EDITORIAL
PATHOGENS AND DEAD CELLS COOPERATE WITH CYTOKINES IN ACTIVATING THE INNATE AND ADAPTIVE RESPONSE

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After microbial invasion and tissue damage, a set of cytokines, including interleukin-1α (IL-1α), IL-1β, IL-6, IL-18 and tumor necrosis factor-α (TNF-α), and microbial and endogenous molecules named pathogen-associated molecular pattern (PAMPs) and damage-associated molecular pattern (DAMPs), are released from activated leukocytes and dead cells and bind to immune receptors to induce the innate and adaptive response. The intracellular signals induced by the multiprotein complex formed by the Toll-like receptors/IL-1 receptors (TLRs), NOD-like receptors (NLRs) and tumor necrosis factor-α receptors (TNFRs) and their ligands and downstream effectors lead to the activation of NF-κB (NF-kappaB) and the interferon regulatory factor (IRF) transcription factors and thereby the synthesis of pro- and anti-inflammatory genes as well as pro- and anti-cell death genes. Depending on cell-intrinsic and extrinsic biochemical events elicited by an inflammatory response, the cells die via apoptosis, necrosis, pyroptosis or autophagy cell death program. This article resumes our current understanding of these processes and how they influence inflammation.
TRAVELLING THROUGH TIME WITH ASPIRIN, A HEALING COMPANION

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Four thousand years ago the willow tree was known for its palliative effects. Ancient Greeks used the extract from the cortex and leaves to treat pain, fever, calluses and to enhance semen quality. Bayer Company and Felix Hoffmann claimed discovery of aspirin, and chemists all over Europe dealt with the synthesis of the drug. During 1988 the use of Aspirin was extended from an analgesic, antipyretic to a life-saving drug as it was suggested that it reduced the danger of cardiovascular accidents. Aspirin is still a drug that can offer much to medicine.
TUMOR NECROSIS FACTOR-ALPHA AND MAST CELLS: REVISITED STUDY

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Mast cells reside in connective tissues and are widely recognized as effector cells important in innate and acquired immunity. These cells are the only ones capable of storing preformed TNFα in their cytoplasmatic granules and release upon activation. TNF-alpha is a potent multifunctional cytokine involved in autoimmune diseases, cancer, allergy, and acute and chronic inflammation. In this study, we revisit the interrelationship between TNFα and mast cells.
SUSCEPTIBILITY AND RESISTANCE TO CANINE LEISHMANIOSIS IS ASSOCIATED TO POLYMORPHISMS OF THE CANINE TNF-α GENE

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The prevalence of canine leishmaniosis (CanL) infection in an enzootic area is considerably higher than the overall prevalence of the disease, suggesting a role of host genetics related to the outcome of the disease. It is accepted that one determining factor for the outcome of CanL is the type of the triggered immune response, which seems to be genetically determined. TNF-α is a cytokine which plays a crucial role during the immune response against Leishmania parasites. In the present study a case-control study with 20 resistant and 20 susceptible dogs was performed. The distribution of breeds was equal in both groups. By Sanger method the nucleotide sequence upstream the Open Reading Frame of the canine TNF-α gene was determined and four polymorphisms were identified (-40 C/A, -1134 T/G, -1150 T/C και -1243 C/G). Statistical analysis showed that the polymorphism TNF-α -40 C/A is correlated with susceptibility to CanL, while the polymorphism TNF-α -1243 C/G is correlated with resistance to CanL. Further statistical analysis, regarding the possible correlation of gender as well as clinical manifestations of the disease with the above-mentioned polymorphisms of the TNF-α gene, showed no significant findings. Further analysis of the above polymorphisms, as well as identification of more polymorphisms in candidate genes, is required to provide a better understanding of the complex underlying immune response in CanL.
VISFATIN/NAMPT/PBCEF AND CYTOKINE CONCENTRATION IN MULTIPLE SCLEROSIS PATIENTS COMPARED TO HEALTHY SUBJECTS

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The aim of the study is to measure IL-1 β, TNF-α, hs-CRP levels and Nampt/visfatin/PBCEF concentrations in patients with multiple sclerosis and to compare them with those of healthy control subjects. In a case-control study a total number of 192 people were recruited. Ninety-six of them were suffering from multiple sclerosis, age 34.80±8.75 years (mean±SD), who were referred form the Iranian Multiple Sclerosis Society. They included relapsing remitting (82 subjects) and both primary and secondary progressive (14 subjects) types of MS. The diagnosis was made according to the diagnostic criteria by a neurology consultant. Ninety-six healthy individuals were recruited from the Iranian Multicenter Osteoporosis Study (IMOS) as the control group. Following an overnight fasting, peripheral blood was taken from all subjects and centrifuged in order to separate serum for measurement of visfatin, Interleukin-1beta (IL-1β), TNF-α, and hs-CRP concentrations. Fat tissue mass was measured using DXA. Levels of visfatin, TNF-α and hs-CRP were significantly higher in MS patients. Besides, significant correlation was found between visfatin levels and those of TNF-α, IL-1β, hs-CRP in MS patients. Regarding the control group, significant correlation was found between visfatin levels and levels of TNF-α. However, we did not find any significant correlation between fat tissue mass and visfatin, TNF-α, IL-1β or hs-CRP levels in the MS group. However, there was a significant correlation between fat tissue mass and TNF-α level in the study population. Our findings demonstrated that pro-inflammatory factor levels were, although not significantly, higher in RRMS patients compared to PPMS and SPMS patients. The results suggest that levels of visfatin and pro-inflammatory cytokines are higher in MS patients compared to healthy subjects. Their higher levels may be, in part, attributable to the MS phenotypes independent of fat mass in patients. We believe that these results may shed some light on a potentially novel source of visfatin as well as explaining its regulating role in the inflammation process.
POST-TRAUMATIC AND PSYCHIATRIC SYMPTOMS AMONG YOUNG EARTHQUAKE SURVIVORS IN PRIMARY CARE CAMP HOSPITAL

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Earthquakes have been found to be associated with increased prevalence of psychiatric disorders: Post-traumatic Stress Disorder (PTSD) with a diagnosis range of 1.5%-74%, depression, anxiety and sleep disorders and substance abuse. Risk factors are varied: exposure to the earthquake, closeness to the epicenter, disruption of social network, financial loss, female sex, low educational level, etc. PTSD diagnosis is difficult because people unconsciously neglect traumatic history and ignore consequences. Between April 6th 2009 and September 2009, 323 young survivors aged between 18 and 30 years were screened for PTSD symptoms at the S.M.I.L.E., a psychiatric service for young people at the L’Aquila Camp Hospital. The screening assessment consisted of: a socio-demographic schedule with questions about earthquake experience, the General Health Questionnaire-12 items (GHQ-12), Impact Event Scale-Revised (IES-R) and Semi-structured Clinical Interview Diagnosis II (SCID-II). Regarding psychiatric morbidity, 16.2% and 37.3% had respectively moderate and high stress levels. Female gender and unemployment were significantly correlated (p<.001) with stress level and Obsessive-Compulsive (OC) trait. After screening assessment, the 66.7% (N=215) of total sample showed a positive post-traumatic symptomatology with 13.8% of PTSD diagnosis. Obsessive-Compulsive trait, female gender, destruction of housing and high level of stress (GHQ ≥ 20) were significant predictors for a PTSD diagnosis when compared with subjects positive for PTSD symptomatology but without a PTSD diagnosis according to DSM-IV criteria. Personality features must be considered important risks for post-traumatic consequences: OC trait was significantly associated with a high score on the GHQ-12 (≥20) and is a significant predictor of PTSD symptoms (“re-experiencing” dimension). Houses destroyed, gender and unemployed were also important risk factors. Our study confirms that a natural disaster produces high levels of mental disorders with significant long-term risk of chronic impairment, such as the development of a PTSD diagnosis (13.8%) with enormously costly consequences for the mental health care system and society. This should be a high priority in a public health program.
EFFECT OF OXYMATRINE COMBINED WITH LOW DOSE 5-FU ON LYMPHATIC VESSEL AND MICROVASCULAR ENDOTHELIAL CELL GROWTH OF GASTRIC CANCER IN A SEVERE COMBINED IMMUNODEFICIENT MOUSE ORTHOTOPIC IMPLANTATION MODEL

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In this study, we explored the effect of Oxymatrine combined with low dose 5-Fu on lymphatic vessel and vascular endothelial growth factor of orthotopic implanted gastric cancer in severe combined immunodeficient (SCID) nude mice. Human gastric cancer cell line SGC-7901 was orthotopically implanted into the gastric tract of nude mice. Nude mice were treated with normal saline (control group), low dose 5-Fu, oxymatrine, oxymatrine combined with low dose 5-Fu using intraperitoneal injection. The expression of LVD, VEGF-C, VEGF-D, VEGF-R-3 and their Ct were analyzed in a severe combined immunodeficient mouse orthotopic implantation gastric cancer model. We found that oxymatrine combined with low dose 5-Fu could decrease LVD and inhibit VEGF expression by a synergistic effect in SCID nude mouse orthotopic implantation gastric cancer model.
ANTI-INFLAMMATORY ACTIVITY OF THE MARINE CYANOBACTERIUM TRICHODESMIUM ERYTHRAEUM AGAINST CARRAGEENAN-INDUCED PAW ODEMA IN WISTAR ALBINO RATS

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Inflammatory diseases, including rheumatic, diseases are a major cause of morbidity of the working force throughout the world. Inflammation is a tissue reaction to infection. The effects are redness (erythema), swelling (oedema) and pain, to the area that can result in loss of function. Cyanobacteria are photosynthetic prokaryotic organisms which are potentially useful in pharmaceuticals, industrial chemicals, and restriction enzymes. Trichodesmium species are non-heterocystous cyanobacteria, commonly found in tropical and subtropical oligotrophic oceans. They occur in filaments of 20-200 cells which often congregate to form larger colonies called blooms that can be seen and often form dense blooms covering vast areas in sub-tropical regions. The present study tested the anti-inflammatory effect of the marine cyanobacterium, Trichodesmium erythraeum in carrageenan-induced inflammation in rats. The aqueous cyanobacterium showed anti-inflammatory activity at a high dosage (500 mg/kg) and this effect was on par with the commercial drug, indomethacin. The inhibition of inflammation volume was 57.5±5.5% and 47.5±4.7% respectively, at higher and lower dosages, in 30 minutes of treatment. The control group without any treatment exhibited an increase in the paw volume. This is the first report on the anti-inflammatory effect of marine-derived Trichodesmium erythraeum.
THE ROLE OF OSTEOPROTEGERIN/NUCLEAR FACTOR kB LIGAND IN CORONARY COLLATERAL DEVELOPMENT

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Osteoprotegrin (OPG), as a member of the TNF family is demonstrated to be a potential regulator of the endothelial function and angiogenesis by neutralization of nuclear factor kB ligand (RANKL). We investigated the OPG and RANKL gene expressions in circulating peripheral blood mononuclear cells (PBMCs) of Coronary artery disease (CAD) patients with different extents of coronary collateral development. In a cross-sectional study, 206 individuals with angiographically documented CAD were recruited. Severity of CAD was defined by the number of involved coronary vessels. The Rentrop scoring system was used to grade the extent of collateral development. Grade 0 or 1 collateralization was considered poor collateralization. RNA extraction and cDNA synthesis were performed. OPG and RANKL gene expressions were evaluated using quantitative real-time PCR. Among patients with CAD, 48.5% (100), 16.5% (34) and 35% (72) were considered to have one to three degrees of coronary artery involvement, respectively. The OPG and the ratio of OPG to RANKL expression were significantly elevated in patients with well-developed collateralization. In a logistic regression, severity of CAD was associated with a better collateral development, and OPG gene over expression was correlated with a better collateralization, independently of other variables. In conclusion, it seems that OPG might have an important role in prognosis of CAD; its up-regulation is parallel with CAD severity while it can enhance collateral development.
ANTI-FROSTBITE EFFECTS OF *PRUNUS TOMENTOSA THUNB* TOTAL FLAVONE

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The aim of this study is to assess the influence of *Prunus Tomentosa Thunb* Total Flavone (PTTTF) on rabbits’ frostbitten ears and on expressions of Matrix Metalloproteinase (MMP-9) in mouse frostbitten tissues and IL-1β in mouse Peripheral Blood Mononuclear Cells (PBMCs). Twelve New Zealand rabbits were randomly divided into two groups, both ears of each rabbit were frostbitten by liquid nitrogen. PTTTF and triamcinolone acetonide acetate ointment (TAAO) were spread on the left ear for 7 days, and the right ear was not treated as control. Therapeutic effects of the drugs and the pathological changes were observed. Drugs (PTTTF and TAAO) were prophylactically spread on the skin of the paws of mice for 5 days. After paw frostbitten models were established, the agents were consecutively spread for another 2 days. Expressions of MMP-9 in frostbitten tissues and IL-1β in PBMCs were respectively detected by the immunohistochemical method and RT-PCR. Compared with controls, four days later, the swelling inhibiting rate of PTTTF was 26.84%, and was 32.52% seven days later. The therapeutic effect of PTTTF was better than that of TAAO. Pathological changes of PTTTF group showed the effusion of a small quantity of neutrophil granulocytes and the tissue dropsy was not obvious. Expressions of both MMP-9 and IL-1β were significantly decreased in PTTTF group compared with those in model control group. There was no significant difference in expressions of MMP-9 and IL-1β between PTTTF group and TAAO group. We concluded that PTTTF produced a significant therapeutic effect on the frostbite of the rabbits’ ears. PTTTF could inhibit expressions of MMP-9 in frostbite tissues and IL-1β in PBMCs to relieve the frostbite inflammation.
MORPHOLOGICAL MODIFICATIONS IN OSTEOARTHRITIS: A SCANNING ELECTRON MICROSCOPY STUDY

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The chondrocyte, the only cellular component of adult articular cartilage, plays a key role in the pathogenesis of osteoarthritis (OA). The evolution of this process is very slow: the first changes involve the cell-matrix morphofunctional unit known as chondron. In this study we analyzed the cartilage of 10 patients with primary osteoarthritis. The cartilage was retrieved during total knee replacement (TKR) and maxillofacial surgery procedures. All patients presented an osteoarthritis of at least grade III. The preparation of the specimens was made by taking cartilage from both well-preserved and macroscopically degenerated areas. Specimens underwent histological evaluation with conventional staining and ultrastructural analysis. Age appeared to be a high risk factor in the development of articular cartilage damages. Depth of injury was also found to be age-related as more extensive lesions were found in the elderly, either in the knee or in the mandibular condyle. Whatever the cause of possible damage, Scanning Electron Microscopy (SEM) observations showed that at the beginning most degenerative changes in articular cartilage involved the chondron unit, a concept first introduced by Benninghoff. These changes generally go through three phases. During OA progression all degenerative changes begin from the chondron, which is why it is extremely important to understand the molecular anatomy and physiology of this pericellular microenvironment and its form, function and failure in adult articular cartilage. It is also fundamental to understand the mechanism of adaptation of the cartilage and bone disruptions, given the physiological relationship between these tissues, essential to maintain normal joint structure and function.
LETTER TO THE EDITOR

ADVERSE REACTIONS TO ANAESTHETICS PREVENTED BY THE USE OF SPECIFIC LABORATORY TESTS

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Adverse reactions to general anaesthetics are quite rare, but may be very severe and even lethal. Unfortunately, the diagnosis is frequently based on medical history and few laboratory tests are reliable. A clinical case is presented: a patient, 75 years of age, was a candidate for urgent coronary artery bypass graft surgery due to the results of the coronary angiogram (severe stenosis of the main stem). The patient reported cardiac arrest in both operations with general anaesthesia, but there was a lack of clinical documentation. Thus, sulfidoleukotriene assay (CAST-ELISA, Bühmann Laboratories) was used to determine the tolerability of general anesthetics in a single patient. The results of this in vitro test was useful in discriminating and excluding the administration of some widely-used standard anaesthetic agents.
LETTER TO THE EDITOR

CONTACT ALLERGY TO DISPERSE BLUE DYE IN GOGGLES FOR SWIMMING-BATH

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We report two unusual cases of contact allergy to blue disperse dyes in two patients who made daily use of blue-dyed goggles for swimming-bath, documented with patch tests. We obtained good results by avoiding the use of these dyed goggles.