (P= 0.010). A Tukey test showed significant differences between male CIDP patients and male controls (P= 0.014). Considering the proposed anti-inflammatory role of IL-38, higher levels of this cytokine in CIDP might reflect the presence of a compensatory mechanism to reduce inflammatory processes in these patients. Further longitudinal assessment of this cytokine is need to test this hypothesis.

Keywords: Il-38, Immune-mediated neuropathy, CIDP, AIDP

(18222)

Evaluation of Expression of STAT Genes in Immune-Mediated Polyneuropathies

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Abstract: Immune-mediated polyneuropathies are acquired conditions that can be categorized to acute and chronic forms based on the disease course. Although the basic mechanism of these conditions has not been clarified yet, genes that regulate immune responses are putative contributors in their development. In the current study, we assessed expression of signal transducer and activator of transcription (STAT) 1-3 and STAT5a genes in peripheral blood of 51 patients and 40 healthy subjects. Expression ofSTAT1was higher in female patients compared with female controls (Posterior Beta = 3.622, P= 0.044). The gender*group interaction was significant for this gene which indicates different direction of association in males and females. Expressions of other STAT genes were not different between cases and controls. The diagnostic power ofSTAT1in female subjects was estimated to be 0.72 with sensitivity of 68.75% and specificity of 84.62%. There was no significant correlation either between expression of different STAT genes or between their expression and age of study participants. The current study potentiates STAT1 as a putative factor in the pathophysiology of acquired immune-mediated polyneuropathies in females and suggests conduction of further functional studies to elaborate the molecular mechanism of this contribution.

Keywords: Immune-mediated polyneuropathies, Signal transducer and activator of transcription, STAT

(18209)

Evaluation of cytokine profile in multiple sclerosis patients

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Background: Multiple sclerosis (MS) is an unpredictable autoimmune disease, which causes neurodegeneration in the central nervous system. Since the main cause of MS remains obscure, in this study, we aimed to evaluate the serum levels of some cytokines, including interleukin-5 (IL-5), IL-8, IL-9, IL-17A, transforming growth factor-beta (TGF-β), and interferon-gamma (IFN-γ) in relapsing-remitting (RR)-MS patients, treated with IFN-β and glatiramer acetate (GA).

Methods: Serum samples of RR-MS patients, treated with high-dose IFN-β1a, low-dose IFN-β1a, IFN-β1b, and GA, were assessed by ELISA assay and then compared with the results of treatment-naive patients and healthy controls.

Results: The findings showed that the serum levels of IL-8, IL-9, and IFN-γ in treatment-naive patients were significantly higher than the healthy controls, while there was no significant difference in terms of other cytokines between the groups. A significant reduction was observed in the levels of IL-9 and IFN-γ, while there was a significant increase in TGF-β level among patients treated with GA. IFN-β1b resulted in a significant decline in the levels of IL-9 and TGF-β. In addition to these findings, some cytokines were positively correlated in different groups.

Conclusion: Overall, the present results support the inflammatory and aggravating effects of IL-8, IL-9, and IFN-γ on MS. Furthermore, based on the results reported in the GA treatment group, we suggest GA as an effective treatment for RR-MS patients.

Keywords: Chemokine, Cytokine, Glatiramer acetate, Interferon- β, Multiple Sclerosis

(18047)

Effect of treatment with thyme extract on urinary levels of melatonin in an experimental autoimmune encephalomyelitis mouse model

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Background: Thymus vulgaris, or thyme belongs to the Lamiaceae family of aromatic plant species and has established antioxidant and anti-inflammatory properties. We examined the association between thyme extract treatments to recovered urinary levels of melatonin, a hormone with neuroprotective effects, in mice induced with EAE.

Methods: Eight B6 mice induced with EAE were randomized into two groups and exposed to either 50 mg/kg of thyme extract or PBS. After EAE induction, mice were injected i.p every other day from day 0 to 21. Four B6 mice without EAE were considered the healthy control group. Urine samples were collected consecutively for two 24 h periods on day 19 and 20. We examined whether thyme extract treatment modified urinary melatonin sulfate concentration (ng/mL) in EAE-induced mice using an ELISA.

Results: The clinical score and body weight in thyme-treated EAE group were significantly lower in comparison to the EAE control group at indicated time points. The urinary melatonin concentration was significantly lower in the EAE control group compared to the healthy mice. There was no significant difference between thyme-treated and EAE groups regarding the urine melatonin concentration.

Conclusion: Our results show that exposing EAE mice to thyme extract improved their clinical symptoms, however, there was no significant effect on urinary melatonin concentration.

Keywords: Enzyme-linked immunosorbent assay (ELISA), Experimental autoimmune encephalomyelitis (EAE), Melatonin, Thymus vulgaris (Thyme), Urine

(17964)

Clinical pattern and laboratory Features of systemic Lupus Erythematosus in Kermanshah

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Background: Systemic lupus erythematosus (SLE) is a worldwide autoimmune disease. The disease has different etiologies, clinical and laboratory symptoms between different geographical and racial groups, and sufficient knowledge of the type of symptoms in each region can play a useful role in diagnosis and treatment. Therefore, this study was performed to evaluate patients with systemic lupus erythematosus in Kermanshah**.**

Methods: The files of 150 patients with lupus during 2016-2018 in Imam Reza Hospital in Kermanshah were reviewed.

Results: Data analysis showed that patients at the time of referral were with musculoskeletal symptoms 37.3%, cutaneous-mucosal 32%, natural 51.3%, renal 62%, cardiac 6.7%, neurological manifestations 17.3%, pulmonary involvement 37.3% and blood 71.3%. Anti-nuclear antibody in 60%, Anti-ds DNA (Anti-double strand DNA Antibody) in 35.4%, CRP (C-Reactive Protein) in 44.6%, RF (Factor Rheumatoid) in 26%, lower level Of normal C3 and C4 in 33.3% and 11.3%, respectively, anticoagulant lupus in 13.3%, Anti-CCP (Antibody Citrulinated Peptide Anti-Cyclic), in 14.9%, anticardiolipin IgM and IgG, in 6% and 9.3% of patients respectively were observed. Also anemia was observed in 34%, leukopenia in 22% and thrombocytopenia in 30.7%. Abnormal ESR (Erythrocyte Sedimentation Rate) was seen in 59.3% of patients. AST (Aspartate aminotransferase) and ALT (Alanine aminotransferase) levels were higher than normal in 16% and 16.7% of patients, respectively, and partial thromboplastin time (PTT) was higher than normal in 10.7% of patients.

Conclusion: Despite the diverse clinical and laboratory manifestations of SLE in different racial and geographical groups, paying attention to these differences in each region can be effective in the correct diagnosis of the disease.

Keywords: Systemic Lupus Erythematosus, Rheumatology, Clinical Signs, Laboratory Symptoms

(17931)

S100 proteins expression in newly diagnosed Systemic Lupus Erythematosus patients: Can they be potential diagnostic biomarkers?

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Background: The S100 proteins are a unique class of calcium-binding proteins that play an essential role in promoting the inflammatory and anti-inflammatory responses under normal and pathological conditions such as systemic lupus erythematosus (SLE). Therefore, the present research aimed to measure mRNA expression of S100A4, S100A8, S100A9, and S100A12 as target genes of the study and evaluation of their diagnostic potentiality in the SLE patients.

Methods: Twenty-three newly diagnosed SLE patients diagnosed and selected by an expert rheumatologist were enrolled based on American College of Rheumatology (ACR) criteria as well as 30 healthy age and sex-matched subjects. Following peripheral blood collection from the subjects, the mRNA level of target genes was measured in isolated leukocytes by the real-time polymerase chain reaction (RT-PCR).

Results: The findings of this study showed that the mRNA level of target genes was higher in SLE patients compared to healthy subjects; however, only gene expression of S100A12 raised significantly. Moreover, the results of the receiver operating characteristics (ROC) curve showed that among the studied genes, S100A12 was highly sensitive to the diagnosis of patients with SLE from the healthy subjects (specificity: 0.80, sensitivity; 0.75, area under the curve (AUC): 0.79). On the other hand, we observe that there was no significant correlation between the expression of target genes and disease activity.

Conclusion: regarding the findings of this study, it can be concluded that S100A12 might be involved in SLE pathogenesis. Also, this molecule may be considered as a potential biomarker candidate for the early detection of SLE. However, further studies are needed to confirm this claim.

Keywords: S100 Proteins, Systemic Lupus Erythematosus, Autoimmune Disease

(17930)

Assessing the Expression of Immunosuppressive Cytokines in the newly diagnosed Systemic Lupus Erythematosus Patients: A Focus on B cells

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Background: The immunosuppressive effects of regulatory B-cells (Bregs) and their immunosuppressive cytokines on immune responses in autoimmune disorders, mainly systemic lupus erythematosus (SLE), have been recently established. Therefore, the purpose of this article has been the exploration of the expressions of cytokines produced by B cells in newly diagnosed SLE patients.
Methods: In this study, a total number of twenty-three newly diagnosed SLE patients identified by an expert rheumatologist based on American College of Rheumatology (ACR) criteria as well as thirty normal-age and gender-matched subjects were enrolled in this investigation. Real-time polymerase chain reaction (RT-PCR) was used to evaluate interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), IL-35 (EBI3 and IL-12p35), programmed death-ligand 1 (PD-L1 or CD274), and Fas ligand (FasL or CD178) gene expression in isolated B-cells. Moreover, serum levels of IL-10, TGF-β as well, as IL-35 were measured via enzyme-linked immunosorbent assay (ELISA).
Results: The findings demonstrated that the gene expression of IL-10, TGF-β, IL-35, PD-L1, and FasL was significantly up-regulated in SLE patients compared to healthy subjects ($P<0.05$). Additionally, the results revealed that serum levels of IL-10, TGF-β, IL-35, PD-L1 were remarkably increased in patients with SLE compared to healthy subjects ($P<0.0001$). However, serum levels of IL-10 and TGF-β decreased significantly with increasing SLEDAI score in studied patients ($P<0.05$).
Conclusion: It was concluded that the release of anti-inflammatory cytokines, particularly IL-10 and TGF-β, might inhibit immune responses and autoreactive immune cells in a compensatory manner in SLE patients with mild to moderate disease activity.
Keywords: Regulatory B-cells (Bregs), Systemic Lupus Erythematosus (SLE), Anti-inflammatory Cytokine

(16570)

Association between Interleukin-35 gene single nucleotide polymorphisms and multiple sclerosis

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Background: Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). In recent years, the prevalence of MS has increased significantly, especially among young people. Interleukin-35 is an anti-inflammatory cytokine of the IL-12 family that has an association with autoimmune diseases. This study aimed to determine the associations between serum levels and polymorphic variants of IL-35 with susceptibility, clinical features and disease severity in MS patients.

Methods: This case control study recruited a total of 362 subjects including 186 MS patients and 195 sex- and age matched healthy controls. Serum levels and polymorphisms of IL-35 were determined by ELISA and restriction fragment length polymorphism (RFLP) – polymerase chain reaction or high resolution melting (HRM) analysis methods, respectively.

Results: Serum levels of IL-35 were significantly differed between MS patients and controls. IL-35 was lower in the patients than that healthy controls ((49.3± 3.7 *vs.* 69.5 ± 7.8, p=0.009). There were significant associations between the polymorphisms of EBI3 rs4740 and the MS patients 2.23; 95% CI, 1.3-3.9, p=0.005). However, there were no differences in the genotype distribution and allele frequencies of IL-35 rs568408 between the patients and controls ($p > 0.05$).

Conclusion: To our knowledge, this is the first study to investigate the association between serum levels and IL-35 genetic variations and MS risk. The results show IL-35 polymorphisms might be a genetic risk factor for the development of MS.

Keywords: Multiple Sclerosis, IL-35, polymorphism, EBI3, high resolution melt analysis

18696

Synergistic effect of selenium and metformin on reduction of Age-associated B Cells in Rheumatoid Arteritis patients

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Background and Aim: Rheumatoid arthritis is an autoimmune inflammatory disease. Immune system aging can be one of the important factors in autoimmune diseases. Aged B cells are cells that have recently been proven to play a role in autoimmune diseases. Given the role of metformin and selenium on the immune system, the present study investigated the effect of these two compounds on the percentage of aged B cells in patients with rheumatoid arthritis.

Methods: In the present clinical trial, 96 women with rheumatoid arthritis were randomly divided into three groups: selenium (200 micrograms/daily), metformin (500 mg/daily) and combination. Intervention was performed for 3 months. At the beginning and at the end of the study, blood samples of patients were evaluated by flow cytometry for aged B cells specific surface markers (CD19+/CD21+/CD11c-). Flowjo software and SPSS24 were used for evaluation of different cell population and statistical analysis, respectively.

Results: The results of this study showed that metformin and selenium decreased percentage of aged B cells but this difference was not statistically significant but could decrease significantly in combination form. Before and after the intervention, the mean of ESR was not significantly different in the study groups. The ESR changes in the metformin, selenium and compound groups were -1.99, -0.56 and -1.27, respectively. BMI changes in metformin group were significantly higher than selenium group ($P < 0.05$) but there was no significant difference between the two groups.

Conclusion: Both metformin and selenium reduced the percentage of peripheral blood in the affected B cells, but the combination of the two performed better than either.

Keywords: Rheumatoid Arthritis, B aged, Metformin, Selenium

18600

Aberrant expression of miR-199a and miR-487b in whole blood of the systemic sclerosis patients

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Background: Systemic sclerosis is a multi-organ auto-inflammatory disease which is characterized with the accumulation of extra-cellular matrix components in the connective tissue, resulting in the fibrosis and organ failure. As of today, there's no certain diagnosis or cure for this disease; hence researchers are focusing on utilizing new approaches for early diagnosis and treatment of systemic sclerosis. Among the new promising tools for detection and treatment of diseases like SSc are microRNAs; which are short nucleotide sequences that contribute to post-transcriptional regulation of many target genes by binding to their 3' UTR.
Methods: After whole blood collection from 70 SSc patients, RNA isolation and cDNA synthesis; the gene expression of two microRNAs including miR-199a and miR-487b were quantified using Taq-Man-qPCR probes and primers. Eventually, relative expression of the mentioned microRNAs were calculated using ΔΔCT method and the results were compared using one way ANOVA.
Results: The statistical analysis demonstrated that miR-199a was significantly down-regulated in the whole blood of SSc patients in comparison with healthy controls; while there was a significant increase between the expression of miR-487b in SSc patients and healthy controls.
Conclusion: Given the aberrant expression of miR-199a and miR-487b in the SSc patients, we can propose a role for these two microRNAs in the pathogenesis of SSc and they could be considered as diagnostic markers for identifying the patients. Also, employing their corresponding mimics or antagonists in the treatment of patients might improve their conditions; but this requires more investigations.

Keywords: systemic sclerosis, microRNA, miR-199a, miR-487b, gene expression

18468

Study of FOXP3 gene variants in systemic lupus erythematosus female patients with history of abortion and the relation to clinical and para-clinical characteristics

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Background: To investigate the association of FOXP3 gene single nucleotide polymorphisms (SNPs) including rs3761548 (C/A) and rs2294021 (T/C) with susceptibility to SLE as well as their relation to disease characteristics in female patients with history of abortion.

Methods: The genomic DNA of 55 female patients with history of abortion with mean age of 37.4±8.9 year and 221 healthy controls with mean age of 34.6±11 year was genotyped for rs3761548 and rs2294021 using the PCR-RFLP method. Patients' information including demographic characteristics, laboratory parameters and clinical features were collected and recorded using a questionnaire. The relationship between the SNPs and patients' characteristics was statistically analyzed.

Results: The data of this study showed that there was a significant association between FOXP3 rs3761548 SNP AA genotype and disease susceptibility, so that the frequency of AA genotype in female patients with history of abortion was significantly higher than the healthy female controls (odds ratio (OR), 3.02; 95% confidence interval (CI), 1.36-6.67, p =0.014). No significant relationship between rs2294021genotypes and disease susceptibility was found (p=0.42). Both SNPs were associated with the development of malar rash. The frequency of rs3761548 CC genotype (p=0.031) and rs2294021 CT genotype (p=0.013) were higher in patients with malar rash manifestation. We also found a significant relationship between rs3761548 and rs2294021 polymorphism with hematological indices such as MCV and MCHC ($p<0.05$). No association was detected between these SNPs and disease activity.

Conclusion: As results of this study showed, FOXP3 rs3761548 AA genotype was associated with risk of SLE in females with abortion history. Association of both SNPs with several clinical and paraclinical features of the patients suggested the effect of these two SNPs on pathogenesis of SLE.

Keywords: Systemic lupus erythematosus (SLE), Single nucleotide polymorphism (SNP), FOXP3

18351

Association analysis of ERAP2 gene single nucleotide polymorphism in susceptibility to ankylosing spondylitis in Iranian population

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Background: Ankylosing spondylitis (AS) is a chronic autoimmune disease, in which genetic polymorphisms are critically important in establishing inflammatory state. *Endoplasmic reticulum aminopeptidase* (*ERAP*) *2* gene has been implied to be involved in AS etiopathogenesis. The current study evaluated the association of *ERAP2* gene single nucleotide polymorphisms (SNPs) with susceptibility to AS in an Iranian population.

Methods: Two hundred and forty AS patients and 240 healthy individuals were recruited. DNA extraction was performed from whole blood samples and RNA content was isolated from peripheral blood mononuclear cells (PBMCs). Real-time allelic discrimination approach was exerted to genotype all subjects for rs2910686, rs2248374, and rs2549782 SNPs. After cDNA synthesis, mRNA expression of cytokines was determined.

Results: None of the SNPs were associated with AS risk in the whole population. However, allele and heterozygote genotype of rs2910686 SNP were associated significantly with higher risk of AS in Human leukocyte antigen (HLA)-B27 positive group. mRNA expression of interleukin (IL)-17A, IL-23, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α was increased in AS patients compared with controls. Nonetheless, mRNA expression of cytokines was not significantly different among HLA-B27 positive AS patients with different three genotypes for rs2910686 SNP.

Conclusions: Although *ERAP2* gene rs2910686 polymorphism was significantly associated with increased risk of AS susceptibility, it might not be involved in regulation of the inflammatory cytokines during AS pathogenesis.

Keywords: Ankylosing spondylitis; Single nucleotide polymorphisms; Endoplasmic reticulum aminopeptidase

18350

ERAP2 polymorphisms are not associated with ankylosing spondylitis susceptibility in Iranian patient

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Background: Ankylosing spondylitis (AS) is a chronic autoimmune disease, in which genetic polymorphisms are critically important in establishing inflammatory state. *Endoplasmic reticulum aminopeptidase* (*ERAP*) *2* gene has been implied to be involved in AS etiopathogenesis. The current study evaluated the association of *ERAP2* gene single nucleotide polymorphisms (SNPs) with susceptibility to AS in an Iranian population.

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Results: None of the SNPs were associated with AS risk in the whole population. However, allele and heterozygote genotype of rs2910686 SNP were associated significantly with higher risk of AS in Human leukocyte antigen (HLA)-B27 positive group.

Conclusions: *ERAP2* gene rs2910686 polymorphism was significantly associated with increased risk of AS susceptibility.

Keywords: Human leukocyte antigen-B27; Ankylosing spondylitis; Single nucleotide polymorphisms; Endoplasmic reticulum aminopeptidase

18292

Study of *Staphylococcal* Enterotoxin E as a superantigen in blood samples of Patients with Rheumatoid Arthritis (RA).

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Background: The role of *Staphylococcal* enterotoxin E (Super antigen E) in rheumatoid arthritis pathogenesis has been considered. This paper aimed at determining *Staphylococcal* enterotoxin E in the blood samples of rheumatoid arthritis patients.
Methods: In this study, 100 blood samples of patients with rheumatoid arthritis were examined. The primers pairs were designed based on the *S. aureus* enterotoxin type E (*entE*) gene, GenBank: M21319.1. All samples were subjected to DNA extraction separately. Then, polymerase chain reaction (PCR) was implemented. Data were analyzed by descriptive statistics.
Results: The PCR results indicated that *Staphylococcal* enterotoxin E gene existed in the blood samples of 19% of patients with rheumatoid arthritis, with a high percentage.
Conclusions: The study results revealed that a high percentage of patients with rheumatoid arthritis have *Staphylococcal* enterotoxin type E gene in their blood. However, further studies are needed to assess other *Staphylococcal* enterotoxins. This finding may provide a model for diagnosing rheumatoid arthritis disease. The results of this study have presented some evidence regarding endogenous origin of involved superantigen in patients with rheumatoid arthritis.

Keywords: Enterotoxin E, Rheumatoid Arthritis, PCR, *Staphylococcus aureus*

18287

Evaluation of *Staphylococcal* Enterotoxin C as a superantigen in blood samples of Patients with Rheumatoid Arthritis (RA).

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Background: The role of *Staphylococcal* enterotoxin C (Superantigen C) in rheumatoid arthritis pathogenesis has been considered.
This paper aimed at determining *Staphylococcal* enterotoxin C in the blood samples of the rheumatoid arthritis patients.
Methods: In this study, 100 blood samples of patients with rheumatoid arthritis were examined. The primers pairs were designed based on the *S. aureus* enterotoxin type C (*entC*) gene, GenBank: AB084256.1. All samples were subjected to DNA extraction separately. Then, polymerase chain reaction (PCR) was implemented. Data were analyzed by descriptive statistics.
Results: The PCR results indicated that *Staphylococcal* enterotoxin C gene existed in blood samples of 23% of patients with rheumatoid arthritis, with a high percentage.
Conclusions: The study results revealed that a high percentage of patients with rheumatoid arthritis have *Staphylococcal* enterotoxin type C gene in their blood. However, further studies are needed to assess other *Staphylococcal* enterotoxins. This finding may provide a model for diagnosing rheumatoid arthritis disease. The results of this study have presented some evidence regarding endogenous origin of involved super antigen in patients with rheumatoid arthritis.
Keywords: Enterotoxin C, Rheumatoid Arthritis, PCR, *Staphylococcus aureus*

18276

Evaluation of *Staphylococcal* Enterotoxin C as a superantigen in Synovial Fluid of Patients with Rheumatoid Arthritis (RA).

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Background: The role of *Staphylococcal* enterotoxin C (Superantigen C) in rheumatoid arthritis pathogenesis has been considered.This paper aimed at determining *Staphylococcal* enterotoxin C in the synovial fluid of rheumatoid arthritis patients.
Methods: In this study, 100 synovial fluid samples of patients with rheumatoid arthritis were examined. The primers pairs were designed based on the *S. aureus* enterotoxin type C (*entC*) gene, GenBank: AB084256.1. All samples were subjected to DNA extraction separately. Then, polymerase chain reaction (PCR) was implemented. Data were analyzed by descriptive statistics.
Results: The PCR results indicated that *Staphylococcal* enterotoxin C gene existed in synovial fluid samples of 18% of patients with rheumatoid arthritis, with a high percentage.
Conclusions: The study results revealed that a high percentage of patients with rheumatoid arthritis have *Staphylococcal* enterotoxin type C gene in their synovial fluid. However, further studies are needed to assess other *Staphylococcal* enterotoxins. This finding may provide a model for diagnosing rheumatoid arthritis disease. The results of this study have presented some evidence regarding endogenous origin of involved superantigen in patients with rheumatoid arthritis.
Keywords: Enterotoxin C, Rheumatoid Arthritis, PCR, *Staphylococcus aureus,* superantigen, Synovial.

18181

Rheumatoid arthritis is associated with KIR2DS4-full among the KIR genes in Lur Population of Iran

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Introduction: Among the approaches to autoimmune disease, especially Rheumatoid Arthritis (RA), we can mention the important role of immune system and the molecules involved. Previously, different types of genetic elements were studied in connection with this disease, however, few studies have been performed on Killer cell Immunoglobulin-like Receptors (KIR) and Human Leukocyte Antigen (HLA) molecules, and in particular their compounds. Therefore, we intend to examine KIR genes, their HLA ligands, and KIR-HLA compounds in patients with RA and healthy controls.
Methods: In this case-control study, 50 patients with RA and 100 healthy individuals were included in the study. DNA samples were evaluated based on PCR method with sequence specific Primers (PCR-SSP). Odds ratio (OR) with 95% confidence interval (CI) were reported.
Results: Among the inhibitor genes KIR2DL5A ($P = 0.0255$, OR = 0.389, 95% CI = 0.210-0.722), and among the activating genes KIR2DS4-full ($P < 0.0001$, OR = 6.163, 95% CI = 3.174-11.968) had a significant association with susceptibility to RA. No significant association was found between KIR genotypes, HLA ligands, and KIR-HLA compounds with a susceptibility to RA.
Conclusion: In our population, KIR2DS4-full increased susceptibility to RA were as KIR2DL5A was a protecting factor based on both cross table and regression analyses. This study should be repeated in other populations.
Keywords: Rheumatoid Arthritis, NK cells, KIR, HLA

18053

Time course of CTGF, SRF, and MRTFA expression in bleomycin-induced pulmonary fibrosis in BALB/c strain

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Background: Interstitial lung diseases (ILDs) has been considered as the most common cause of death in systemic sclerosis (SSc) patients. The precise mechanism and effective treatment of SSc-related ILD remained to be elucidated. The profibrotic genes like connective tissue growth factor (CTGF) and Serum response factor (SRF), in partnership with its coactivators, myocardin-related transcription factor A (MRTF-A) represent the potential target of anti-fibrotic therapy. The objective of this study was to examine the expression of CTGF, SRF, and MRTFA in lung tissues of a mouse model of scleroderma at different time points during the 60-day time-course.

Methods: BALB/c mice were divided into five groups and treated with bleomycin for 28 consecutive days. At days 10, 28, 35 and 60, mice were sacrificed under lethal anesthesia and lung tissues were harvested for histological assessment, hydroxyproline measurement and qPCR.

Results: Our results indicated the persistent lung fibrosis until day 60. The expression of CTGF mRNA significantly increased at the early time point tested and during the fibrotic process of lung fibrosis. Moreover, the SRF and MRTF-A mRNA significantly increased prior to collagen deposition and by the time decreased until day 60.

Conclusion: This study provided detailed information from the time-course of bleomycin-induced lung fibrosis in BALB/c mice and implicated that ILD model closely mimics pathologic manifestations of human SSc-ILD. Our data confirmed the contribution of CTGF at the time preceding and during the pulmonary fibrotic process, and also support the role of SRF/MRTF-A signaling pathway throughout the course of pulmonary fibrosis, especially the initiation phase of lung fibrosis. Accordingly, considering the timing, these factors may represent the valuable targets for anti-fibrotic therapy in ILD.

Keywords: Systemic sclerosis (SSc), Induced pulmonary fibrosis, Connective tissue growth factor, Serum response factor (SRF), Myocardin-related transcription factor A (MRTF-A)

17972

Evaluating Propolis on Interleukin-23 Gene Expressionin Animal Model Rheumatoid Arthritis Disorder

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Background: Rheumatoid Arthritis, also known as Joint rheumatism is concerned as the most prevalent autoimmune arthritis. The disorder occurs once an event happens in the immune system in which small joints like hand wrist or fingers become involved and eroded or destructed. RA is a systemic disorder which may damage many parts of the body. Changes occur in Pro-inflammatory cytokines including Interleukins 15-17-23-TNFα[3] are the most common complications of the disorder.

Materials & Methods: In this study, IL-23 change occurrence in the mice developing animal RA has been evaluated and the impact of Propolis has also been demonstrated on the inflammation attenuation. 28 female BALB/C mice aged 6-8 weeks were purchased from Pasture Institution and the initial injection was given a week after the mice adaptation, including PBS, bovine collagen type II and complete freaund's adjuant 50 µg/mouse, then therapeutic oral treatment began with Propolis doses 0, 6.7 and 20 mg/gr for different test groups and the gene expression was evaluated by Elisa.

Results: The study findings showed that expression of IL-23 in experimental groups administrated by propolis reduced compared to the control group ($p < 0/05$) and the significance was also seen in IL-23 gene expression attenuation in the test groups.

Conclusion: In this study, the effect of Iranian Propolis on IL-23 expression was investigated. Considering these results, Iranian propolis can be a good candidate to be replaced with chemical drugs for treatment of RA.

Keywords: Rheumatoid Arthritis, Propolis, Interleukin 23, Autoimmune disease,Inflammatory cytokine

16735

Assessment of cell adhesion molecules in ankylosing spondylitis patients following treatment with β-D-Mannuronic acid (M2000)

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Background: To investigate the effects of β-D-mannuronic acid (M2000) on LFA-1 expression and L-selectin shedding as a mechanism of action that this drug exerts.
Methods: To study molecular consequences of M2000 on LFA-1 gene expression, we used qRT-PCR technique. Moreover, we assessed the effect of M2000 on L-selectin shedding by using flow cytometric analysis.
Results: The level of LFA-1 gene expression in AS patients was higher than healthy controls (P = 0.046). The level of LFA-1 gene expression after 12-week treatment with M2000 significantly reduced (P = 0.01). After 12 weeks therapy with M2000, the frequency of CD62L-expressing CD4+ T cells in AS patients, was not significantly changed, in comparison to the frequency of them in the patients before therapy (P = 0.5). Also, after 12 weeks treatment with M2000, L-selectin expression levels on CD4+ T cells in AS patients, were not significantly changed, in comparison to the patients before treatment (P = 0.2).
conclusions: This study for the first time indicated that M2000 is able to interfere with events of adhesion cascade. In addition, M2000 presented an acceptable benefit to patients with AS. Based on these results, M2000 could help in the process of AS management.
Key words: Ankylosing spondylitis, β-D-Mannuronic acid, LFA-1, L-Selectin, M2000, NSAIDs

Congress Abstracts

Treatment of COVID-19

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18622)

Therapeutic Effects of Mesenchymal Stem Cell (MSC) Therapy on Covid-19 Respiratory Symptoms

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Background: COVID-19 is a major worldwide public health emergency. The most important COVID-19-related death is reported to be of respiratory complications. Patients may suffer from acute inflammatory lung and alveolar injury caused by pro-inflammatory cytokines such as IL-5, IL-6, IL-8, TNFα, and IL-1β, IFNα, IFNβ, IFNγ and MCP-1. Mesenchymal stem cells have been shown to have immunoregulatory and regenerative effects. In this review study, effects of MSC cell therapy on COVID-19 patients with pneumonia and respiratory symptoms was investigated.

Methods: In the present study, we searched articles within Google scholar, PubMed and Science Direct with keywords COVID-19, cell therapy and MSC. Review articles were excluded. Sixty-four articles were found. Fifty-six articles were removed after reading the title or abstract. Eight articles were selected for this review based on our inclusion criteria. A total of 102 COVID-positive patients with severe respiratory symptoms received MSC cell therapy (IV).

Results: MSC cell therapy improved respiratory symptoms, downregulated cytokine storm by inhibiting the secretion of pro-inflammatory cytokines (including IL-1, TNF-α, IFN-γ and IL-6), prevented pulmonary fibrosis and promoted tissue repair in lungs. It improved dyspnea and oxygenation index in patients and made the recovery time shorter. X-ray results showed absorption of exudate tissues in lungs in most patients. In addition, lymphocyte count recovery was reported in most of the studies. No adverse effects were observed. Only one study reported transient fever in some patients that resolved within 24 hours.

Conclusion: Despite the limited number of studies, MSC therapy appears to be safe and beneficial for COVID-19 patients with respiratory complications. It improves clinical status of the patients faster, regulates inflammatory response and protects lung's microenvironment.

Keywords: COVID-19, Coronavirus, Cell therapy, MSC

(18104)

Effects of curcumin on serum levels of inflammatory cytokines in COVID-19 patients

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Introduction: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become the cause of more than 1 million deaths worldwide and showed an increasing incidence all over the world. Several lines of evidence show the effect of curcumin in the control of cytokine storms and associated complications. We aimed in this study to evaluate the effects of curcumin on the serum levels of TNF-α, IL-1β, and IL-6 as inflammatory cytokines in patients with COVID-19.

Methods: Sixty patients with COVID-19 were randomized to receive Nano-curcumin capsules (Exir Nano Sina, Iran) and placebo and for seven days along with standard antiviral treatment. Before and after the procedure, we evaluated clinical symptoms, and blood samples were collected to evaluate serum levels of TNF-α, IL-1β, and IL-6 inflammatory cytokines using ELISA (Karmania Parsgene, Iran).

Results: Along with improved clinical symptoms, while serum levels of all three cytokines were decreased in the curcumin group, only the IL-1β decrease was significant compared to the placebo group ($p=0.042$).

Conclusion: Our study showed that curcumin administration as a complementary treatment route might positively affect elevated inflammatory condition and cytokine storm in COVID-19 patients that lead to improved clinical symptoms and better survival of them.

Keywords: Coronavirus-2019, SARS-CoV-2, Curcumin, Inflammatory cytokines

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18081

Hydroxychloroquine and azithromycin: As a double edge sword for COVID-19?

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Background: Hydroxychloroquine with or without azithromycin was one of the common therapies at the beginning of the COVID-19 pandemic. They can prolong QT interval, cause Torsade de Pointes, and lead to sudden cardiac death. We aimed to assess QT interval prolongation and its risk factors in patients who received hydroxychloroquine with or without azithromycin.
Methods: This was a retrospective cohort study. 172 patients with COVID-19 included hospitalized at hospitals of Babol University of Medical Sciences between March 5, 2020, and April 3, 2020. Patients were divided into two groups: hydroxychloroquine alone and hydroxychloroquine with azithromycin. Electrocardiograms were used for outcome assessment.
Results: 83.1% of patients received hydroxychloroquine plus azithromycin vs 16.9% of patients received only hydroxychloroquine. The mean age of patients was 59.2 ± 15.4. The mean of post-treatment QTc interval in the monotherapy group was shorter than the mean of post-treatment QTc interval in the combination therapy group, but it had no significant statistical difference (462.5 ± 43.1 milliseconds vs 464.3 ± 59.1 milliseconds; P = 0.488). Generally, 22.1% of patients had a prolonged QTc interval after treatment. Male gender, or baseline QTc ≥ 450 milliseconds, or high-risk Tisdale score increased the likelihood of prolonged QTc interval. Due to QTc prolongation, 14 patients did not continue therapy after 4 days.
Conclusion: Hospitalized patients treated by hydroxychloroquine with or without azithromycin had no significant difference in prolongation of QT interval and outcome. But numbers of patients with prolonged QT intervals in this study emphasize careful cardiac monitoring during therapy, especially in high-risk patients.

Keywords: Hydroxychloroquine, Azithromycin, QTc interval, Torsade de pointes, COVID-19, novel coronavirus

(18628)

Development of novel neutralizing monoclonal antibodies against SARS-CoV-2

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Background: Prophylactic and therapeutic strategies are critical to control newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Neutralizing monoclonal antibodies (MAbs) targeting the receptor binding domain (RBD) of the viral spike protein are promising tool for COVID 19 immunotherapy and prophylaxis.

Methods: We have developed a panel of eight mouse MAbs against RBD of SARS-CoV-2 spike protein using hybridoma technology. These MAbs were structurally characterized using indirect and competitive binding ELISA assays and Western blotting.

Results: The results demonstrated specific binding of MAbs to linear and/or conformational epitopes within the recombinant spike and RBD proteins. The affinity of binding to RBD varied from 0.36 to 1.71 nM. Pepscan analysis of the MAbs with 20-aa overlapping peptides spanning the whole length of RBD sequence revealed recognition of two linear epitopes by four MAbs. Virus neutralization potency of these MAbs was assessed by Vero cells cultured in the presence of wild type virus.

Conclusion: Our findings demonstrate different viral neutralization at µg to ng concentrations by six out of eight antibodies. Altogether, these MAbs may potentially be valuable for COVID 19 immunotherapy and design of effective peptide-based vaccines strategies.

Keywords: SARS-CoV-2, Neutralizing monoclonal antibodies, Prophylaxis, COVID-19

(18377)

Adjuvant use of melatonin as a potent anti-inflammatory to improve clinical outcomes in COVID-19 patients

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Background: Excessive immune-inflammatory responses and cytokine storm play a major role in the progression of coronavirus disease 2019 (COVID-19). Melatonin has been known as an anti-inflammatory agent and immune modulator that may address progressive pathophysiology of COVID19. Hence, in this study it was aimed to evaluate the clinical efficacy of melatonin in COVID-19 patients.
Methods: This clinical trial study was conducted on patients with confirmed COVID-19 who were admitted to Baqiyatallah Hospital in Tehran, Iran. A total of 74 COVID-19 cases were enrolled, and were randomized in a 1:1 ratio into control and intervention to receive standard therapy and oral melatonin as adjuvant at a dose of 9 mg daily for two weeks, respectively. The clinical outcomes were assessed by measuring the neutrophil-lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and clinical symptoms.
Results: There was a significant reduction in the level of CRP (4.2% vs. 25%; $P = 0.045$) in the intervention group compared to the control group. Compared with the control group, respiratory symptoms in the intervention group had significantly improved ($P < 0.05$), indicating the anti-inflammatory effect of melatonin in improving the disease. No adverse drug-related events were observed in patients receiving melatonin.
Conclusion: In this study of COVID-19 patients, melatonin adjuvant treatment was associated with statistically significant clinical improvement.
Keywords: Melatonin, COVID-19, Anti-inflammatory, Adjunctive therapy

(15489)

Investigation of Nanocurcumin effects on cytokine profile of the Th17 cell in mild and severe COVID-19 patients Compared to the placebo group

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Background: The ongoing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) from *Wuhan, China,* namely coronavirus disease 2019 (COVID-19) is commonly characterized by fever, dyspnea, sore throat, dry cough, and fatigue symptoms. Increased frequency of TH17 cells is led to overproduction of pro-inflammatory cytokines during the SARS-CoV2 infection, which elicits hyper inflammation and lung injury. A nanomicellar formulation of Curcumin, so-called Nanocurcumin, can inhibit the inflammation in patients with anti-inflammatory function. The present study investigated the effects of SinaCurcumin® on the expression and secretion levels of TH17-related cytokines in mild and severe COVID-19 patients compared to the placebo group.

Methods: The mRNA and expression levels of TH-17-related cytokines (IL-17, IL-21, IL-23, and GM-CSF) were assessed in serum samples of 40 severe COVID-19 ICU-admitted patients and 40 mild stage patients in both nanocurcumin and placebo groups before and after treatment utilizing the Real-time PCR and ELISA techniques, respectively.

Results: The expression levels of all IL-17, IL-21, IL-23, and GM-CSF were found to be considerably decreased in nanocurcumin treated group compared to the placebo-treated group in both mild and severe COVID-19 patients. Moreover, a higher level of expression was detected in the severe patient group in comparison with mild stage patients. Findings also revealed that nanocurcumin was associated with the significant decrease in serum levels of the abovementioned cytokines in nanocurumin treated group after treatment vs before treatment in both mild and severe COVID-19 patients; while in the placebo group, there was no significant difference before and after treatment.

Conclusions: The study results indicated that SinaCurcumin® could significantly decrease the expression and secretion levels of TH17-related cytokines (IL-17, IL-21, IL-23, and GM-CSF) in nanocurcumin-treated patients compared to placebo-treated ones in both mild and severe stages. So it could be applied as a therapeutic agent to mitigate the inflammation in COVID-19 patients.

Keyword: COVID-19; TH17; Cytokine; Nanocurcumin

(15492)

The Nanocurcumin effects on the Treg cell frequency and FoxP3 expression in mild and severe 2019-novel coronavirus patients

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Background: At the end of December 2019, an outbreak of novel SARS-CoV2 originated from Wuhan, China. In COVID-19, the downregulated number of Treg cells and their transcription factor (FoxP3) is led to hyper inflammation derived from the overactivation of inflammatory cells and factors during the infection. In the current study, we investigated the nanocurcumin effects on the Treg cell population and expression level of FoxP3 in mild and severe 2019-nCoV patients compared to placebo.

Methods: 80 COVID-19 infected patients (40 severe and 40 mild stages) were selected and classified into nanocurcumin and placebo arms. In both mild and severe patient groups, the Treg cell frequency and the gene expression level of the Treg cell transcription factor (**FoxP3)** were evaluated before intervention with healthy controls. Then they were measured and compared in nanocurcumin and placebo groups before and after treatment.

Results: In both mild and severe COVID-19 patients, the number of Tregs and the expression of FoxP3 was significantly lower compared to the control group. After the intervention, nanocurcumin could considerably upregulate the frequency of Treg cells and the expression level of **FoxP3** in the nanocurcumin-treated group when compared with the placebo-treated group. Moreover, a meaningful increase in the mentioned parameters was found in nanocurumin-treated group after treatment vs before treatment; while, no significant alterations were detected in the placebo group after treatment vs before treatment.

Conclusions: The decreased frequency of Treg cells and lower expression levels of FoxP3 during the SARS-CoV2 infection might have an important role in disease progression. Our findings showed the SinaCurcumin® effective function in upregulating the frequency of Treg cells and the expression level of FoxP3 in the nanocurcumin-treated group than in the placebo-treated group in both mild and severe patients. Hence, it could be considered as a potent therapeutic agent in improving SARS-CoV2 infected patients.

Keyword: COVID-19; T regulatory cell; FoxP3; Nanocurcumin

(18785)

An In silico study on the design of a coronavirus vaccine based on E-Peptide structure

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Background: Since the 2019-nCoV pandemic is the main disaster for global health, researchers design various examinations on it to reach an effective vaccine against this new strain, COVID-19. One of the pathogenic proteins that were a candidate for the design of this vaccine is the 2019-nCoV E protein, which has an outstanding role in pathogenesis. In this study, the 2019- nCoV E protein was analyzed to achieve an effective vaccine using bioinformatics methods.

Methods: The sequences of 2019-nCoV-associated E protein were extracted from NCBI and subjected to the IEDB software to evaluate the most potent epitopes. Besides, the capacity of the interactions of MHC-I and MHC-II molecules with selective peptides was studied in the next step. Then the sequence was subjected to T cell tests to realize the most promising peptides that could act as COVID-19 vaccine.

Results: Among the tested peptides for T cell-test, this study projected two epitopes of T cell (VSEETGTLI and LTALRLCAY) that exhibit high binding affinity as a strong indicator to MHC-I and MHC-II alleles together. Besides, these results were showing excellent interaction with the MHC molecule with the tested peptides.

Conclusion: 2019-nCoV E protein can be a suitable candidate for the COVID-19 vaccine, due to the immunogen epitopes, to which MHCs are capable interact.

Keywords: 2019-nCoV, E protein, vaccine

(18570)

Evaluation of the level of COVID-19 specific IgM and IgG among a group of patients

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Background: COVID-19 pandemic has caused more than 1.6 million deaths and still continues to cause causalities. Regarding the broad spectrum of the non-specific symptoms among patients and the difficulty and expense of molecular method or CT-scan, assessment of COVID-19 specific antibodies in serum can be helpful in confirming exposure to virus particularly in seroepidemiololgical studies. In addition, the titer of specific antibodies gives us valuable information about type and duration of immune response to virus. The aim of this study was to evaluate the level of COVID-19 specific IgM and IgG among a group of patients in Birjand city, Iran.

Methods: Information about the age, sex and titer of COVID-19 specific IgG and IgM antibodies were extracted from Shafa laboratory of Birjand. The level of antibodies in patients' sera was measured by commercial ELISA kit. Patients who were positive for either IgM or IgG antibodies enrolled in the study.

Results: In total 252 patients (mean age: 44 years, M/F ratio: 1.8) enrolled in this study. The mean level of IgG and IgM was 9.99 and 2.86 respectively. There was no significant difference in the level of antibodies between male and female. There was a weak but non-significant correlation between age and the level of both antibodies. The level of two antibodies was significantly correlated.

Conclusion: The results of this study show that the level of COVID-19 specific antibodies is not affected by age or sex of the patients and even old people can produce enough antibodies.

Keywords: COVID19, antibody, ELISA

(18470)

Combination Therapy for Covid-19: Picking the Right Medications Based on Mechanistic Appropriateness

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COVID-19 is an infectious disease causes by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and it is now one the major global public health threats. Covid-19 in its sever complications contribute to cytokine storm following the few days of hospitalization. Several studies have shown an elevated levels of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, TNF-α, in COVID-19 patients with severely and critically condition(1-3) in which interleukin6 plays a key role in this condition(2,4-6)

Recent study revealed hemoglobin abnormality in 99 patients with covid-19 pneumonia. Most of these patients have low hemoglobin level and significant increase in the serum ferritin (7). Higher production of IL-6 and IL-8 can be contributed to abnormalities in iron metabolism and it is possibly lead to macrophages over stimulation (8). During inflammation and reactive iron increase, ferriten increases to sequester excess iron and high ferritin levels may result of increased oxidative damage of pulmonary tissue(9).

Natural substances have gained attention because of their safety and low toxicity. Ellagic acid, is a naturally occurring polyphenolic compound which is found in many fruits. Ellagic acid has been shown multiple biological effects including antiviral, anti-inflammatory, anti-oxidant and anti-cancer. Ellagic acid reduces TNF-α, IL-6 and IL-1 β production and on the other hand increases the anti-inflammatory cytokine IL-10. In mice ALI model, pretreatment with ellagic acid following by LPS challenge revealed a protective effect of ellagic acid in LPS-induced ALI in mice (10, 11). Previous study also demonstrated an inhibitory effect of ellagic acid on HIV- 1 infection (12). Ellagic acid has been shown to activate anti thrombin-III (AT-III) and protein C which are important anticoagulants factors (13). So, ellagic acid by its specific mechanism may play a regulatory role between immune and coagulation system and combination therapy with ellagic acid and interleukin inhibitors like anakinra and tocilizumab may lead to regulation of inflammatory responses, ferritin and coagulatory system irregulations and prevention of sever conditions.

Keywords: COVID-19 infectious, cytokine storm, ferritin disorder, interleukin inhibitors, Ellagic acid

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

(18526)

The Role of Type I Interferon in Treatment of COVID-19

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Background: Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). No antiviral therapeutics or vaccines are approved to end this ongoing global threat. Type I IFNs are currently being evaluated for their efficacy in the treatment of COVID-19 infected patients. In this review, we aim to describe the latest findings towards the role of type I IFN-mediated innate antiviral response against SARS-CoV-2 and discuss the use of IFNs as a medication for COVID-19.
Methods: The review involved keyword searches of electronic databases, including PubMed, Science Direct, Scopus, Web of science, and google scholar. Review search terms included "type I IFN", "Interferon-alpha", "Interferon-beta", and "COVID-19". The study included reviews, clinical studies, observational studies, and case studies. The review was conducted in two phase: initially, abstracts were retrieved and assessed against the review criteria followed by the retrieval and assessment of full papers against review criteria.
Results: According to the inclusion criteria, 15 articles were selected. Clinical studies have reported that SARS-CoV induces impaired IFNs expression following infection. Besides, other studies suggest that IFNs expression can be delayed during SARS-CoV pathogenesis. A growing body of evidence indicated that human bronchial epithelial cells, rather than a complete absence shows promoting active but delayed IFNs response to SARS-CoV-2 and MERS-CoV infection. Studies have demonstrated that IFNs administration before the viral peak and inflammatory phase of disease could offer a highly protective effect. In contrast, IFN treatment during the inflammatory phase and severe stage of the disease would instead cause immunopathology and long-lasting harm for patients. Therefore, it is critical to notice the best time window for IFNs administration. IFNs administration prior to viral peak and inflammatory phase of disease could offer a highly protective effect. Based on the literature we reviewed, Interferon therapy, in general, is known to be effective in improving some clinical aspects of COVID-19 and reducing the mortality rate if utilized at the proper time and in the proper combination but the effect is not definite in all the study groups and might depend on patients' polymorphisms or the phase of their illness. In addition to the essential role of early administration of IFNs for COVID-19 patients, studies also showed that homozygosity for the C allele of rs12252 in the interferon-induced transmembrane protein 3 (IFITM3) gene supports the severity of disease in an age-dependent manner. This report supports the question about the fact that why a minority of infected patients progress the disease and show severe and lethal infection, while other ones manifest mild or moderate symptoms. Herein, appropriate and well-timed IFN treatment in this group of patients may protect them from lethal and pathogenic infection.
Conclusion: It's been firmly suggested that IFN administration prior to the viral peak exerts the maximum protective effect without adverse pathological consequences. Further investigation of the clinical effectiveness of interferon for patients with mild to severe COVID-19 as well as its optimal timing and route of administration can be amazingly helpful to find a safe and functional antiviral therapy for COVID-19 disease.
Keywords: Type I IFN, Interferon-alpha, Interferon-beta, COVID-19

(18732)

Is Convalescent plasma a safe and efficient therapy for COVID-19?

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Background: Recently a new coronavirus SARS-Cov-2 has been identified, that's responsible for the COVID-19 pandemic. Still there is no treatments approved for COVID-19. Thus experts are studding the efficacy of classical interventions to control COVID-19, one of them is Convalescent plasma therapy (CPT). In this study we investigate the potential of CPT in treatment of COVID-19.

Methods: Data of this review was collected by searching valid databases such as PubMed, Google scholar, Scopus, and Embase from 2019 to 2020. In our search, 25 articles were found in which 10 were the most relevant.

Result: CPT is a classic adaptive immunotherapy that seems to be effective Du to the following reasons. similar features of SARS and MERS with COVID-19 and the success of CPT in those outbreaks shows the possible efficacy of CPT in treating COVID-19, CPT was used while there was no certain treatment for influenza infections before, it means it may work in the COVID-19 pandemic too, passive Ab administration in CPT offers a faster immunity for vulnerable individuals, the main source of CPT which is the blood of donators is easily available. A study on 5000 patients and one on 20000 found out the safety and the impact on mortality rate (reduced from 14.9% to 8.6%) of CPT and also determined serious adverse events (SAEs) which has been observed in <1% and most of them had satisfactory outcomes. A study on the efficacy of CPT shows that it makes good results in some of those patients who doesn't respond to antivirals and hydroxychloroquine properly. Although, the time for applying CPT, and the donor's plasma (if the person has the symptoms or not) is important.

Conclusion: It seems that CPT is a potential therapy for COVID-19 and in the current situation that there is no definite treatment, it could be justifiable.

Keywords: Convalescent plasma therapy, COVID-19, adaptive immunotherapy.

(15490)

The Nanocurcumin effects on the Treg cell cytokine profile in mild and severe 2019-novel coronavirus patients compared to placebo

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Background: In *Wuhan, China*, SARS-CoV2 has arisen as a new infection, namely COVID-19. During the infection, the reduced frequency of Treg cells and their anti-inflammatory cytokines play a role in increasing the inflammation and disease progression mediated by inflammatory cells over-activation. This study aimed to evaluate the nanocurcumin effects on expression and serum secretion levels of the Treg cell cytokines in mild and severe COVID-19 patients compared to placebo.
Methods: 40 severe and 40 mild COVID-19 patients were included in the study and both of them were allocated into nanocurcumin (n=20) and placebo (n=20) groups. Before the intervention, the expression and secretion levels of Treg cell cytokines (IL-10, IL-35, and TGF-β) were assessed in patient and control groups. After treatment, the expression and secretion levels of mentioned cytokines were detected in nanocurcumin and placebo-treated groups in both mild and severe COVID-19 patients.
Results: In both mild and severe COVID-19 patients, the expression and secretion levels of IL-10, IL-35, and TGF-β cytokines were significantly lower compared to healthy subjects. After treatment, in both mild and severe patients, nanocurcumin could remarkably enhance the mRNA expression and serum secretion levels of mentioned cytokines in the nanocurcumin-treated group when compared with the placebo-treated group. Moreover, a significant elevation of expression and concentration of cytokines were found in the post-treatment with nanocurcumin before pre-treatment conditions. By contrast, it has been observed no notable alterations in the placebo group after treatment vs before treatment.
Conclusions: Dysfunction of Treg cells in inhibiting the inflammation during the COVID-19 infection result in disease progression. Our findings indicated that SinaCurcumin® could efficiently increase the Treg cell-mediated cytokines in the nanocurcumin-treated group in both mild and severe patients. Hence, it would be an efficient therapeutic agent in suppressing the inflammation and rehabilitating COVID-19 patients.
Keyword: COVID-19; T regulatory cell; Nanocurcumin; Cytokine

(18283)

Chloroquine/Hydroxychloroquine: An Inflammasome Inhibitor in Severe COVID-19?

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Background: chloroquine and hydroxychloroquine belong to the aminoquinolone drugs. Studies revealed that chloroquine and hydroxychloroquine shows antagonism activity against COVID-19 under laboratory conditions. ARDS and ALI are conditions that occur in patients with COVID19 as the main pathological complications of cytokine storm.
Methods: web of science and PubMed databases were searched. We surveyed the potential inhibitory effect of chloroquine and hydroxychloroquine on inflammasome.
Results: inflammasomes play a key role in the pathogenesis of many diseases associated with destructive inflammation. NLRP3 inflammasome has been shown to play a key role in the pathogenesis of viral diseases. The possible role of NLRP3 inflammasome inhibitors in the treatment of COVID-19 has been considered. Studies indicate that one of the possible anti-inflammatory mechanisms of chloroquine and hydroxychloroquine is inhibition of the activity of NLRP3 inflammasome.
Conclusion: understanding the exact mechanism of action of this drug can lead to its proper use and increase its effectiveness.
Keyword: chloroquine - hydroxychloroquine – COVID-19-inflammasomes

(18347)

Does prior immunization with measles, mumps and rubella vaccines affect the antibody response to COVID-19 antigens?

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Background: Seroepidemiological studies suggest that prior immunization with some vaccines may provide cross-protection against COVID-19 infection. This together with the fact that the incidence and severity of this infection are significantly lower in children and teenagers compared to elderly people, may propose that some vaccines routinely administered to neonates and children may induce cross-reactive antibodies effective for control of COVID-19 infection.

Methods: In the present study, antibody responses to measles, mumps, and rubella (MMR), and tetanus vaccines, as well as nucleocapsid (NP) and receptor-binding domain (RBD) of SARS-CoV2 virus, were determined in 53 patients affected with COVID-19 infection and 52 age-matched healthy subjects by enzyme-linked immunosorbent assays to assess cross-protection by prior MMR vaccinations in patients.

Results: Our results revealed significant differences in anti-NP ($p < 0.0001$) and anti-RBD ($p < 0.0001$) IgG levels between patients and healthy controls, as expected. While the levels of rubella and mumps specific IgG were similarly represented in both groups of subjects, measles-specific IgG was significantly higher in patients ($p<0.01$). The serum titer of anti-tetanus antibody, however, was significantly lower in patients compared to healthy individuals ($p < 0.01$).

Conclusion: Our findings suggest that measles vaccination may induce B cells cross-reactive with SARS-CoV2 antigens leading to production of increased levels of measles specific IgG in these patients.

Keywords: SARS-CoV2, Antibody response, Cross-protection, MMR

(18731)

Anti-inflammatory role of tocilizumab in COVID-19 patients

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Background: COVID-19 caused by corona virus SARS-Cov-2 is an infectious disease that's highly contagious. So far 72 million cases have been confirmed and 1.6 million have died from COVID-19, thus searching for possible therapeutic targets is necessary. IL-6 is one of the cytokines that increases during the hyperinflammation phase of COVID-19, so using IL-6 inhibitors like TCZ (Tocilizumab) could be an effective therapy.

Methods: to collect the data used in this review, we searched through the databases PubMed, Google scholar, Embase and Scopus. We found 40 articles in which 8 were the most relevant.

Results: TCZ is a humanized IL-6 monoclonal antibody that binds to the soluble and membrane-bound IL-6 receptors and inhibits the inflammatory function of IL-6. This drug is often used in rheumatoid arthritis, inflammatory conditions such as juvenile idiopathic arthritis (JIA) and autoimmune diseases. since the serum level of IL-6 is high in severe and critical COVID-19 patients, using single dose (400 mg, IV) or multiple doses (a second dose after 12 hours if necessary) of TCZ in the patients who doesn't show a significant improvement in symptoms, lowers the rate of serious lung injury and mortality in them and reduces the need to mechanical ventilation and ICU hospitalization. However, TCZ isn't used as a regular treatment and it's used when the standard treatment doesn't have acceptable results. in a study in china on 21 critical COVID-19 patients who received TCZ, all the patients showed an improvement in the symptoms like fever and 75% of them needed less supplemental oxygen. Also there is some evidence of the improvement of radiological outputs after treating by TCZ.

Conclusion: It seems that TCZ has a direct impact on the symptoms of severe and critical COVID-19 patients who shows an elevated levels of IL-6 and dealing with cytokine storm syndrome and hyperinflammation.

Keywords: COVID-19, Tocilizumab, cytokine storm syndrome, hyperinflammation

(17950)

Convalescent plasma transfusion, new hope and potential therapy in COVID-19 patients

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Background: The global prevalence of COVID-19 disease, which is a global health crisis, many proceedings have been taken to treat and prevent this disease. Although definitive treatment for this disease has not yet been proven. One of these proceedings, convalescent plasma transfusion, has been successful in the treatment of infectious diseases such as SARS-1 and MERS in the past. This study aimed to review the effects of plasma therapy in the treatment and severity of Covid-19 disease.
Methods: This study is a review. After searching for the keywords COVID-19, SARS-COV-2, convalescent plasma transfusion, from 2019 to 2020, 42 related articles according to the inclusion criteria were extracted from Pubmed, Embase, Scopus, and Uptodate databases and analyzed.
Results: The findings indicate that most studies have described convalescent plasma transfusion as a potential therapeutic benefit in Covid-19 patients. There are also some limitations, including concomitant use of antivirals, steroids, or other therapies, small sample size, and no control group. The results showed that early administration was more effective. This method was also effective in reducing mortality.
Conclusion: Convalescent plasma transfusion can be a possible alternative for the treatment of Covid-19 patients. Therefore, randomized clinical trials are recommended at the earliest opportunity to treat Covid-19 patients.
Key words: COVID-19, SARS-COV-2, Convalescent plasma transfusion.

(18532)

Potential beneficial effects of chitin and chitosan against COVID-19

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The newly emerged coronavirus, SARS-CoV-2, as the causative agent of COVID-19 has caused fatal outcomes worldwide. COVID-19 control requires consistent collaboration of all health care systems and investigators from around the globe. Research on this infectious disease is actively pursued as there is so far no officially approved drug or vaccine for the disease. Chitin and its derivatives including chitosan can be employed against viral infections due to their multi-faceted effects including direct antiviral activities, immune system associated effects (as adjuvants or antigen-delivery system) as well as their application as vehicles for targeted delivery of antiviral drugs. In the context of direct antiviral activity, chitin and chitosan cause structural damages in the viruses through electrostatic interactions. According to the very recent report on the inhibitory effects of a chitosan derivative on the infection of SARS-CoV-2, chitosan and related polymers hold substantial promises to be clinically employed against COVID-19 in near future. On the other hand, chitin and chitosan are capable of boosting antiviral immune responses. These polymers, by stimulating the innate immune cells (such as macrophages and NK cells); create protective responses against pathogenic challenges. It is shown that they can increase the number of phagocytes (blood PMNs or macrophages) and the N-acetyl-glucosamine residues in chitosan molecules can raise the production of reactive oxygen species (ROS), secretion of nitric oxide (NO) and myeloperoxidase activity in phagocytes. With respect to chitosan-based drug delivery, Bioavanta-Bosti has introduced the potential of aerosol formulations of Novochizol™ nanoparticles, as a chitosan based formulation, for efficient and targeted delivery of anti-COVID-19 drugs. On such a basis, chitin and chitosan could be considered as an appropriate tool to be exploited in the fight against this devastating pandemic disease.

Key words: SARS-CoV-2, COVID-19, Chitin, Chitosan, Immune responses

(18217)

Assessment of Th1 and Th2 Mediated Immunity in Patients with COVID-19 Following the Adjuvant Therapy with Melatonin

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Background: Coronavirus (SARS-CoV-2) is spreading rapidly in the world and is still taking a heavy toll. Studies show that cytokine storms and imbalances in Th1/Th2 play a significant role in most acute cases of the disease. A number of medications have been suggested to treat or control the disease but have been discontinued due to their side effects. Melatonin, as an intrinsic molecule, possesses pharmacological anti-inflammatory and antioxidant properties that decreases in concentration with age; as a result, older people are more prone to various diseases.

Methods: In this study, patients who were hospitalized with a diagnosis of COVID-19 were given a melatonin adjuvant (9 mg daily, orally) for fourteen days. In order to measure Th1 and Th2 derivate inflammatory cytokines (such as IL-2, IL-4, and IFN-γ) as well as the expression of Th1 and Th2 regulatory genes (STAT4, STAT6, GATA3, and T-bet), blood samples were taken from patients at the beginning and end of the treatment.

Results: Adjuvant therapy with melatonin controlled and reduced inflammatory cytokines in patients with COVID-19. Melatonin also controlled and modulated the dysregulated genes that regulate the humoral and cellular immune systems mediated by Th1 and Th2.

Conclusion: In this study, it was shown for the first time that melatonin can be used as a medicinal adjuvant with anti-inflammatory mechanism to reduce and control inflammatory cytokines by regulating the expression of Th1 and Th2 regulatory genes in patients with COVID-19.

Keywords: Melatonin, COVID-19, humoral immunity, cellular immunity, T helper, adjunctive therapy

(18168)

Evaluation of anti-inflammatory effects of Hydro-ethanolic extract of mango leaf on respiratory tract inflammation in patients with COVID-19

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Background: Inflammation caused by COVID-19 cause's respiratory system involvement. In severe cases, the disease is followed by the production of pro-inflammatory cytokines such as IFN-α, IFN-γ, IL-6, IL-10, TNFα, TGFβ and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10 Inflammation of the lung tissue occurs. Drugs such as aspirin, Remdesivir, and hydroxyl chloroquine sulfate, currently used to control coronary heart disease and inflammation, have side effects and toxicity such as renal failure, allergic reactions, hearing loss, and ocular side effects; therefore, the existence of alternative and effective treatment seems necessary and obvious.
Methods: Databases such as Google Scholar, PubMed, Scopus, etc. were used for this study.
Discussion: Flavonoids are one of the secondary metabolites of plants that have many antioxidant, anti-inflammatory and anti-allergic effects. By inhibiting the NF-kB and MAPK signaling pathway in RAW264.7 macrophages, flavonoids reduce the production of inflammatory mediators NO, IL-1B, IL-6 and TNF-α and play a crucial role in preventing exacerbation of inflammation and chronicity. It plays. According to phytochemical research on Mangifera indica leaves, the presence of flavonoids in the leaf organs of this plant is evident. On the other hand, Márquez study was performed on the inflammatory model of sodium dextran sulfate colitis (DSS) in rats. In this study, aqueous extract of Mangifera indica leaves was used to treat rats. The results of this study showed a decrease in the expression of iNOS, COX-2, TNF-α and TNF R-2 in colon tissue and a decrease in IL- 6 and TNF-a are serum levels.
Conclusion: According to several studies, mango leaf extract has a significant amount of flavonoids. Based on this, it has shown the ability to inhibit inflammation in the cellular and animal phases. Due to the fact that no side effects have been reported from mango leaf and its products in animal models and human studies, it is recommended that its effects on the COVID-19 disease process be evaluated in a clinical trial. To take.
Keywords: Covid-19, Inflammation, Flavonoids, Markophage RAW264**.7**

(18140)

Treatment of critical COVID-19 patients with hyperimmune convalescent plasma in Urmia, Iran

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Background: To assess if hyperimmune convalescent plasma might be effective in the treatment of critical COVID-19 patients.
Methods: 4 critical COVID-19 patients with RT-PCR -confirmed COVID-19 and acute respiratory distress syndrome (ARDS) with the following criteria: SpO2 < 88%; PaO2/FiO2 < 300; and mechanical ventilation. Patients received transfusion with convalescent plasma.
Results: Following plasma transfusion in 3 critical patients, clinical signs, SpO2, and PaO2/FiO2 improved within 14 days. Also, serum inflammatory cytokines (IL-1, TNF, IL-6, and IL-17) decreased within 14 days. Furthermore, the frequency of T $CD4^+$ and T $CD8^+$ also increased within 14 days and blood inflammatory markers including CRP, D-dimer, ESR, and LDH decreased within14 days. Finally, ARDS resolved in 3 patients at 12 days after transfusion and these patients have been discharged from the hospital.
Conclusion: Administration of hyperimmune convalescent plasma could improve the clinical and laboratory status of critical COVID-19 patients in the current uncontrolled study.
Keywords: ARDS, COVID-19, Hyperimmune convalescent plasma, inflammatory cytokines

(18107)

Nanocurcumin, an anti-inflammatory therapeutic agent in coronavirus disease

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Background: Coronavirus disease (2019-nCoV) is a worldwide health concern, in which cytokine storm, hyperinflammation, and disease progression are caused by the increased frequency of Th17 cells and their overactivation, mediated by producing large amounts of proinflammatory cytokines. In the current study, we aimed to evaluate the therapeutic effects of nanocurcumin, as an anti-inflammatory agent, on the frequency and responses of Th17 cells in mild and severe COVID-19 patients in comparison with placebo.

Methods: Totally, 40 severe COVID-19 ICU-admitted patients and 40 mild stage patients were enrolled in our study. Each group were divided into two groups, receiving nanocurcumin and placebo. The frequency of Th17 cells were assessed by flowcytometry. The gene expression of Th17 cell-mediated parameters (RORγt, IL-17, IL-21, IL-23, and GM-CSF), and the serum levels of mentioned cytokines were detected using real-time PCR and ELISA technique, respectively, in both nanocurcumin and placebo groups before and after treatment.

Results: Nanocurcumin was able to decrease the number of Th17 cells, the expression levels of Th17 cell-related factors, and the secretion levels of Th17 cell relevant cytokines in mild and severe COVID-19 patients in comparison to the placebo-treated group. The mentioned parameters were also considerably decreased in the nanocurcumin group after treatment vs before treatment, while no significant difference was observed in the placebo group before and after treatment.

Conclusion: Our findings demonstrated that nanocurcumin could meaningfully reduce the frequency of Th17 cells and its related factors in both mild and severe stages. So it would be considered as a potent therapeutic agent in improving the COVID-19 patient's inflammatory condition.

Keywords: COVID-19, T helper 17, Nanocurcumin, inflammatory

(16715)

The possible of Convalescent plasma therapy as an alternative strategy for COVID-19

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Coronavirus disease 2019 (COVID19) is a new member of coronavirus family that has been recently identified and caused an acute respiratory syndrome around the world. To date, there is no effective vaccine or specific drugs for treatment of patients who suffering from COVID19. Nevertheless, convalescent plasma that provide by recovered individuals from COVID19 might have the ability to reduce morbidity and mortality rate. So, there are some countries which approved the administration of convalescent plasma to severe and critical patients. Herein, we considerate the possible use of convalescent plasma therapy as an alternative strategy to treatment of COVID19. Further we summarized the potential benefits and discussed related concern of convalescent plasma therapy.
Keywords: COVID19; SARS-CoV2; Coronavirus; Convalescent plasma; Plasma Therapy.

(18753)

The place of medicinal plants in treatment of Coronavirus infection - a systematic review

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Background: COVID-19 is a new infectious disease caused by the novel corona virus (SARS-CoV-2) that has spread rapidly around the world. This necessitates the use of effective treatments. Long history of using medicinal herbs in traditional Iranian medicine is one of the appropriate solutions. Thus, we decided to study this area and draw a conclusion

Methods. This study was performed by online review articles published in the last six monthswith the keywords of medicinal herbs, Coronavirus ،infection in pubmed, sciencedirect, Google Scholar databases. Due to the conditions consider, ie similarity of subject with work, 33 articles were included in the study.

Results: According to the studies, the findings show that information on effectiveness of medicinal herbs in treatment of Coronavirus infection and herbs such as Glycyrrhiza Glabra،Terminalia Chebula ،Nigell sativaah ،Mint،Thyme،Propolis،Garlic are effective on Coronavirus ،infection.

Conclusion: Considering the importance treatment of Coronavirus ،infection and roots of traditional medicine in Iran for ten thousand years, research in traditional medicine literature seems logical to find new drugs because Iran is rich in herbal medicines.

Keywords: medicinal herbs, Coronavirus ،infection

(18360)

Review on the Potential Therapeutic Effects of Bruton's Tyrosine Kinase Inhibitors on COVID-19

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Background: Bruton's tyrosine kinase (BTK) has an essential effect on B-cells. It plays a crucial role in innate immune responses and also regulates the production of proinflammatory cytokines. BTK is highly expressed in the pathogenesis of some cancers and many autoimmune diseases. BTK inhibitors show promising clinical results regarding the treatment of said conditions and are suggested as a drug for treating lung abnormalities caused by excessive inflammation. Patients with severe COVID-19 show a hyperinflammatory immune response. This study aims to explain the therapeutic effects of BTK inhibitors on COVID-19.

Methods: This review has been done by analyzing articles from scientific databases such as PubMed, Science Direct, Scopus and Web of science. We reviewed 32 articles from 2000 to 2020 and chose 11 articles with the keywords: "Bruton's tyrosine kinase", "Viral disease" and "COVID-19."

Results: Many anti-inflammatory drugs, such as tocilizumab, siltuximab and sarilumab, are used to manage COVID-19. BTK inhibitors also show anti-inflammatory effects; they modulate inflammatory responses dominated by macrophages. Administering acalabrutinib, a BTK inhibitor, to 19 patients with the age median of 61 showed 72.2% success in patients on supplemental oxygen and 25% success in patients on mechanical ventilation. Out of 6 COVID-19 patients with Waldenstrom macroglobulinemia (WM) receiving ibrutinib, another BTK inhibitor, 83.3% showed fast recovery and 16.7% required hospitalization and mechanical ventilation but ultimately recovered.

Conclusion: The unconventional nature of this disease and lack of various studies on this topic make it challenging to make deductions on the effects of different medications on disease progression. However, the studies' results show that using BTK inhibitors for managing COVID-19 symptoms can have therapeutic benefits. More studies on the effects of different BTK inhibitors on the severity of symptoms in COVID-19 patients could lead to a better and more sufficient treatment protocol.

Keywords: Bruton's tyrosine kinase, COVID-19, Viral disease

(15493)

The effects of Nanocurcumin on the frequency of Th17 cells in mild and severe 2019-novel coronavirus patients

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Background: An acute respiratory syndrome Coronavirus2 (SARS-CoV2) that causes the Coronavirus disease 2019 (COVID-19), is ranged from cold-like symptoms to acute respiratory disease syndrome (ARDS) and lethal injury. Increased number and responses of Th17 cells play a critical role in hyper inflammation and disease progression in infected patients. Nanocurcumin, a nano range formulation of curcumin can apply in infected patients as an anti-inflammatory therapeutic agent. The current study focused on evaluating the therapeutic effects of nanocurcumin (SinaCurcumin®) on the frequency of Th17 cells and the expression level of RORγt transcription factor in mild and severe COVID-19 patients in comparison with the placebo group.

Methods: 40 severe COVID-19 ICU-admitted patients and 40 mild stage patients were included in the study and each stage was distributed into nanocurcumin and placebo groups. The frequency of Th17 cells and the gene expression level of Th17 transcription factor (RORγt) were detected in both nanocurcumin and placebo groups before and after treatment.

Results: The flow cytometric analysis indicated a significant reduction in the number of Th17 cells in the nanocurcumin treated group after treatment vs before treatment in mild and severe COVID-19 patients ($P=0.0001$ and $P<0.0001$, respectively; while no significant difference was observed in the placebo group ($P=0.08$ and $P=0.02$, respectively). Also, a remarkable decrease in the expression level of RORγt was found in the nanocurcumin treated group after treatment vs before treatment, in mild and severe infected patients ($P=0.002$ and $P=0004$, respectively), whit no considerable difference in the placebo-treated group.

Conclusions: Findings revealed that SinaCurcumin® could meaningfully reduce the frequency of Th17 cells and its transcription factor (RORγt) in nanocurcumin-treated patients compared to placebo-treated ones in both mild and severe stages. So it would be considered as a potent therapeutic agent in improving the COVID-19 patient's inflammatory condition.

Keyword: COVID-19; Th17; RORγt; nanocurcumin

(18469)

Effect of Tocilizumab in Patients with Severe and Critical COVID-19: A review

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Background: The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a worldwide crisis causing over 1.6 million deaths up until December 2020. SARS-CoV-2 is an enveloped, positive-strand RNA virus that can be transmitted by respiratory droplets from infected patients. Pro-inflammatory markers (such as IL-6) play a significant role in the disease severity of patients with COVID-19, tocilizumab is a humanized monoclonal antibody capable of blocking IL-6 (causing cytokine release syndrome (CRS), and cytokine storm) receptor, and potentially reducing the cytokine release, improving the clinical outcomes. In this research, we study the effects of tocilizumab in COVID-19.

Methods: PubMed, Scopus, Magiran, and google scholar were searched using keywords: "Tocilizumab", "COVID-19" or "SARS-CoV-2 infection", and "Interleukin-6", until Dec 2020.

Results: SARS-CoV-2 selectively prompts a high level of IL-6 and results in exhaustion of lymphocytes. Also, the pro-inflammatory IL-6 is a reliable criterion correlated with inflammation severity. Studies show that there's no evidence of tocilizumab efficacy or immunity improvements against disease, although tocilizumab acts well as an anti-inflammatory therapy and an IL-6 inhibitor with effectiveness and safety.

Conclusion: Although treatment with tocilizumab may be associated with more favorable outcomes compared to standard care in patients with severe or critical COVID-19, the safety and efficacy of tocilizumab are not completely discovered. Also, there've been concerns regarding the possibility of secondary infection, so the use of this drug should be limited to clinical trials while considering side effects.

Keywords: Tocilizumab, COVID-19, Interleukin-6

(18770)

Natural Killer (NK) cell therapy as a promising immunotherapeutic approach for the treatment of COVID-19

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Background: Coronavirus disease 2019 (COVID-19) has become a serious global viral respiratory disease caused by severe acute respiratory coronavirus-2 (SARS-CoV-2). Severe inflammatory response is the main pathologic feature of late COVID-19 infection, leading to severe lung damage and acute respiratory distress syndrome (ARDS). Natural killer (NK) cells are innate immune lymphocytes and have a significant role in the initial immune response against SARS-CoV-2; however, studies have suggested the role of NK cells in the immunopathology of severe inflammatory response in late stages of COVID-19 infection. Here, we aim to discuss the role of NK cells in the immune response in COVID-19 infection, immunotherapeutic methods to clear SARS-CoV-2, and mediating the hyper-inflammatory responses using NK cells.

Results: NK cells have a significant role in the initial immune response and clearance of the SARS-CoV-2. NK cells exert their anti-viral immune response by inducing the apoptosis in target cells by TRAIL/Fas death receptors, exerting direct toxicity on target cells by perforin/granzyme mechanism, and promoting adaptive immune responses by producing gamma interferon (IFN-γ). However, some hurdles may limit the antiviral effects of NK cells in COVID-19. Suppression of IFN-γ production, overexpression of the NK cell-inhibiting receptor NKG2A, and increased proliferation of NK cells leading to hyper-inflammatory responses and cytokine release syndrome (CRS) are some examples of NK cell dysfunction during COVID-19 infection.

Conclusion: In conclusion, NK cells have dual roles in the immune response against SARS-CoV-2. In the first stages of infection, the NK cell-mediated immune response leads to production of IFN- γ and activation of other inflammatory cells, such as macrophages and lymphocytes, which lead to clearance of the virus. However, late NK cell-mediated immune response during late stages of infection contributes to the hyper-inflammation and ARDS. Therefore, NK cell-promoting strategies could lead to superior immune response and clearance of the virus in the initial stages/mild infection with COVID-19. Examples of this approach are the adoptive NK cell therapy (cynk-001) and chimeric antigen receptor (CAR) NK cell treatment. NK cell promoting approaches must only be used in the first stages of COVID-19 infection to obtain stronger immune response against the virus.

Keywords: Immunotherapy, Natural Killer (NK) cell, COVID-19, inflammation

(18767)

Targeting T helper 17 as a promising therapeutic candidate in covid-19 patients through reducing hyper-inflammation condition: a narrative review

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Background: Some covid-19 patients, unfortunately, died because of Acute Respiratory Distress Syndrome (ARDS). Studies showed that a high level of pro-inflammatory cytokines can be a reason for ARDS. It has also shown that T helper (Th) 1 and 17 activities are the main orcheaster of the cytokine storm. In this study, we are going to introduce T helper 17 and its related pro-inflammatory cytokines effect in covid-19.

Methods: PubMed and Google Scholar were searched from 1st of December 2019 to 10th of December 2020 with the following keywords. 33 articles found that 8 of them were chosen based on our inclusion and exclusion criteria.

Discussion and Conclusion: Studies showed that cytokine storm is a condition responsible for acute lung injury and other organs, as well. Th-17 and its related cytokines: IL-17A, IL21, IL-22 play a pro-inflammatory role against SARS Cov-2. It has demonstrated that T helper 17 populations and its related cytokines increase in ICU covid-19 patients, too. Surprisingly, IL-17 can promote apoptosis of alveolar epithelial cells and progression to fibrosis that could result in poor prognosis. So, we showed the T helper 17 fundamental roles in hyper inflammation condition in covid-19 patients and its complications. T helper 17 is mainly accepted as a pro-inflammatory cell that plays an important role in the immune response against the SARS CoV-2. The important point is that hyper-activation of this cell results in poor clinical outcomes. So we suggest that targeting T helper 17, its related cytokines, upstream or downstream pathway may be a promising method in controlling hyper inflammation condition in severe covid-19.

Keywords: covid-19, T helper 17, inflammation, interleukin 17

(18226)

Therapeutic potential of resveratrol against COVID-19

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Background: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected >70 million people worldwide and deaths exceed 1.5 million. Virological features of SARS-CoV-2, including its genomic sequence, have been identified but the mechanisms governing coronavirus disease 2019 (COVID-19) immunopathogenesis have remained uncertain. Severe COVID-19 is associated with a cytokine storm, chronic inflammation, neutrophilia, lymphocyte dysfunction, lymphopenia, reduction in T-lymphocytes and natural killer (NK) cells, disruption in viral clearance, and neutrophil/macrophage infiltration in the lungs. In many cases, patients develop acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and/or multiple-organ dysfunction syndrome (MODS).
Methods: Web of Science and PubMed databases were searched for therapeutic potential of resveratrol under a variety of pathological conditions.
Results: resveratrol reduces the expression of inflammasome activators such as thioredoxin-interacting protein (TXNIP) and nuclear factor erythroid 2 (NrF2) and increases that of the inflammasome inhibitor, i.e., NAD-dependent deacetylase sirtuin-1 (SIRT1). Resveratrol is able to inhibit the production of reactive oxygen species (ROS) and the activation of inducible nitric oxide synthases (iNOS). It impacts on signaling pathways including mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) thereby further inhibiting inflammasomes.
Conclusion: because of its anti-inflammasome, anti-inflammatory, and anti-oxidant effects and considering the key role of inflammation and cytokine storm in disease severity and poor patient outcomes, it is concluded that resveratrol can be useful in the treatment of COVID-19.
Keywords: Resveratrol, COVID-19, Inflammasome, Therapy, Pandemic

(18227)

Immunotherapy for COVID-19: Where are we now?

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Background: COVID-19 is an acute respiratory syndrome caused by SARS-COV-2 which has now become a huge pandemic worldwide. However, the specific and non-specific immunotherapies such as convalescent plasma (CP) are widely performed to treat patients with severe COVID-19, there is no definitive evidence to suggest the effectiveness of these treatments. Hence, this review aimed to highlight the current and most recent studies to identify the new immunotherapeutic for COVID-19 disease.

Methods: This study was conducted on 108 studies according to Mesh keywords including COVID-19, SARS-COV-2, and detailed Immunotherapy strategies (convalescent plasma, IVIG, Cellular therapy, signaling inhibitors, Monoclonal Antibodies) in Pubmed, Web of Science, Scopus, and other related databases.

Findings: This review shows that lymphocytopenia is mainly caused by hyperinflammation and lymphocyte destruction by SARS-CoV-2. Antiviral IgM and IgG were shown to disappear six months after COVID-19 disease onset. Convalescent plasma therapy significantly improves fever and reduces the level of virus antigens. Mesenchymal stem cell-based therapy showed improvement of symptoms and negative RT- PCR for new coronavirus.

Conclusion: The combination of anti-inflammatory therapies, including glucocorticoids, Tocilizumab (66) and sarilumab (107) IL-6 inhibitors, JAK inhibitors such as Baricitinib, MSC-based therapy may be more suitable for the treatment of patients with severe SARS-COV-2 infections.

Keywords: COVID-19, Coronavirus, Immunotherapy, Lymphopenia, SARS-COV-2

(18132)

Treatment with convalescent plasma for COVID-19 with respect to experience from prior coronavirus epidemics

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Abstract: The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a major concern all over the world. Attempts are currently being made to find a specific treatment for covid-19. Using convalescent plasma obtained from patients who had recently recovered from infection as a therapeutic intervention in previous coronavirus-related pandemics including SARS-CoV and MERS-CoV was effective and it seems to be promising in COVID-19 as well. The presence of neutralizing antibodies which specifically recognize SARS-CoV-2 are thought to mediate antiviral effects before patient develop their own humoral immune responses leading to cytokine storm and disease severity. Herein, we aim to review the existing literature on convalescent plasma for the treatment of MERS-CoV, SARS-CoV, and COVID-19. Attempts were made to evaluate the effect of plasma therapy on patients. Clinical studies compared the effectiveness of plasma therapy with other standard treatments, and the results of convalescent plasma treatment were promising. However, a small number of reviewed studies were randomized clinical trials and most of them had a small sample size. Overall, data from studies using convalescent plasma in COVID-19 suggest clinical improvements such as reduced viral load, oxygen requirement, and radiographic resolution. Although randomized clinical trials describing the benefit of convalescent plasma in COVID-19 are limited but these studies point to better outcomes of convalescent plasma treatment when administered earlier in the course of the disease. However, more precise randomized trials are needed to investigate different indications such as time of plasma administration and/or combination with other antiviral treatments.

Keywords: Convalescent plasma, Covid-19, SARS-CoV-2

15th Virtual International Congress of Immunology and Allergy
27-29 January 2021 | AJUMS | Ahvaz, Iran

(16674)

Evaluation of the effectiveness of cognitive therapy ct and behavioral therapy on anxiety and depression in patients with Covid 19

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Background: Acceptance of stress and how to cope whit it is an important factor in the treatment of diseases, especially new disease; covid19.
Methods: This study was performed as experimental study with pre-test and post-test and control group with the aim of influencing cognitive-behavioral interventions on anxiety and depression in patients with corona virus. The statistical population included 44 corona patients who were screened by observation and interview; the control and experimental groups (n = 22). In this study, which used Beck Depression Anxiety Inventory, the experimental group was given 10 sessions of two-hour cognitive-behavioral therapy and necessary training based on reducing anxiety and depression in corona patient's and respiratory function. The control group did not receive any intervention. The groups were tested for depression and anxiety before and after the interventions, and the analysis of covariance was used to analyze the data obtained from the tests.
Results: The result of this study showed that the mean score of anxiety and depression after the interventions in the experimental group significantly decreased compared to the control group.
Conclusion: According to the above findings, this treatment can be useful in accepting the disease as well as reducing anxiety and depression and maintaining mental health.
Keywords: Mental Health, Covid19, Stress, Depression

(16926)

Can Lambda Interferons be a Survival Factor in New Coronavirus Disease-2019 Patients?

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Background: The most recently discovered interferon (IFN) family, type III IFNs or lambda IFNs (IFN-λs) are caused by viral infection and act in mucosal barriers, such as the respiratory tract. Here, we assessed the serum levels of IFN-λs in new coronavirus disease-2019 (COVID-19) patients.
Methods: Sixty-four COVID-19 patients were enrolled in the present study. All cases were divided into the intensive care unit (ICU) and non-ICU groups according to their symptoms. Fourteen samples of healthy controls were also included. The serum levels of IFN-λ1 and IFN-λ2 were analyzed by specific enzyme-linked immunosorbent assay (ELISA) kits.
Results: The concentrations of IFN-λ1 and IFN-λ2 induced in the serum of non-ICU patients (836.7 ± 284.6 and 798.8 ± 301.5 pg/ml, respectively) were higher than the healthy controls (85.57 ± 33.63 and 65.82 ± 21.26 pg/ml, respectively; $P = 0.03$ and $P = 0.04$, respectively). There were also significant differences between patient groups regarding the IFN-λ1 and IFN-λ2 levels ($P = 0.004$ and $P = 0.006$, respectively). Meanwhile, no significant differences were found in the concentration of both cytokines between the ICU patients and healthy controls.
Conclusion: We conclude that higher levels of IFN-λs are associated with decreased clinical manifestations in COVID-19 patients. These cytokines could be a promising therapeutic agent to avoid the overwhelming consequences of COVID-19.
Keywords: Lambda interferons, new coronavirus disease-2019, IFN-λ1, IFN-λ2

(18766)

TLR7 as a key player role in COVID-19, lesson for innate immunity and immunization

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Abstract: The cause of the COVID-19 global pandemic is SARS-CoV-2, a member of the Coronaviridae family with a positive-sense single-stranded (ss) RNA genome. Basically, these types of viruses are recognized via innate pattern recognition receptors (PRR), such as Toll-like receptor 7 (TLR7). The innate immune activated downstream signaling to eventually induce transcription factors in the nucleus, which in turn promote the synthesis and release of types I and III IFNs and other important pro-inflammatory cytokines. Thus, TLR7 seems to be an essential component of the innate immunity against SARS-CoV-2. Patients with severe COVID-19 exhibit an impaired type I IFN response and lower viral clearance. We hypothesized that TLR7 deficiency leads to impaired viral clearance with a high viral load, thereby increasing the cytopathic viral effects and ensuing hyper-inflammatory response, which puts these individuals at risk for severe COVID-19. Recent studies have revealed that the rare variants include 4-nucleotide deletion (c.2129_2132del; p.[Gln710Argfs*18]) and a missense variant (c.2383G>T; p.[Val795Phe]) in TLR7 identified in the COVID-19 patients result in defective upregulation of type I IFN–related genes in the TLR7 pathway. The resulting amino acid change affects the leucine-rich repeat region carboxy-terminal domain, which is highly intolerant to changes and has deleterious effects on the function of the protein. These data suggest an association between the presence of loss-of-function TLR7 variants in patients with severe COVID-19 and functional immunological defects of type I and II IFNs. Clarifying the genetic determinants of severity and susceptibility to SARS-CoV-2 infection would allow for the stratification of individuals according to risk so that those at high risk would be prioritized for immunization. This is to persuade personalizing approaches considering the genetic background in IFNL genes as a host-specific indicator for the outcome of COVID-19 viral infections.

Keywords: COVID-19, TLR7, innate immunity

(16808)

Covid-19, Immune evasion strategies and Treatment options

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Background: Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of the 2019 Coronavirus (COVID-19) pandemic. Understanding the underlying physiological and immunological Factors that processes underlying clinical manifestations of COVID-19 is critical to identifying and rationally designing effective treatments. The virus uses a variety of ways to escape the immune system, which is associated with disruption of host cell signaling pathways. We will review antiviral therapies for the recovery of patients with COVID-19 disease.

Methods: In this study, the method of library collection, search of different texts and valid scientific articles was used

Result: Understanding the virus's escape strategies from the immune system helps us predict treatment outcomes, including interaction with the ACE 2 enzyme, inhibition of TRAF transcription factors 3 and 6, as well as disruption of the NFKB and IRF signaling pathways 3 and 7, which suppress primary pro-inflammatory responses. Immune cells, especially tissue monocytes or macrophages, are found to have a low expression of ACE 2, which reduces the risk of infection in this way, but there is still the possibility of infection and in some ways leads to increased inflammation and the storm becomes cytokine. In the treatment department, drugs such as (Hydroxy-) Chloroquine, azithromycin, remdesivir and nucleoside analogues, LPV / r protease, ACE 2 recombinant solution, type 1 interferons and plasma therapy are examined. Studies found that even the MMR vaccine in children could be a reason for them not to infected COVID-19 disease.

Conclusion: Because no definitive cure has been found for this disease yet and the rate of infection is high, it is seriously dangerous and it seems that the factors were mentioned should be used as a goal for effective treatment and vaccine production, although this is not an easy task and the process In this case will be long.

Keywords: COVID-19, Immune evasion, treatment, strategies

(18522)

Evaluation of the mechanism of effectiveness of useful drugs in the treatment of Covid-19 virus caused by increased bradykinin in the body

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Background: The entry of Covid-19 virus into the body causes an increase in ACE2 receptors on the surface of the body. Increased bradykinin causes many psychological effects such as confusion, seizures, delirium, increased cerebral vascular permeability and hypotension

Methods: The present study, which is a review, was prepared by searching for keywords such as ACE2, bradykinin, renin angiotensin system and Covid-19 individually and in combination in pubmed and google scholar databases between February and August 2020.

Results: Numerous drugs target the angiotensin renin system which can reduce the amount of bradykinin in the body.1_ Danazole, Stanozole and Ecallantide: reduce bradykinin and stop its effects.2_ Icatibant: reduce bradykinin signaling and block its effects 3_vitamin D: Angiotensin interferes with the renin system and by reducing renin can have a beneficial effect in the treatment of Covid-19. It can also prevent the formation of bradykinin. The entry of Covid-19 virus into the body due to its mechanism of action on ACE2 receptors can increase bradykinin in the body. As mentioned above, this increase can cause very wide symptoms and side effects in the body. Different drugs can reduce bradykinin in the body, which can also be used in the treatment of Covid-19. However, the use of these drugs requires further studies.

Keywords: Covid-19, bradykinin, drugs

(18607)

mTOR inhibition as a potential therapeutic option for Covid-19

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Lately, a new coronavirus called SARS-CoV-2 has appeared in Wuhan, China, which is spreading rapidly around the world. This virus belongs to the beta-coronaviruses class and can bind to human angiotensin-converting enzyme 2 (ACE2) as a receptor in host cells for infection. No certain treatment has yet been found for this condition. Several studies have highlighted the importance of the mammalian target of rapamycin (mTOR) pathway in the pathogenicity of SARS-CoV-2. mTOR is a conserved serine/threonine protein kinase that functions in two complexes, mTOR complex 1 (mTOR1) and mTOR complex 2 (mTOR2), and is involved in the regulation of protein synthesis, growth of cells, and metabolism of energy. Some studies indicate that mTOR inhibition may affect COVID-19 by reducing the proliferation of conventional T lymphocytes, which may mitigate the cytokine storm, and maintaining the growth and activity of Treg, which may decrease immune hyper-reactivity during the critical phase of the disease. Also, a number of studies have stated that the mTOR inhibitors might effectively inhibit viral replication in the human respiratory tract and lung cells. Since approved mTOR inhibitor drugs are available in the market, so, targeting the mammalian target of rapamycin (mTOR) pathway may be a promising therapeutic way to combat COVID-19, alleviate symptoms, and reduce mortality rates.

Keywords: mTOR, Covid-19, SARS-CoV-2, Therapeutics

(18409)

Curcumin suppresses NLRP3 inflammasome in COVID-19 infection

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Background: curcumin is the effective ingredient of turmeric, sometimes used as a painkiller in traditional medicine. It has extensive biological properties such as anti-inflammatory and antioxidant activities. SARS-CoV2 is a betacoronaviruse developing severe pneumonitis. **Methods:** web of science and PubMed databases were searched for therapeutic potential of curcumin under a variety of pathological conditions.

Results: inflammasome is one of the most important components of innate immunity, which exacerbates inflammation by increasing IL-1β and IL18 production. Studies on viral infections have shown overactivity of inflammasome and thus the occurrence of destructive and systemic inflammation in patients. NLRP3 inflammasome has been shown to play a key role in the pathogenesis of viral diseases. The proliferation of SARS-CoV2 in a wide range of cells can be combined with numerous observations of direct and indirect activation of inflammasome by other coronaviruses. Activation of the inflammasome is likely to be involved in the formation of cytokine storm. Curcumin regulates several molecules in the intracellular signal transduction pathways involved in inflammation, including IBB, NF-kBERK1,2, AP-1, TGF-β, TXNIP, STAT3, PPARγ, JAK2-STAT3, NLRP3, p38MAPK, Nrf2, Notch-1, AMPK, TLR-4, and MyD-88.

Conclusion: Due to anti-inflammatory and anti-inflammasome properties without any special side effects, the curcumin can potentially play a role in the treatment of COVID-19 infection along with other drug regimens.

Keywords: Curcumin, inflammation, inflammasome, COVID-19, NLRP3, Acute lung injury, acute respiratory distress syndrome, SARS-CoV2

18102

Passive immunotherapy approaches in COVID-19 treatment and management

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In 2019, the world was confronted with a major challenge named Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Millions of people passed away as a result of COVID-19. Currently, there is no absolute treatment for this emerging disease. However, the vaccine of COVID-19 has made but its efficacy on humans should be completely investigated. Furthermore, it seems that the vaccine can be used only for healthy people, not for critical patients. Also, vaccination of the population of the world is time-consuming. For these reasons, using passive immunotherapies is necessary to manage COVID-19 patients. These approaches are based on reduced inflammation as a consequence of inhibition of cytokine storm phenomenon, immunomodulation, preventing acute respiratory distress syndrome (ARDS), viral neutralization, and decreasedviralload.

Keywords: COVID-19, Immunotherapy, IVIG, Passive Immunotherapy

18049

A review study of the effect of plasma therapy on the treatment of infectious diseases with emphasis on the treatment of Covid 19

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Background: With the outbreak of coronavirus in 2019, efforts to achieve a reliable treatment with minimal clinical complications increased. One of the suggested ways was to use plasma therapy. Can the plasma of a person recovering from an infectious disease provide immunity for other people with the same disease? And can improved plasma be used to treat Covid_19? These questions and other tips prompted us to do this research on research done today and review the history of this type of treatment.

Methods: In this review study conducted in 1399, articles indexed in PubMed, SID, Google scholar, Scopus and IranDock databases were used .Other scientific books have been used to write the text. In this study, Persian and English articles were used. Articles whose text was not available were excluded from the study and a total of 15 articles were reviewed for this study.

Conclusion: Considering the studies performed in using this method in the treatment of diseases and the therapeutic history of this method, it can be used as a reliable method in the treatment of corona pandemic, although it needs extensive study by researchers and scientists around the world And it is not possible to be certain just by the positive function of this method on some patients and hospitals. Plasma therapy is more than a century old. In the 1890s, this method was used to treat diphtheria. The method has also been used in recent decades to treat SARS, Mers and Ebola, but now with new findings many countries are researching this treatment to make sure it is effective on Covid 19 disease.

Keywords : plasma plasma therapy infectious diseases coronavirus

16648

The effects of cancer therapies on the outcomes of COVID-19 in patients with cancer: A systematic review study

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Background: Today COVID-19 becomes a worldwide disaster and during this pandemic, cancer patients are a group of people who are in serious danger. Therefore, we conducted the current study to investigate whether cancer immunological therapies can affect COVID-19's outcomes or not.
Methods: A systematic search was done through electronic databases including PubMed, Scopus, Embase, and Web of Science with the related English keywords. Finally, the cohort studies which were determined the outcomes of the COVID-19 in cancer patients according to their cancer therapy subtype were reviewed.
Results: According to the including and excluding criteria, seven cohort studies with 787 participants were reviewed. The cancer therapies were categorized into five types including immunotherapy, chemotherapy, radiotherapy, targeted therapy, hormone therapy, and surgery. We found that the cancer patients who have been received any cancer therapy within 4 weeks before the onset of the COVID-19's symptoms blurt severer outcomes of the disease in comparison with the patients who did not do any cancer therapy. Chemotherapy was the most common therapeutic method was done for cancer patients and an obvious relationship was observed between the chemotherapy and the COVID-19's outcomes severity; In the other words, chemotherapy could be a risk factor for the outcomes severity and deaths due to COVID-19. Interestingly, the studies expressed that immunosuppressive therapies may not worsen the outcomes of COVID-19, however, this could be due to treatment side effects.
Conclusion: Different cancer treatments have different effects on the patients; therefore, giving attention to the cancer patients who get infected by COVID-19 and their cancer therapy could be very important to our management. Although the current studies determined immunotherapy could have some side or beneficial effects on the COVID-19's outcomes, but more studies need to investigate this relationship.
Keywords: COVID-19, Cancer, Immunotherapy

Congress Abstracts

Vaccine & COVID-19 Vaccine

15th Virtual International Congress of Immunology and Allergy (ICIA2021)

(18379)

Evaluation of protection induced by *in vitro* maturated MoDCs presenting CD8$^+$ T cell stimulating peptides after a heterologous vaccination regimen in BALB/c model against *Leishmania major*

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Background: Although there is no confirmed vaccine for the complex vector-borne disease "Leishmaniasis", dendritic cells (DC)-based subunit vaccine which relies on inducing strong and long-lasting T cell immunity, mediated by both CD4+ Th1 and CD8+ T cells, can be promising. The aim of this study was to examine the protective potential of a heterologous DC-DNA based vaccine both encoding the same CD8+ and CD4+ T cell inducing epitopes against murine cutaneous leishmaniasis.
Methods: BALB/c mice were sub-cutaneously immunized with DCs loaded *in vitro* with CD8$^+$ and CD4$^+$ T cell epitopes (peptides were pre-selected from parasite proteome). DCs were further maturated in the presence of CpG-oligonucleotides. After three weeks, peptide coding pcDNA was used as a booster and *L. major* infectious challenge was performed three weeks after boosting. Cellular responses were investigated before and at weeks 4 and 8 post challenge.
Result: The pre-challenge cellular response was deviated towards Th1 (higher IFN-γ/IL-5 ratio and lower IL-10 level). Early after challenge clinical signs indicated less inflammation at the injection site and less parasite burden in the draining lymph nodes which was well justified by dominant Th1 response. However eight weeks post-challenge the response was directed towards Th2 (with markedly increased IL-10) despite significant lower footpad inflammation.
Conclusion: Collectively, DC prime-DNA boost epitope regimen was found to be a promising approach for Th1 polarization however the constituent epitopes undoubtedly make a significant contribution in the protection outcome of the vaccine. These results further confirmed that CD8$^+$ T cell responses at the beginning of the infection are important in disease control and are invaluable components to be considered in effective vaccine design.

Keywords: cutaneous leishmaniasis, dendritic cell, peptide-vaccine, DNA

(18170)

NanoInterleukin-29-adjuvanted genetic vaccine improves cell-mediated immune responses against Herpes simplex virus Type I

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Background: In practice, both low delivery efficiency and low stability of current DNA vaccines are two significant shortcomings of their application against infection diseases. To overcome these disadvantages, in this study, the pIL-29-loaded PLGA NPs (nanoIL-29) and pgD1-loaded PLGA NPs (nanoVac) were simultaneously used to boost immunologic responses against HSV-1.

Methods: NanoIL29 and Nanovac were produced using simplified double-emulsion-solvent evaporation method, and characterized in terms of size, size distribution and zeta potential by DLS, morphology by Scanning Electron Microscope and encapsulation efficiency, loading capacity, product yield and release kinetic using PicoGreen assay. Then Balb/c mice were immunized twice with "nanoVac+nanoIL-29", "Vac+IL-29", "nanoVac", "Vac", "nanoIL-29" and or "IL-29". Cellular immunity was evaluated via lymphocytes proliferation assay (flowcytometry), cytotoxicity test (ELISA), and the measurements of IFN-γ, IL-4, and IL-2 cytokines (ELISA).

Results: We generated spherical nanoparticles at a high encapsulation efficiency and sustained release of plasmids from them. Both antigen-specific lymphocyte proliferation and Granzyme B release elicited significantly in mice which were vaccinated by the "Nanovac+NanoIL29". The T helper1-type (Th1) cytokines [IL-2 and IFN- γ] were increased significantly in these mice compared to all other groups. However, the production of IL-4 significantly decreased.

Conclusion: These experiments indicate that the "NanoIL29+Nanovac" candidate vaccine against HSV-1 infection efficiently enhance CTL and Th1-immune responses, as a result, this newly introduced vaccine may be a good candidate for future studies.

Keywords: IL-29, PLGA NPs, Genetic vaccine, HSV-1.

(17994)

Development of a novel chimeric multi-epitope vaccine via cancer-testis antigens against colorectal cancer using immunoinformatics and reverse vaccinology approaches

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Background: The prevalence of colorectal cancer (CRC) is on the rise, and the prognosis for patients with metastatic or recurrent disease is very poor. however, radiation therapy and chemotherapy can ameliorate survival rates, it is necessary to integrate different strategies such as immunotherapy to ameliorate outcomes for patients with advanced CRC. Thus, the current study was conducted to design a multi-epitope based vaccine against CRC through immunoinformatics approaches using cancer-testis antigens (CTAs).

Methods: The T CD4+ and TCD8+ cells along with IFN-γ inducing epitopes were selected from MAGEA3, OY-TES-1, NY-ESO-1, PLAC1, and AKAP4 antigens. Moreover, to stimulate strong helper T lymphocytes (HTLs) responses, two regions of TTFrC was applied. Furthermore, RS09 as a TLR4 agonist was added to the vaccine construct. Physico-chemical properties, allergenicity, antigenicity, solubility, secondary and tertiary structures of the subunit construct were assessed. Finally, homology modeling, refinement, Molecular dynamics simulation, and molecular docking were performed to evaluate the construct tertiary structure and protein-protein interaction, respectively.

Results: By adding the CTL, HTL and IFN-γ predicted epitopes along with proper adjuvant and linkers, a multi-epitope vaccine was constructed with a TAT sequence of HIV at the N-terminal. Insilico analyses confirmed a probable soluble and non-allergic protein with a molecular weight of 49.978kDa and high antigenicity. Besides, the stability of the multi-epitope construct was established and indicated the strong potential to induce humoral and cell-mediated immune responses. Also, through molecular docking and dynamic simulation, the microscopic interaction among the subunit vaccine and TLR-4 was verified.

Conclusion: Immunoinformatics analysis indicated that the modeled multi-epitope vaccine can properly induce the both T and B cells immune responses and could potentially be utilized for prophylactic or therapeutic usages against colorectal cancer.

Keywords: colorectal cancer; cancer testis antigen; immunotherapy; mmunoinformatics; Multi-epitope vaccine

(16661)

Evaluation of Leishmanization using *Iranian Lizard Leishmania* mixed with CpG-ODN as a candidate vaccine against experimental Murine Leishmaniasis

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Abstract: The live non-pathogenic Leishmania tarantolae has recently provided a promising approach as an effective vaccine candidate against experimental leishmaniasis. Here, we evaluated the immunoprotective potential of the live Iranian Lizard Leishmania (ILL) mixed with CpG adjuvant against *L. major* infection in BALB/c mice.

Four groups of female BALB/c mice were designed for this study. The first and second groups received PBS and CpG, respectively. The immunized groups received 2×10^5 ILL promastigotes and the CpG-mixed ILL (ILL+CpG). All group were injected subcutaneously in the right footpad. Three weeks later, all mice were challenged with 2×10^5 meta-cyclic promastigotes of *Leishmania major*^{EGFP}; inoculation was done in the left footpad. The footpad swelling and *in vivo* fluorescent imaging were determibed to evaluate disease progress during infection course. Eight weeks after challenge, all mice were sacrificed and the cytokines levels (IFN-γ, IL-4 and IL-10) and sera antibodies concentrations (IgG2a and IgG1) using ELISA assay, nitric oxide production using Griess assay and arginase activity in cultured splenocytes, were measured. In addition, direct fluorescent microscopy analysis and qPCR assay were used to quantify the splenic parasite burden.

The results showed that mice immunized with ILL+CpG have a less parasite burden rather than other groups and were protected against the development of the dermal lesion. Moreover, the observed protection was associated with higher production of IFN-γ, as well as a reduction in IL-4 level. Additionally, the results demonstrated that arginase activity was decreased in ILL+CpG group compared to other groups.

Conclusion: Immunization using ILL+CpG induces a protective immunity; indicating that ILL with an appropriate adjuvant would be a suitable choice for vaccination against leishmaniasis.

Keywords: Adjuvant, CpG, Iranian Lizard Leishmania, Live Vaccine

(18730)

The effect of different culture methods and growth enhancers on production of virulence factors by Bordetella pertussis

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Background: Whole cell pertussis vaccines (wPV) have been widely replaced with acellular pertussis vaccines (aPV) in most developed countries. Bordetella pertussis toxin (PT) and filamentous hemagglutitin (FHA) are two main components of aPV. These virulence proteins are produced and secreted by different strains of Bordetella pertussis. In this study we assessed the effect of various growth medium enhancers and two conventional culture methods on production of these two components in different strains of .B. pertussis.

Methods: Synthetics stainer-scholte culture media supplemented with heptakis (2,6-0-dimethyl-β-cyclodextrin), methylcellulose, and yeast extract were used. For evaluating the effect of culture methods on the production of pertussis antigens, different strains of B. pertussis were cultured using one-step and two-step methods. Secreted antigens were quantified in culture supernatant by a sandwich enzyme-linked immunosorbent assay (ELISA) using PT and FHA specific polyclonal and monoclonal antibodies and standard antigens.

Results: The growth enhancer substances differentially supported the production of pertussis antigens in the culture media. Our results demonstrated that haptakis had the highest effect in inducing the production of pertussis antigens (PT and FHA) in comparison to methylcellulose and yeast extract. Moreover, it was observed that a combination of heptakis, methylcellulose and yeast extract was more effective to trigger antigen production than other combinations. Among the four B. pertussis strains tested, BP134 strain demonstrated the best performance with regards to PT production, while FHA was produced similarly by all four tested strains.

Conclusion: The combination of heptakis, methylcellulose and yeast extract in a two-step culture method enhances the production of PT and FHA in different strains of B. pertissis. Upscale of this culture in a fermentor method may increase productivity of these antigens.

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Keywords: Bordetella pertussis, Medium supplements, Pertussis toxin, Filamentous hemagglutinin

(18621)

Tuberculosis vaccines

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Background: Tuberculosis (TB) is still one of the deadliest infectious diseases globally today being resulted in 1.8 million deaths in 2020. Although BCG vaccine can protect infants and young children from the deadly forms of TB, it fails to provide persistence protection in others. The aim of this study was reviewing available TB vaccine candidates in preclinical and clinical phases.
Methods: We searched a combination of Embase, MEDLINE, Web of Science, and Google Scholar English data bases to collect all articles related to TB vaccines.
Results: There are two TB vaccine candidates in preclinical phase (H64+CAF01 and rBCGΔais1/zmp1), four TB vaccine candidates in clinical phase I (MVA85A, MTBVAC, ChAdOx1.85A, and Ad5 Ag85A), five TB vaccine candidates in clinical phase IIa (TB/FLU-04L, RUTI, H1/H56: IC31, H4: IC31, and ID93+GLA-SE), and five TB vaccine candidates in clinical phase IIb (rBCGΔureC:Hly, M72+AS01E, and DAR-901). *Mycobacterium vaccae* vaccine is the only novel TB vaccine candidate currently under development in clinical phases III and researches showed that *M. vaccae* vaccination can provide protection against *Mycobacterium tuberculosis* pulmonary infections.
Conclusion: We need novel TB vaccines that are effective in not infected and latently infected adults to cut new TB cases, stop TB deaths and achieve the aims of "World Health Organization End TB Strategy". The mentioned TB vaccine candidates in clinical phases IIb and III are hoped to provide encouraging safety and immunogenicity in adolescents and adults.
Keywords: Tuberculosis, vaccine, Mycobacterium vaccae, Mycobacterium tuberculosis

(18566)

Advantages and disadvantages of DNA-vaccines for prostate cancer

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Background: Prostate cancer is the second death leading cancer. Usual approaches such as surgery, chemotherapy, Androgen deprivation therapy (ADT), and radiation can be effective in the early stages of the disease but, in metastasis neoplasms, they offer no survival advantages. Clinical and preclinical data show that immunotherapy can target cancer-cells better, improving the results, or even curing the disease. DNA-vaccines are closed circular DNA plasmids designed to encode different antigens or epitopes to cause the resulting immune response. In this review, we discuss the advantages and challenges of DNA-vaccines as a great candidate for cancer immunotherapy.

Methods: This systematic review is the result of data collection from PubMed, Google Scholar, Scopus, Embase, and web of science databases. 250 articles were founded that 28 of them from 2012 to 2020 were chosen to be studied.

Results: DNA-vaccines offer more advantages than other anti-tumor vaccines because of their safety, simplicity, stability, cost-effectiveness, and ease of manufacturing. Results from several clinical trials show that they are well-tolerated by patients with little or no side effects. They provide the opportunity of engineering protein and peptide antigen expression with more detailed design and delivery parameters as well as other various immunomodulatory molecules to manipulate the immune system. Also, it was demonstrated that intramuscular injection of plasmid DNA can trigger long-term gene expression and activation of both humoral and cell-mediated immune responses.

Despite all advantages, DNA-vaccines coding endogenous self-antigens face immune tolerance. Using strategies like encoding exogenous antigens or fusion antigens to molecules activating T-cells can enhance the immunogenicity of the vaccine.

Conclusion: Therapeutic DNA-vaccines are new approaches for prostate cancer treatment with great potential to translate to the clinics. Combination of the vaccination with chemotherapy, radiation, or ADT can be more effective to enhance outcomes, rather than used alone.

Keywords: DNA-vaccine, Prostate cancer, Immunotherapy

(18389)

Eevaluation of novel multiantigenic DNA vaccine against Toxoplasma gondii by Real-time Q-PCR

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Background: Toxoplasma gondii is an obligate intracellular parasite, which is capable of infecting wide range of mammals and bird species, causing serious public health problem. Up to now lots of DNA vaccines against Toxoplasma gondii have been evaluated to prevent of this pathogen. In this work, it was aimed at evaluating the effects of cocktail DNA vaccine to reduce the T. gondii load following experimental study in BALB/c mice.

Methods: three mice from each immunized and controls groups randomely were sacrificed,two days after challenge and their brains and spleens were removed. Thereafter DNA were extracted according to the manufacturer's instructions by commercial kit (sinagen,iran) and then Q-PCR was performed. Samples were run in triplicate in 3 independent experiments then means and standard deviation (SD) were calculated.

Results: The results of this study were expressed as T. gondii tachyzoite-equivalents per mg of tissue. The results were shown significantly reduction of parasite load in immunized mice tissues than control groups that injected with empty Pvax plasmid or phosphate buffered saline ($P<0.05$). However, there were no differences in parasite load between control groups ($P>0.05$).

Conclusion: Our current study showed that the introduction of multiantigenic DNA vaccine is powerful and efficient way to stimulate immune protective responses against T. gondii infection. It also demonstrated that the DNA vaccine was able to reduce the
Parasite load in brain, and spleen tissues.

Keywords: Toxoplasma gondii, DNA vaccine, DNA extraction,Q-PCR

(18263)

Prediction of T-cell epitopes of human papillomaviruses 16 and 18 L1, L2 and E7 proteins for design of a multi-epitope peptide vaccine candidate

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Background: High-risk HPV types, HPVs 16 and 18 are the most prevalent types associated with cervical cancer in the world. HPV L1 and L2 capsid proteins as well as E7 oncoprotein have critical functions in HPV-related diseases, and can be applied as target antigens for development of efficient preventive and therapeutic vaccines.

Methods: In this study, to design novel immunodominant epitopes of the L1, L2 and E7 proteins from HPV16 and 18 for developing effective vaccine against HPV infection, different bioinformatics and computational tools were utilized. For this purpose, NetMHCpan 4.0 and NetMHCIIpan, and IEDB web servers were used to predict T-cell epitopes of human and mouse. Afterwards, epitopes with good binding affinities to human and mouse MHC alleles were selected. Then, immunogenicity, population coverage, toxicity, and allergenicity were estimated by IEDB tools, ToxinPred, and Alg-Pred web servers. In addition, secretion of cytokines as a critical step was evaluated by web servers which established by Raghava's groups. Next, GalaxyPepDock server was used for molecular docking against human and mouse MHC alleles.

Results: Using immunoinformatics tools, the immunodominant, conserved and non-toxic epitopes were determined. These epitopes included L1 (aa 416-430 and aa 12-21), L2 (aa 11-20 and aa 281-297), E7 (aa 43-57) from HPV-16, and L1 (aa 8-22, aa 461-471), L2 (aa 11-20, aa 274-290), E7 (aa 78-91) from HPV-18.

Conclusion: We used bioinformatics tools to predict immunodominant and conserved epitopes of HPV16 and 18 L1, L2 and E7 proteins to design a multi-epitope peptide vaccine candidate against HPV infection. The selected epitopes were non-allergenic, non-toxic and immunogenic.

Keywords: HPV, Capsid protein, Oncoprotein, Immunoinformatics tools

(18197)

Evaluation of protective antibody titer against HBs antigen in students of Gonabad University of Medical Sciences in 2018

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Background: Hepatitis B infection is one of the common diseases worldwide and the most prevalent communicable virus transferred by blood to the healthcare personnel. Active immunity, due to vaccination is the most effective way to prevent hepatitis B infection. The present study aimed at determining protective antibody titer against HBs antigen in Gonabad University of Medical Sciences students in Iran, 2018.

Materials and Methods: The present cross sectional study were conduct on 416 students of Gonabad University of Medical Sciences. The HBsAb level was determined in blood samples by enzyme-linked Immunosorbent Assay (ELISA) kit made in Iran. Independent t test, chi-square test were used to analyze the data. The level of significance was < 0.05.

Results: HBsAb level of 217 (51.8%) cases was below 10 mIU/L, 96 (61.3%) had an HBsAb level between 10 and 100 mIU/L, and in 106 (36.5%) cases, HBsAb level was above 100 mIU/L. There was no statistically significant difference among the means of HBsAb in terms of gender, age, and BMI ($P<0.05$).

Conclusions: In general, it can be conclude that more than 50 percent of participant in this study had mild immunity in contrast of Hepatit B viruses. Therefore, in high-risk individuals, it is recommended that the anti-hepatitis B antibody titer be monitored every 6 months.

Keywords: HBsAb, Hepatitis B, Medical Students, Vaccine efficacy

(18163)

Targeting cell physiology in the aging vaccinology; an interesting experience on H1N1 Influenza Vaccine in aged mice.

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Background: Immune response decline in the elderly and regardless of virus mutations, this is the main causative of Influenza vaccine inefficacy in the aged people. Herein, we hypothesized that if α-tocopherol added to the influenza vaccine formulation may reinforce the responding cells of aged people at vaccine injection site and thereby increase vaccine potency and efficacy.
Methods: Hemagglutinin of H1N1 virus formulated in Alum and tocopherol and then aged (16-20-month-old) and young (6-8-week-old) mice were immunized subcutaneously two times with two-week-interval with 5µg of different formulations of vaccine. Two weeks after final boosting IFN-γ, IL-4 cytokines assessed with ELISA. Humoral immune responses of experimental groups assessed by hemagglutination inhibition. In addition, vaccine efficacy is determined by experimental intranasal viral challenge of mice with mouse adapted H1N1 virus.
Results: Results show that our vaccine formulation improved IFN-γ and IL-4 cytokines response in the experimental mice but the increase was evident mainly in aged group and little in young group. The results of HI assay show that α-tocopherol in the vaccine formulation increased HI activity in both young and aged groups. Furthermore, α-tocopherol as adjuvant increased protectivity of influenza vaccine in both aged and young groups through decrease of lung viral load and increase of survival rate of experimental mice.
Conclusion: In general, it seems that α-tocopherol can be used as a component of the vaccine formulation for the purposes of the elderly population and can also empower old and worn out cells to increase the effectiveness of the vaccine in the elderly population.
Key words: Influenza Vaccine, elderly, Adjuvant, α-tocopherol

(16864)

Evaluation of immunization with live and killed nonpathogenic *Iranian Lizard Leishmania* mixed with Chitin microparticles in an experimental murine leishmaniasis model

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Background: Vaccination is an effective approach to controlling infectious diseases such as leishmaniasis. In the previous studies, we showed that a leishmanization using Iranian lizard Leishmania (ILL) mixed with chitin microparticles (CMP) elicited a protective immune response against leishmaniasis in experimental animal models. In the current study, we compared the immune response in BALB/c mice after immunization with a live or killed ILL that mixed with CMPs.

Methods: Totally, 100µg/ml CMPs (<40µm in size) were mixed with 1×10^7 live ILL (ILL [Lv] +CMP) or whole-cell killed ILL (ILL [K] +CMP) and injected subsequently in the right footpad of BALB/c mice. Control groups received only live ILL (Lv), killed ILL (K), Chitin, or PBS. Fourteen weeks later, all mice were challenged with 2×10^5 L. major^{EGFP} promastigotes, in their left footpad. Footpad swelling and in vivo imaging were used to follow up the infection course. Eight weeks after the challenge, quantitative parasite burden (real-time PCR), cytokines levels (IFN-γ, IL-4, and IL-10), antibody concentration (IgG2a and IgG1), nitric oxide production, and arginase activity were measured.

Results: The results of the in vivo imaging study revealed that the fluorescent intensity in the inoculation site of the challenge with L. major^{EGFP} in the ILL [Lv] +CMP group was lower than other groups; moreover, the smallest footpad swelling was observed in this group. The qualitative parasite burden assay using qPCR confirmed the mentioned findings. In addition, higher IFN-γ and lower IL-4 concentrations were observed in mice immunized with ILL [Lv] +CMP in comparison with other groups. Immunized mice with live parasites also had higher nitric oxide concentration and lower arginase activity than the non-immunized and ILL [K] +CMP group. **Conclusion:** Ultimately, it was achieved that immunization with live Iranian Lizard Leishmania mixed with CMPs protect BALB/c mice more effectively than whole-cell killed ILL mixed with CMPs against L. major^{EGFP} challenge.

Keywords: Chitin micro particles, Iranian Lizard Leishmania, Leishmania, vaccine

(16565)

A review on beta-Glucan; Combined adjuvant-delivery system in novel Vaccine Design

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Background: Despite of being as one of the greatest triumphs in the history of medicine, effective vaccines remain elusive for many infectious diseases. Among all different platforms (live attenuated, inactive and subunit vaccines) many existing vaccines are live, attenuated organisms and confer long-lasting immunity, but tend to have adverse effects especially in immunocompromised individuals. The two latters are intrinsically safer, but need to accompany with an adjuvant to elicit adequate immune responses.

The solely adjuvant in most licensed subunit vaccines, alum, generally induces Th2 immune responses and antibody production. In the case of pathogens including intracellular chronic infections T cell mediated immunity is required. So, vaccine-mediated T cell protection is a challenging factor to confer vaccines against diseases lacking effective vaccines, yet.

Glucan particles (GPs) are spherical hollow particles, mainly consist of β-1, 3-d-glucans. β-1, 3-d-glucans are the major pathogen-associated molecular patterns (PAMPs) of fungi. Its recognition via receptors by macrophages, neutrophils, and dendritic cells lead to events including particle uptake, oxidative burst, and release of pro-inflammatory chemokines/cytokines in these antigen-presenting cells. And then T and B cell responses will also initiated. Therefore, GPs can be utilized as a vaccine adjuvant induces strong CD4+ T cell responses and antibody production.

Another promising approach in vaccine design is to use vaccine delivery systems to efficiently target antigen to the APCs of the immune system.

Remarkably, β-glucan microparticles could be regarded as antigen delivery platform. Porous structure of the shell and hollow cavity inside the GPs provide it as a carrier for proteins (including antigens), DNA, siRNA, and small molecule drugs.

According to previous studies, GP-based vaccines containing antigen extracts prepared from *Cryptococcus neoformans* protected mice against lethal *C.neoformans.*

Conclusion: The low intrinsic immunogenicity, lack of toxicity, immunomodulatory properties, good biocompatibility, and cost-effectiveness are some of characteristics to take β-glucan in consideration for novel vaccinology.

Key Words: β-glucan, adjuvant, T cell immunity, vaccine

(16529)

Vaccination is a useful solution in MS patients: A systematic review study

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Introduction & Objective: MS involves disorders of the central nervous system. The myelin sheath is the fatty tissue that surrounds the nerve fibers in the central nervous system; In MS, the sheath gradually becomes inflamed and disappears. The body's immune system plays an important role in the progression of the disease and its strengthening helps to reduce the symptoms of the disease and maintain health, including vaccination.

Methods: This study is a comprehensive and in-depth review using the World Wide Web with Keywords: Vaccination, MS, Antibody, Immune system in the period from 2010 to 2020 in Iranian and international bases IranMedex، IranDoc، PubMed، Eric، ProQuest and Ovid 38 articles were extracted and research findings were extracted from them.

Results: Studies show that the risk of hospitalization, Mortality, morbidity and recurrence are increased in MS patients with influenza; therefore, it is recommended that MS patients use the vaccine to prevent catching the flu. But the important point is that those who take immunosuppressive drugs may Due to the inhibition of the immune system, the vaccine no longer works and cannot protect the person In this case, it is recommended to perform antibody testing 4 weeks after vaccination and if the antibody does not rise, re-vaccination is recommended.

1- In patients who inject ampoules once a week or every other day They take remiflunomide like interferon and oral tablets The flu vaccine works and protects them against the virus.

2 - In patients taking drugs such as Synotec or Difuzel and Retaxib It is not known whether the vaccine is effective or not But given the potential impact, vaccination is still recommended; In general, vaccines are administered between drug cycles.

Conclusion: Based on the results of many studies that have been done in this field and most show the positive effects of vaccination, and since this is a simple method, Cheap and needless equipment, it can be used as an effective solution in MS patients.

Keywords: Vaccination, MS, Antibodies, Immune system

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(16863)

Evaluation of long lived immunologic response after leishmanization with live nonpathogenic *Iranian Lizard Leishmania* mixed with Chitin microparticles as a candidate vaccine against experimental murine leishmaniasis

Mina Noroozbeygi[1], Nafise Keshavarzian[1], Sepideh Haghdoust[1], Mostafa Hajimollahoseini[1], Farshid Yeganeh*[1]

[1]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Background: Recently, we reported that leishmanization using nonpathogenic to human Iranian lizard Leishmania (ILL) mixed with chitin microparticle (CMPs) or mixed with CpG-ODN effectively protect BALB/c mice against leishmaniasis. In the current study, we investigated the long-lived immune response after immunization with live ILL mixed with CMPs against L. major^{EGFP} challenge in BALB/c mice.

Methods: Briefly, 1×10^7 live ILL were mixed with CMPs (<40µm in size, 100µg/mL) and inoculated subcutaneously in the right footpad of BALB/c mice. Mice were challenged in left footpad with 2×10^5 L. major^{EGFP} promastigotes either fourteen weeks (long-lived) or three weeks (short-lived) after immunization. After challenge with L. major^{EGFP}, footpad swelling and in vivo imaging was used to evaluate infection course. Eight weeks after challenge spleen parasite burden (real-time PCR), cytokines levels (IFN-γ, IL-4 and IL-10), antibody concentration (IgG2a and IgG1), nitric oxide production and arginase activity were measured.

Results: The results showed that, mice immunized with ILL+CMP (in short and long-lived responses) had smaller foot-pad swelling than control groups. Additionally, in vivo imaging study revealed that the fluorescent intensity in the inoculation site of challenge in immunized groups was lower than control groups. This finding was confirmed by parasite burden assay using qPCR. Moreover, IFN-γ concentrations were higher in mice vaccinated with ILL+CMP, not only in short-lived response but also in long-lived response; while the IL-4 was lower in comparison with their control groups. Furthermore, the IL-10 concentration in the CMP control group was significantly higher when compared with other groups. In long-lived and short-lived responses, the immunized mice had higher nitric oxide concentration and lower arginase activity than non-immunized group. However, no significant differences were observed in total IgG subclasses among groups.

Conclusion: the results confirmed that Immunization with ILL+CMP is able to induce a long term protective response in BALB/c mice against L. major infection.

Keywords: Chitin micro particles, Iranian Lizard Leishmania, Leishmania, vaccine

(16862)

Evaluation of leishmanization using *Leishmania major* and *Iranian lizard Leishmania* in combination with Chitin microparticles as an immunization approach against experimental murine leishmaniasis

Mina Noroozbeygi[1], Nafise Keshavarzian[1], Sepideh Haghdoust[1], Mostafa Hajimollahoseini[1], Farshid Yeganeh[*1]

[1]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Background: Leishmaniazation has provided promising results in order to control Leishmaniasis. Our previous studies showed that chitin microparticles (CMPs) promote immune responses as an adjuvant. In the present study, immunization in BALB/c mice with a combination of non-pathogenic Iranian lizard Leishmania (ILL) mixed with CMPs was compared with a combination of L. major and CMPs.

Methods: ILL+CMP group (n=4) received 1×10^7 live ILL mixed with CMPs (<40µm in size, 100µg/mL). The second group (n=4) was immunized with 1×10^7 live L. major mixed with CMPs (L.major+CMP). The third group (n=4) received PBS (70µL). All injections were done to the right footpad of BALB/c mice. Three weeks later, mice were challenged with the 2×10^5 L. major^{EGFP} promastigotes in the left footpads. Footpad swelling and in vivo imaging were used to follow up parasite burden during the infection course. Eight weeks after challenge, parasite burden (using real-time PCR), cytokines levels (ELISA for IFN-γ, IL-4, and IL-10), antibody concentration (IgG2a and IgG1), nitric oxide production, and arginase activity were measured.

Results: immunized mice had significantly lower footpad swelling than the non-immunized group. This finding was confirmed by the results of in vivo imaging. However, the parasite burden in the L.major+CMP group was higher than the others. Furthermore, the parasite burden in the ILL+CMP group was lower than the others. Moreover, higher IFN-γ and lower IL-4 concentrations were observed in ILL+CMP group in comparison with other groups. In addition, IL-10 concentration was significantly higher in the L.major+CMP group when compared with other groups. Immunized mice with ILL+CMP also showed the lowest arginase activity among other groups. Nevertheless, no significant differences were observed in NO production and total IgG subclasses levels.

Conclusion: The results revealed that immunization with live non-pathogenic ILL parasite mixed with CMPs induced a protective response.

Keywords: Chitin micro particles, Iranian Lizard Leishmania, Leishmania major, vaccine

(18003)

A review of SARS-CoV-2 vaccine candidate

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Background: As an emerging virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is pathogenic, leading to the recent global pandemic known as coronavirus disease (COVID-19). Significant attempts are currently being conducted to develop safe and effective vaccines and drugs against SARS-CoV-2. Vaccine, including nucleic acid-based vaccines, vector vaccines, and inactivated vaccines, have initiated clinical trials.
Methods: The clinical and experimental data resulting from recent SARS-CoV-2 vaccines trials were reviewed in the present study, and potential safety problems that should be taken into account in the development of vaccines were highlighted aiming at helping planning efficient therapeutic methods for coping with SARS-CoV-2.
Results and Conclusion: Current vaccine approaches for some pathogenic viruses were reviewed, aiming at improving vaccine safety and effectiveness in coping with SARS-CoV-2. Antigen design has a significant impact on immunogenicity maximization. The important epitopes should be considered, while the unimportant ones should be excluded. Besides, the immunogen's structural design needs further research. It is also crucial to use an appropriate delivery system for vaccine effectiveness. Determination of the best performance of the approaches is dependent on various factors, such as the vaccination routes and types of vaccines. Moreover, it is critical to add adjuvants to different types of vaccines for enhancement of immunogenicity. Thus, it is crucial to select suitable adjuvants for the development of SARS-CoV-2 vaccines.
Keywords: Vaccine, SARS-CoV-2, Immunogenicity, Adjuvant

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Application of Nanotechnology in Immunotherapies	Dr. Aminreza Nikpoor	Hormozgan University of Medical Sciences
How to Publish an Article in Reputable Journals	Dr. Maryam Nourizadeh	Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences
Stem cells (Classification, Properties, Separation methods, Therapeutic application)	Dr. Dian Dayer	Cellular and Molecular Research center, Ahvaz Jundishapur University of Medical Sciences
CRISPR Advanced Training Course and Operation	Dr. Abbas Doosti	Biotechnology Research Center, Islamic Azad University, Shahrekord Branch
DNA Aptamer	Dr. Ali Ganji	Arak University of Medical Sciences
miRNAs: Introduction, Biogenesis, Function and Quantitative Detection by Real time PCR	Dr. Saeid Abedian Kenari	Immunogenetics Research Center, Mazandaran University of Medical Sciences
Basics of Working with Viral Vectors	Dr. Nazanin Mojtabavi	Immunology Research Center, Iran University of Medical Sciences

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Immunogenetics and Pyrosequencing	Dr. Kaveh Baghaei	Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences
Analyzing Real time PCR data	Dr. Farshid Noorbakhsh	Tehran University of Medical Sciences
Introductory Bioinformatics, an overview of NCBI Databases	Dr. Farshid Noorbakhsh	Tehran University of Medical Sciences
Magnetic Activated Cell Sorting	Dr. Mousa Mohammadnia Afrouzi	Immunoregulation Research Center, Babol University of Medical Sciences
Key Points in Multi-color Flow Cytometry Panel Design	Dr. Mahmood Bozorgmehr	Simorgh Diagnostic Lab
Preparation of CAR T cells	Dr. Fatemeh Rahbari Zadeh	Medical Biotechnology Department, Tarbiat Modares University
Western Blot	Dr. Sanaz keshavarz shahbaz	Mashhad University of Medical Sciences

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Theoretical and Practical Aspects of Purification, Production and Characterization of Immunogens	Dr. Reza Falak	Iran University of Medical Sciences
Phage display	Dr. Fatemeh Faraji	Iran University of Medical Sciences
Introduction of Theoretical and Practical Standard Approaches for RT-PCR Method in Basic Science Research	Dr. Majid Khoshmirsafa	Immunology Research Center, Iran University of Medical Sciences
Introduction and presentation of different statistical graphs with Excel and Graph Pad Prism software	Dr. Majid Khoshmirsafa	Immunology Research Center, Iran University of Medical Sciences
Basic Methods and Application of Flow Cytometry	Ehsan Janzamin	Cell Baft Azma
Introduction to Lymphocyte Proliferation Assessment Methods with Emphasis on CFSE Method and Its Flow Cytometric Analysis in Flowo-jo Software	Mahdieh Motiee	Tarbiat Modares University
Training Theoretical and Practical Principles of Immunohistochemistry	Maryam Nikoonezhad	Tarbiat Modares University

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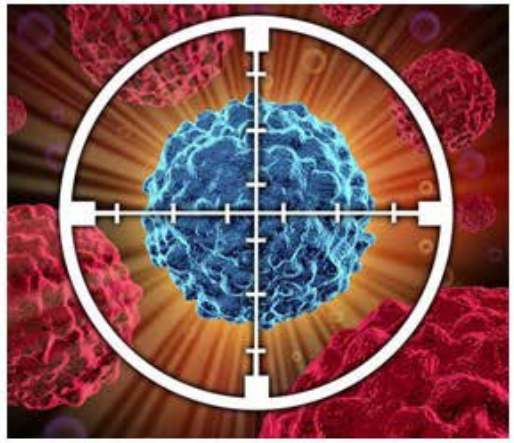

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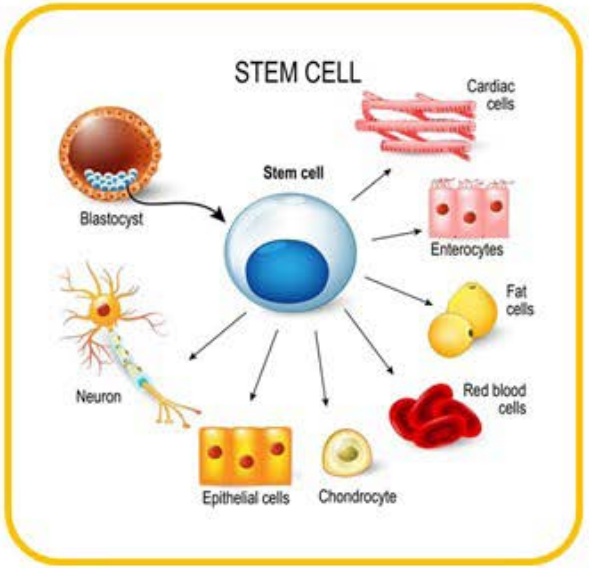

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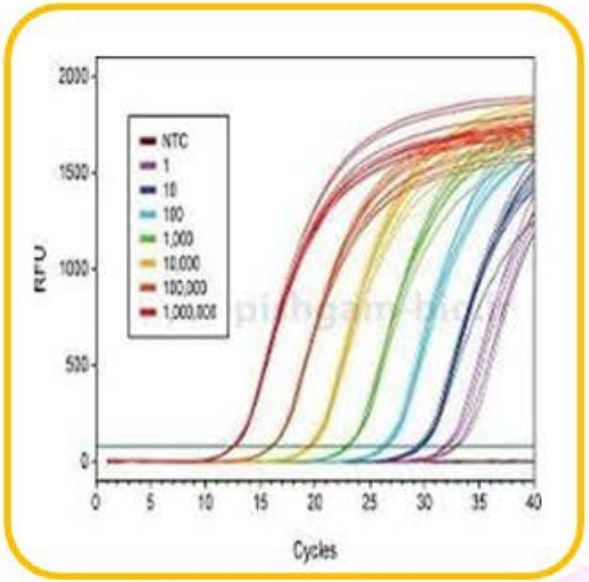
MIRNAS: INTRODUCTION, BIOGENESIS, FUNCTION AND QUANTITATIVE DETECTION BY REAL TIME PCR

Dr. Saeed Abedian Kenari

Immunogenetics Research Center, Mazandaran University of Medical Sciences



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INTRODUCTORY BIOINFORMATICS, AN OVERVIEW OF NCBI DATABASES

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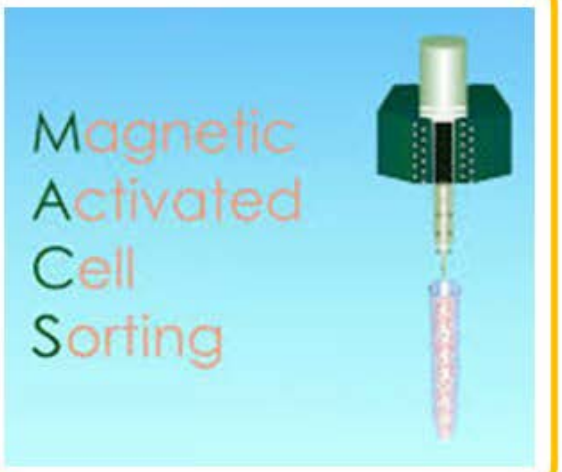
MAGNETIC ACTIVATED CELL SORTING

Dr. Mousa Mohammadnia Afrouzi

Immunoregulation Research Center, Babol University of Medical Sciences



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KEY POINTS IN MULTI-COLOR FLOW CYTOMETRY PANEL DESIGN

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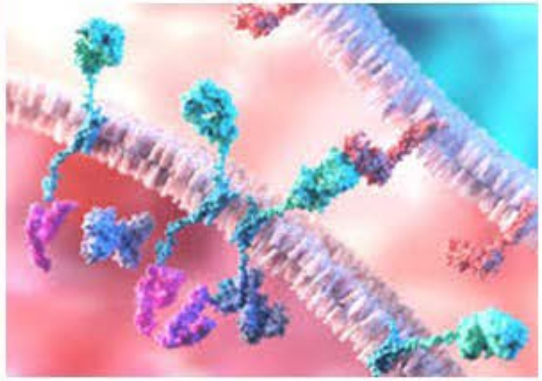
PREPARATION OF CAR T CELLS



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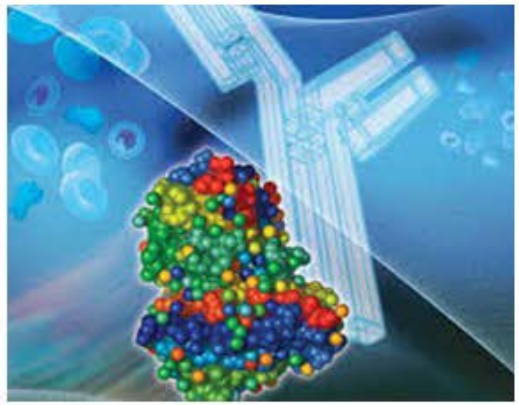
THEORETICAL AND PRACTICAL ASPECTS OF PURIFICATION, PRODUCTION AND CHARACTERIZATION OF IMMUNOGENS



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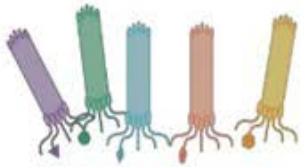
PHAGE DISPLAY

Dr. Fatemeh Faraji

Iran University of Medical Sciences

Phage Display Technology



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INTRODUCTION OF THEORETICAL AND PRACTICAL STANDARD APPROACHES FOR RT-PCR METHOD IN BASIC SCIENCE RESEARCH

Dr. Majid Khoshmirsafa

Immunology Research Center, Iran University of Medical Sciences

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INTRODUCTION AND PRESENTATION OF DIFFERENT STATISTICAL GRAPHS WITH EXCEL AND GRAPH PAD PRISM SOFTWARE

Dr. Majid Khoshmirsafa

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GraphPad Prism

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BASIC METHODS AND APPLICATION OF FLOW CYTOMETRY

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Cell Baft Azma

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INTRODUCTION TO LYMPHOCYTE PROLIFERATION ASSESSMENT METHODS WITH EMPHASIS ON CFSE METHOD AND ITS FLOW CYTOMETRIC ANALYSIS IN FLOWO-JO SOFTWARE

Mahdiyeh Motiee

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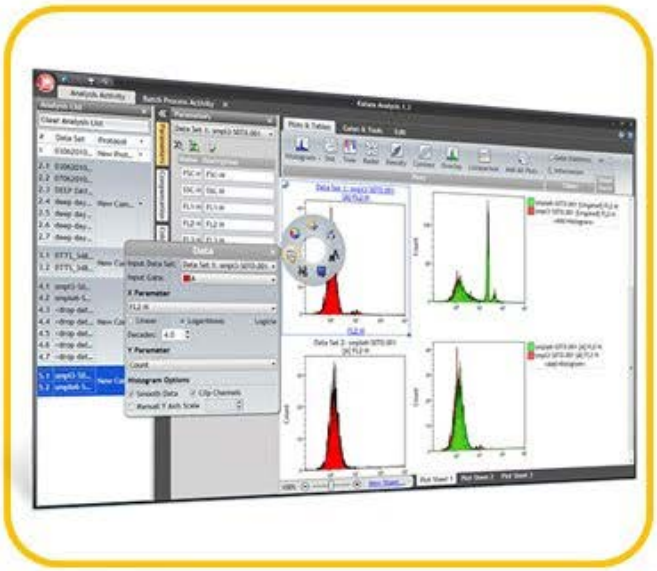

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TRAINING THEORETICAL AND PRACTICAL PRINCIPLES OF IMMUNOHISTOCHEMISTRY

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