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THE TUMOR NECROSIS FACTOR-α-INDUCED PROTEIN 8 FAMILY IN IMMUNE HOMEOSTASIS AND INFLAMMATORY CANCER DISEASES

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Within the immune system homeostasis is maintained by a myriad of mechanisms that include the regulation of immune cell activation and programmed cell death. The breakdown of immune homeostasis may lead to fatal inflammatory diseases. We set out to identify genes of tumor necrosis factor-α-induced protein 8 (TNFAIP8) family that has a functional role in the process of immune homeostasis. Tumor necrosis factor-α-induced protein 8 (TNFAIP8), which functions as an oncogenic molecule, is also associated with enhanced cell survival and inhibition of apoptosis. Tumor necrosis factor-α-induced protein 8-like 2 (TIPE2) governs immune homeostasis in both the innate and adaptive immune system and prevents hyper-responsiveness by negatively regulating signaling via T cell receptors and Toll-like receptors (TLRs). There also exist two highly homologous but uncharacterized proteins, TIPE1 and TIPE3. This review is an attempt to provide a summary of TNFAIP8 family associated with immune homeostasis and inflammatory cancer diseases.

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IMMUNOSTIMULANTS AND PREVENTION OF RECURRENT RESPIRATORY RESPIRATORY TRACT INFECTIONS

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Recurrent respiratory tract infections (RRTIs) are very common in children and a major challenge for pediatricians. They affect the children's quality of life, cause absences from school and lost parental working days, and repeated medical examinations, hospital admissions as well as antibiotic therapies lead to high costs for society. Given their prevalence and clinical importance, various prevention strategies have been developed. One of the most widely used is the administration of immunostimulants: i.e. molecules of bacterial or synthetic origin that interact with immunological mechanisms *in vitro* and *in vivo*. A number of studies have investigated their effects on cellular and innate immunity, and their clinical efficacy, but there is no consensus as to their real usefulness. The main aim of this review is to analyse the available data concerning the activity and efficacy of immunostimulants in preventing pediatric RRTIs. The majority of studies have shown that the number of infections decreases after immunostimulant treatment, but they are affected by various methodological weaknesses. Further studies are urgently needed to confirm whether, when and which immunostimulants should be used.

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EDITORIAL

PSYCHONEUROIMMUNOLOGY AND HEALTH PSYCHOLOGY: INFLAMMATION AND PROTECTIVE FACTORS

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A common clinical observation is the adverse relationship between stress and human diseases. The attention of scientific research on health has been disproportionately focused on risk factors that predict the onset of certain health outcomes, in particular there has been an increasing interest in the role of inflammation as a common mechanism of disease in a number of medical and neuropsychiatric diseases. Despite the importance of such research being undisputed, it is necessaryto emphasize what the protective factors are that promote psychosocial recovery processes and increased survival rates in a biopsychosocial perspective. This article aims to understand the relationship between psychosocial factors and immune system in the interests of health psychology, highlighting the protective factors that promote recovery, resiliency and resistance to disease.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

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EDITORIAL

RESISTIN – FROM GENE EXPRESSION TO DEVELOPMENT OF DIABETES

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Adipocyte-originated hormonal factors, playing a role of signaling particles, are widely engaged in energy control, feeding behavior and general glucose or lipid metabolism. One of them – resistin – has been suspected to initiate or develop insulin resistance and diabetes. From the moment of discovery of resistin, during last 13 years, numerous investigations put some light on a potential role of this hormone in mammals. In this review knowledge on resistin, including its structure, physiological role related to obesity and diabetes, as well as, gene sequence and phenotypic effects of the identified polymorphisms in human and domestic mammals is discussed.

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MAST CELL INVOLVEMENT IN RHEUMATOID ARTHRITIS

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Autoimmunity is a failure of self-tolerance resulting in immune reactions against autologous antigen. Rheumotoid arthritis is characterized by inflammation of synovium associated with destruction of the join cartilage and bone. A role of mast cell-mediated inflammation and antibodies are involved in this disease. Numerous cytokines such as IL-1, TNF, IL-8, IL-33 and IFN gamma have been implicated in rheumatoid arthritis and in particular in the synovial joint fluid. Since TNF is believed to activates resident synovial cells to produce collagenase that mediate destruction of cartilage, antagonists against the inflammatory cytokine TNF have a beneficial effects in this disease. Here we review the interrelationship between rheumatoid arthritis and mast cell activation.

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ZINC DEFICIENCY ADVERSELY INFLUENCES INTERLEUKIN-4 AND INTERLEUKIN-6 SIGNALING

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Zinc deficiency is accompanied by a severe impairment of the immune system, causing a high risk for infections and autoimmune diseases due to altered functionality of B- and T- cells. The influence of zinc deficiency on T- and B- cells via alteration of cytokine expression is well established. The aim of this study was to examine potential direct effects of zinc deficiency on the reactivity of B- and T- cells. Zinc deficient B- and T- cells revealed divergent reaction patterns compared to zinc sufficienT-cells. This was manifested by a stronger proliferative response following IL-6 and IL-2 stimulation on the one hand, but less proliferation following IL-4 stimulation on the other hand. Moreover, these results were supported by the finding that the B- and T-cell signaling cascades activated by IL-4 or IL-6, respectively, were affected directly by zinc deficiency, resulting in reduced Stat6 phosphorylation and increased Stat3 phosphorylation. Whereas the transcription factor Stat6 is involved in IL-4 signaling, Stat3 is activated by IL-6 signaling. Consequently, these results show opposing effects of zinc deficiency on IL-4 and IL-6/IL-2 signaling pathways, thus underlying the importance of zinc for proper immune function.

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GUANOSINE PROMOTES PROLIFERATION OF NEURAL STEM CELLS THROUGH cAMP-CREB PATHWAY

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In previous studies, we have found that extracellular guanosine can stimulate endogenous progenitor/stem cell proliferation in the spinal cord following chronic injury and in the subventricular zone of the brains of rats afflicted with Parkinson's Disease. In this study, using neural stem cells isolated from one-day old rats, we found that guanosine could stimulate neural stem cell proliferation, and that the proliferation was not due to the guanosine metabolism mechanism since guanine, which is interconverted by an ecto-purine nucleoside phosphorylase from guanosine, has no stimulating effect on the proliferation of neural stem cells. We determined that second messenger cAMP was involved in the pathway as results showed that 100 µM guanosine stimulated cAMP accumulation. Using western blot analysis, we found that 100 µM guanosine can activate the phosphorylation of CREB without changing the total amount of CREB. In conclusion, guanosine can stimulate neural stem cell proliferation, and the cAMP-CREB pathway is involved in this biological effect.

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THE EFFECTS OF INTERLEUKIN-10 OR TRANSFORMING GROWTH FACTOR BETA ON ANTI-CD3/CD28 INDUCED ACTIVATION OF $CD8^+CD28^-$ AND $CD8^+CD28^+$ T CELLS IN ALLERGIC ASTHMA

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The $CD8^+CD28^-$ and $CD8^+CD28^+$ T cells play a primordial role in peripheral tolerance, but little is known about their implication in allergic asthma. This study was designed to determine the changes in a proportion of human circulatory $CD8^+$ subsets before and after short term culture in the presence of anti-CD3/CD28 and IL-10 or TGF-β. Flow cytometry analysis revealed increased percentage of $CD8^+CD28^-$ T cells but decreased percentage of $CD8^+CD28^+$ T cells enriched from peripheral blood of adult allergic asthma individuals compared to controls (baseline). In comparison to the baseline, co-stimulation with anti-CD3/CD28 and IL-10 decreased the proportion of $CD8^+CD28^-$ T cells in severe allergic asthma subjects, whereas it increased this value in mild to moderate asthmatic subjects and controls. Adding TGF-ß decreased the proportion of $CD8^+CD28^-$ T cells from allergic asthma subjects, whereas it has opposite effects on this subset from controls. IL-10 and TGF-β had some plethoric effects on FoxP3 expression in anti-CD3/CD28 activated $CD8^+CD28^-$ T cells. Thus, these findings indicate that a control mechanism involving IL-10 and TGF-β might be defective in allergic asthma subjects.

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INVOLVEMENT OF RENAL CYTOCHROMES P450 AND ARACHIDONIC ACID METABOLITES IN DIABETIC NEPHROPATHY

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Diabetic nephropathy (DN) is one of the most serious complications of type I and type II diabetes. DN is characterized by hyperfiltration, hypertrophy, extracellular matrix accumulation, and proteinuria. This advances into renal fibrosis and loss of renal function. Reactive oxygen species (ROS) and TGF-β have been implicated in the pathogenesis of diabetic nephropathy. Early stages of diabetic nephropathy are also associated with alterations in renal sodium handling as well as hypertension; both are processes linked by involvement of the arachidonic acid (AA) metabolites, 20-hydroxyeicosatetraenoic acid (20-HETE, produced by cytochrome P450-4a, (CYP4A) and epoxyeicosatrienoic acids (EETs). Indeed, metabolism of AA is increased in a rat model of diabetes. In this study, we demonstrate that rats with streptozotocin-induced diabetes of 1 month duration develop renal hypertrophy and increased fibronectin and TGF-β1 expression/cortical levels concomitant with an increase in CYP4A expression and 20 HETE production. These results were also paralleled by an increase in reactive oxygen species (ROS) production and NADPH oxidase activity. Treatment of diabetic rats with HET0016, selective inhibitor of CYP 4A, prevented all these changes. Our results suggest that diabetes-induced induction of CYP4A and 20-HETE production could be a major pathophysiological mechanism leading to activation of ROS through an NADPH dependent pathway and TGF-β1 thus resulting in major renal pathology. Inhibitors of 20-HETE production could thus have an important therapeutic potential in the treatment of diabetic nephropathy.

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THE DUAL AURORA KINASE INHIBITOR ZM447439 PREVENTS ANAPLASTIC THYROID CANCER CELL GROWTH AND TUMORIGENICITY

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The anaplastic thyroid cancer (ATC) is among the most aggressive human tumors which fail to respond to all the currently available therapeutic approaches. As a consequence most patients die within a few months from diagnosis. In the present preclinical study, the effects of the ZM447439, a functional inhibitor of Aurora kinases, on the growth and tumorigenicity of a panel of ATC derived cell lines (CAL-62, 8305C, 8505C and BHT-101) were evaluated. The treatment of the different ATC cells with ZM447439 inhibited proliferation in a time- and dose-dependent manner, with IC_{50} comprised between 0.5 mM and 5 mM. Moreover, the drug remarkably impaired the formation of colonies in soft agar of all the cell lines. Consistently with Aurora inhibition, immunofluorescence and immunoblotting experiments demonstrated that Aurora auto-phosphorylation following drug treatment was completely abrogated, and treated cells were characterized by the presence of multiple spindles with short microtubules. In the same experiments we observed the loss of histone H3 phosphorylation on Ser10, specifically due to Aurora-B, after ZM447439 treatment. Time-lapse videomicroscopy and flow cytometric analysis demonstrated that in presence of ZM447439 the cells were able to enter mitosis but not to complete it, becoming polyploid. Almost all the ATC cell lines studied showed increased apoptosis after only 48 h of treatment. In conclusion, our data demonstrate that ZM447439 is effective in reducing cell growth and tumorigenicity of different ATC derived cell lines, and further investigations are needed to exploit its potential therapeutic value for ATC treatment.

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EFFECTS OF *BERBERIS ARISTATA/SILYBUM MARIANUM* ASSOCIATION ON METABOLIC PARAMETERS AND ADIPOCYTOKINES IN OVERWEIGHT DYSLIPIDEMIC PATIENTS

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Nutraceuticals and functional foods have attracted considerable interest as potential alternative therapies for treatment of different cardiovascular disorders and insulin resistance. We evaluated the efficacy of a combination of *Berberis Aristata/Silybum Marianum* extract (Berberol®) in a sample of overweight, dyslipidemic patients at low cardiovascular risk. We enrolled 105 Caucasian, euglycemic, overweight, dyslipidemic patients, of either sex. At baseline all patients underwent a 6 months run-in period during which they followed an adequate diet and practiced physical activity. At the end of the run-in period, patients were randomised to take placebo or a combination of *Berberis aristata/Silybum marianum*, 1 tablet during the lunch and 1 tablet during the dinner, for three months, in a double-blind, placebo-controlled design. *Berberis aristata/Silybum marianum* and placebo were then interrupted for 2 months (wash-out period), and all patients continued with only diet and physical activity. At the end of the wash-out period, patients re-started *Berberis aristata/Silybum marianum* or placebo twice a day for further 3 months. We evaluated during the run-in period, at randomisation, before and after the wash-out period these parameters: body weight and BMI, fasting plasma glucose, lipid profile, insulin resistance, retinol binding protein-4 (RBP-4), adiponectin (ADN), resistin. Total cholesterol, LDL-C, and Tg decreased, and HDL-C increase after 3 months of *Berberis aristata/Silybum marianum*, both compared to baseline and placebo. *Berberis aristata/Silybum marianum* decreased fasting plasma insulin, and HOMA-IR, both compared to baseline and to placebo. Moreover, there was a decrease of RBP-4, and resistin, and an increase of ADN after 3 months of *Berberis aristata/Silybum marianum*. All these positive effects disappeared after the wash-out period, and re-appeared after the re-introduction of the drug. We observed a significant correlation between HOMA-index decrease and resistin, and RBP-4 decrease, and between HOMA-index decrease and ADN increase in *Berberis aristata/Silybum marianum* group, but not in placebo group. *Berberis aristata/Silybum marianum* fixed combination seems to be safe and effective in improving lipid profile, but also in improving insulin resistance and adipocytokines levels.

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TRANSCRIPTIONAL PROFILE CHARACTERIZATION FOR THE IDENTIFICATION OF PERIPHERAL BLOOD BIOMARKERS IN PATIENTS WITH CEREBRAL ANEURYSMS

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We tried to identify molecular markers in peripheral blood to predict high risk of aneurysm rupture. Extraction of the total population of peripheral blood mononuclear cell (PBMC) from total blood volume, total RNA extraction from PBMC and Agilent One Color Gene-expression Oligo-Microarray were performed on peripheral venous blood samples from 45 patients with ruptured, unruptured cerebral aneurysms and control group (15). Mean foreground/ background signal intensities and A (log2(R*G)/2) values were calculated for each spot. Genes with absolute fold change (FC) ≥ ±1.5 and p-value < 0.05 were considered differentially expressed in the 3 groups (Student T-test). Genes coding for MMPs were strongly underexpressed in ruptured aneurysms group, suggesting a possible role in aneurysms development more than their rupture. Genes coding for adhesine proteins of the extracellular matrix (ICAM1) and cytoskeleton (WIPF1,TUBA4A) were underexpressed in ruptured aneurysms. Genes coding proteins involved in the regulation of apoptotic processes may be important in aneurysm development and rupture, resulting into an increased rate of remodeling processes in the arterial wall. Fas coding gene, SUMO1, ZFAT, BCL2, CCR5 genes were all over-represented in unruptured aneurysms. The coexisting over-representation of pro-apoptotic genes and the underexpression of cytoskeleton and extracellular matrix genes confirms that aneurysms development and evolution are part of a degenerative process of the arterial wall not involved in aneurysms rupture. MMPs may be involved in repairing chronic damages to the arterial walls and preventing SAH. Unexpectedly, Heat Shock Proteins (HSP90AA1, HSPA1A, HSPB1), G and RAS proteins, generally activated by stress situations were under-represented in aneurysmal walls. Further PCR and Western Blotting studies are needed to confirm such findings and to identify diagnostic and prognostic markers in order to define screening protocols for intracranial aneurysms.

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NEGATIVE FEEEDBACK INTERACTION OF HO-1/iNOS IN PBMC OF ACHF PATIENTS

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Heart failure (HF) is a common clinical syndrome with frequent exacerbations requiring hospitalization. Among the various mechanisms that underlie the pathogenesis of HF, the activation of the immune system leads to a progressive and redundant release of proinflammatory cytokines responsible for a variety of deleterious effects in heart failure, such as endothelial dysfunction, apoptosis of myocytes, activation of MMPs (Matrix Metallo Proteinases) and oxidative stress, with the result of decreased inotropism and clinical syndrome such as pulmonary edema,. The condition of oxidative stress induces the expression of genes coding for the proteins inducible nitric oxide synthase (iNOS) and heme oxygenase-1 (HO-1). Twenty-five hospitalized cardiology patients with symptomatic acute congestive HF (NYHA Class III-IV) and impaired left ventricular (LV) function (ejection fraction <35%) were included in the study. The aim of this study was to evaluate the cytokines plasma concentrations and the expression and activity of iNOS and HO-1 proteins in peripheral blood mononuclear cell (PBMC) extracted from patients in comparison to control group (IL-1α 3.8±1.7 pg/ml *vs* 7.3±0.4; IL-6 10.8±2.1 pg/ml *vs* 80.3±5.3; INF-γ 1.2±0.3 pg/ml *vs* 5.4±0.8; TNF-α 3.5±0.8 pg/ml *vs* 27.1±1.3). In ACHF; left ventricular ejection fraction (LVEF) percent was reduced. Furthermore; iNOS and HO-1 expression and cytokines plasma levels were significantly higher in patients with ACHF as compared to controls group. Moreover the enzyme activity presents an opposite trend compared to that obtained in the analysis of the transcript and proteins. Our studies suggest a negative feedback interaction between iNOS and HO-1 important in the physiopathology of heart failure that could be considered a good candidate as a future therapeutic target for the development of new drugs.

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PLASMA MYELOPEROXIDASE IN PATIENTS WITH ERECTILE DYSFUNCTION OF ARTERIOGENIC- AND NON-ARTERIOGENIC ORIGIN: ASSOCIATION WITH MARKERS OF ENDOTHELIAL DYSFUNCTION

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Endothelial dysfunction and the disruption of the nitric oxide-cyclic guanosine monophosphate (cGMP) pathway have been considered the early mechanisms for the development of erectile dysfunction (ED). Myeloperoxidase (MPO), a heme-containing enzyme mainly released by activated neutrophils and monocytes, may contribute to endothelial dysfunction by promoting oxidation of different substrates and thus may play a role in ED. MPO level and its correlation with different plasma biomarkers of endothelial dysfunction were studied in patient with ED of arteriogenic (A-ED) and non-arteriogenic (NA-ED) to assess potential differences between the two ED subgroups. Diagnosis of ED was based on the International Index of Erectile Function Score. Its etiology was classified with penile echo-color Doppler at baseline and after intracavernous injection of prostaglandin E1. MPO, soluble (s) cGMP, sICAM-1, sVCAM-1 and sP-Selectin were measured by enzyme-linked immunosorbent assay. MPO concentration in A-ED was significantly higher compared to control subjects and NA-ED patients. Plasmatic cGMP level resulted lower both in A-ED and in NA-ED patients, whereas no difference has been observed between the two ED groups. sICAM-1 concentration resulted higher in A-ED compared both to controls and NA-ED. sVCAM-1 level was the same in controls, A-ED and NA-ED patients. sP-Selectin concentration resulted higher both in A-ED and in NA-ED patients than in controls, whereas no difference has been observed between the two ED groups. Correlation analysis indicated a positive correlation between plasmatic MPO, sICAM-1 and sP-Selectin levels. MPO may represent an important link between oxidation, inflammation and cardiovascular diseases and may also represent a potential marker to distinguish between the two subgroups of ED patients. Moreover, in ED subjects circulating cGMP may reflect the local signaling dysfunction. The use cGMP as a potential marker for monitoring the disease needs further investigation.

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DHT AND IGF-1 IN PERIPHERAL BLOOD LYMPHOCYTES: NEW MARKERS FOR THE BIOLOGICAL PASSPORT OF ATHLETES

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We performed a pilot study using human peripheral blood lymphocytes (PBL) as a novel system to identify new biomarkers of dihydrotestosterone (DHT) and insulin-like growth factor-1 (IGF-1) abuse in sport. First, to obtain a gene signature, we treated cultures of lymphocytes from sedentary males with three doses of 0.237 µg/ml DHT, each of which is 80-fold the physiological concentration in young adult male serum, at days 0, 2 and 4, or with a single dose of 1.25 µg/ml IGF-1, which is 5-fold the physiological concentration in young adult male serum. We then used the Human Genome U133 Plus 2.0 microarray to identify a gene signature related to DHT or IGF-1 administration. Gene expression was evaluated after 7 and 21 days of DHT treatment, and after 24 h, 72 h and 7 days of IGF-1 treatment. Microarray analysis yielded a list of genes whose expression was altered after DHT or IGF-1 treatment. Among these we selected the genes that are most representative of the pathways associated with skeletal and muscular disorders using the IPA bioinformatics tool. We identified six (IDO1, CXCL13, CCL1, GZMB, VDR and IL2RA) and two (FN1 and RAB31) genes that were up-regulated in lymphocytes from sedentary subjects after 7 days of DHT and IGF-1 treatment, respectively. The expression of these genes in lymphocytes from differently trained athletes was either down-regulated or similar to that in lymphocytes from sedentary subjects. This finding suggests that up-regulation was due to the drug and not to physical exercise. In conclusion, we demonstrate that PBL can be useful in anti-doping checks, and we describe new biomarkers of DHT and IGF-1 abuse which can be included in the Athlete's Biological Passport.

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7T μMR IN THE ASSESSMENT OF ACUTE ARTERIAL MESENTERIC ISCHEMIA IN A RAT MODEL

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To validate a rat model of acute arterial mesenteric ischemia correlating MRI patterns with macro and microscopic changes in the small bowel. Thirty Sprague-Dawley rats were assigned to two experimental groups (Group I and Group II) of fifteen rats each. Group I underwent surgical procedure of superior mesenteric artery (SMA) ligation, followed by macroscopic observation. In Group II, a loop was tied loosely around the SMA without occluding the vessel. Three days after surgery, the loop was tied by external tips to completely occlude the artery. 7T μMR (7Tesla microMR) was performed before and 8 hours after SMA occlusion. At predetermined time-points the histopathological examinations were performed in both of groups. Macroscopic monitoring revealed thinning of mesenteric vessels, hypotonic reflex ileus and chromatic change of some loops. 7T μMR sequences evidenced loop dilation with gas-fluid mixed stasis, intraperitoneal free fluid and bowel wall hyperintensity. There were no significant differences in the histological analysis between the two groups. The gap of three days from surgery, adopted in the Group 2, allowed to avoid signs of peritoneal and mesenteric irritation which could bias imaging patterns. MR succeeded to identify the signs of arterial mesenteric ischemia.

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EFFECT OF MN (III) TETRAKIS (4-BENZOIC ACID) PORPHYRIN BY PHOTODYNAMICALLY-GENERATED FREE RADICALS ON SODs KERATINOCYTES

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Superoxide, a reactive form of oxygen, can be produced *in vivo* either in normal and under pathophysiologic conditions or by photosensitizing chemicals, as during photodynamic treatment. Photodynamic therapies (PDT), widely adopted in Dermatology and Oncology, are known to generate reactive oxygen species (ROS) and may contribute to structural alterations and oxidatively generated modifications of cellular antioxidants. We hypothesized that over-production of free radicals would decrease the enzymatic activities of endogenous cellular antioxidants. To test this hypothesis, keratinocytes were treated with the photosensitizer Photofrin plus visible light to produce free radicals and CuZnSOD and MnSOD activities were measured. Photodynamic treatment of keratinocytes increases malonylaldehyde production, nitrotyrosine staining and superoxide production. The enzymatic activities of CuZnSOD and MnSOD were significantly decreased after Photofrin plus visible light treatment. Our results suggest that the main cellular antioxidant system can be inactivated by photodynamically generated ROS. Pretreatment of keratinocytes with free radicals scavenger such as Mn (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP) was able to restore the endogenous antioxidant system activities, inhibiting the MDA formation, nitrotyrosine staining and superoxide formation. Antioxidant therapy could therefore be a useful tool in protecting healthy epidermal cells against common side effects induced by antitumor targeted therapies.

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ARE HMGB1 PROTEIN EXPRESSION AND SECRETION MARKERS OF UPPER AIRWAYS INFLAMMATORY DISEASES?

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Taking into account the mechanisms at the origin of the airways inflammatory pathologies, our attention has been recently addressed to the study of HMGB1, a protein belonging to the group of alarmins. Alarmins are those molecules which in homeostatic conditions carry out specific metabolic and/or structural functions; furthermore, after a direct trauma or an infection, these molecules are released in the extracellular milieu becoming there activators of the innate immunity and powerful inflammatory factors. In a previous research we found in patients affected with chronic rhinosinusitis with/without nasal polyposis (CRSwNP) an increased expression of this protein in the nucleus of nasal mucosa epithelial cells. HMGB1 was overexpressed also as focal subepithelial infiltration and in the inflammatory cells of patients in comparison with controls. These results suggested a possible pathogenetic role of HMGB1 in CRSwNP. The aim of the present study was to investigate if the expression and localization (nuclear, cytoplasmic and extracellular) of the HMGB1 protein-cytokine is somehow related to the severity and complexity of the histological and clinical picture. We noticed values which have around statistical significance between nuclear HMGB1 and eosinophils infiltrate (p=0.0607) and between nuclear HMGB1 and inflammatory infiltrate (P=0.0524). Even more significant was the correlation between extra-cellular HMGB1 expression and the presence of allergic-hyper reactive conditions such as asthma, allergic rhinitis, NSADs intolerance, antibiotic allergy. HMGB1 was significantly more expressed in the nucleus (p=0.0499) and in the intercellular space (p=0.0380) in allergic patients than in non-allergic subjects and as extra-cellular infiltrate in patients with NSADs intolerance (p=0.0022). These results confirm the role of HMGB1 in the pathogenesis of chronic rhinosinusitis with/without nasal polyposis; besides the higher extra-cellular expression in patients with a more severe clinical and inflammatory picture and the presence of associated co-morbidities suggests to seek for new compounds: these compounds, decreasing the extra-cellular release of this alarmin through a scavenger mechanism, could keep under control the inflammatory process without interfering with the nuclear transcriptional messengers.

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TOXICITY OF CADMIUM ON SERTOLI CELLS FUNCTIONAL COMPETENCE: AN *IN VITRO* STUDY

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Cadmium (Cd), an ubiquitous environmental metal, mainly used for industrial purposes, may be toxic at level of the reproductive system. Testis tubular-based Sertoli cells (SC), play a major role in constituting the blood-testis barrier and provide a unique microenvironment for the genesis and differentiation of germ cells. Hence SC strictly control sperm qualitative and quantitative parameters. We aimed to assess whether exposure to Cd would adversely affect superior mammal SC viability and function. We isolated and purified SC from pre-pubertal pig testes according to our method and incubated the retrieved cells with three different Cadmium chloride concentrations (5-10-15 μM). Parameters of SC function such as inhibin B and anti-Mullerian hormone (AMH) were depressed by Cd exposure, contrary to what observed in untreated controls. No impairment of the FSH receptor integrity on the SC, as assessed by 17-β-estradiol production, upon stimulation with FSH, was observed in either 5 μM Cd-treated or untreated controls. Differences, on the contrary, were observed for higher Cd concentrations (10 and 15 mM), in terms of FSH receptor integrity, that was altered, as compared to untreated controls, in terms of lower production of 17-β-estradiol. In addition, the apoptotic test showed a significant increase of early (ANNEXIN V-/Propidium Iodide+) (AV-/PI+) and late apoptotic cells (AV+/ PI+) in all Cd -treated SC conditions as compared to controls. In conclusion, the Cd -related toxicity on SC, clearly demonstrated by our study, even at low concentrations, is expected to damage spermatogenesis that directly is dependent upon retention of SC viability and function.

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ROLE OF 3D MRI WITH PROSET TECHNIQUE IN THE EVALUATION OF LUMBAR RADICULOPATHY

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The aim of this study is to demonstrate the effectiveness of 3-Dimensional Magnetic Resonance Imaging (3D MRI) using the ProSet technique in the diagnosis of lumbar radiculopathy and to compare morphological findings with clinical and neurophysiological data. 40 patients suffering from L5 or S1 mono-radiculopathy caused by a disc herniation were evaluated through preliminary clinical assessment and electromyography (EMG) technique. Both conventional spin-echo sequences and 3D coronal FFE with selective water excitation (ProSet imaging) were acquired. Indentation, swelling and tilt angle of the nerve root were assessed by means of a 3D MR radiculography. 3D ProSet multiplanar reconstructions (MPR) were used for quantitative measurements of L5 and S1 nerve root widths. Widths of the symptomatic nerve root were compared with those of the contralateral nerve. Data were processed using Epi Info 3.3 software (CDC, Atlanta, GA, USA) and were compared through a paired t-Student test. We observed an abnormal tilt angle in 22 patients (57,2%, $P<0.05$). Morphologic alterations such as monolateral swelling or indentation of the involved roots were found in 36 patients (90%, $P<0.01$) using 3D MR radiculography. In 10 patients, EMG revealed more nerve roots involved, while 3D FFE with ProSet technique shows a single root involved. In 2 patients, alterations were demonstrated only through EMG technique. We suggest that 3D MR radiculography can provide more information than other techniques about symptomatic disc herniation, supporting the detection of morphological changes of all nerve segments. 3D FFE with ProSet technique demonstrates high sensibility to exactly identify the level of the root involved and can provide an extremely useful tool to lead a surgical planning.

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EXPRESSION AND FUNCTION OF ANGIOPOIETINS AND THEIR TIE RECEPTORS IN HUMAN BASOPHILS AND MAST CELLS

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The Angiopoietin/Tie system is a key regulator of vascular remodeling, maturation, angiogenesis and lymphangiogenesis. In humans there are three angiopoietins: Angiopoietin-1 (Ang1), Angiopoietin-2 (Ang2), and Angiopoietin-4 (Ang4). Ang1 and Ang2 are the best characterized angiopoietins. The angiopoietin receptor system consists of two type I tyrosine kinase receptors (Tie1 and Tie2). Tie2 binds all known angiopoietins. We sought to characterize Ang1, Ang2, Tie1 and Tie2 expression and functions in human basophils and mast cells. Basophils, LAD-2 cells and Human Lung Mast Cells (HLMCs) constitutively express Ang1 and Ang2 mRNA. Intracellular staining for Ang1 and Ang2 was stronger in basophils than in mast cells. Immunoelectron microscopy demonstrated Ang1 in cytoplasmic vesicles of basophils. The protein kinase C activators phorbol diester (PMA) and bryostatin 1 (Bryo1) stimulated basophils to rapidly release a large amount of Ang1. PMA-induced Ang1 release was inhibited by brefeldin A. Tie1 and Tie2 mRNAs were expressed in basophils, LAD-2 and HLMCs. Basophils, LAD-2 and HLMCs expressed Tie1 on the cell surface. HLMCs and LAD-2 expressed Tie2 on the cell surface, whereas basophils did not. Ang1, but not Ang2, induced migration of mast cells through the engagement of Tie2. Neither Ang1 nor Ang2 induced basophil chemotaxis. We have identified a novel mechanism of cross-talk between human basophils and mast cells mediated by the Ang1/Tie2 system that might be relevant in the orchestration of inflammatory and neoplastic angiogenesis.

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NOVEL PATH TO IL-6 TRANS-SIGNALING THROUGH THROMBIN-INDUCED SOLUBLE IL-6 RECEPTOR RELEASE BY PLATELETS

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Interleukin (IL)-6 is a multifunctional cytokine with a critical role in inflammatory, immunoregulatory and haemopoietic responses. Its receptor consists of an ubiquitously expressed membrane transducing element (gp130) and of the specific element IL-6Rα (gp80), present only on hepatocytes and some leukocyte subsets. IL-6Rα also exists as soluble protein (sIL-6R) that, in the presence of IL-6, forms a complex able to bind gp130 and, thanks to the mechanism called trans-signaling, transduces IL-6 effect through tyrosine phosphorylation and activation of the signal transducer and transcription activator (STAT)-3. The aim of this study was to analyze the bidirectional relationships between platelet aggregation and IL-6-dependent effects. While platelets do not produce IL-6, we found that resting platelets express gp130, but not gp80, on their membranes. Upon activation by thrombin or calcium ionophore A23187, but not by ADP, the IL-6Rα is released in soluble form, while cangrelor, the specific inhibitor of P2Y12 receptor, can partially inhibit sIL-6R release. This sIL-6R is biologically active and, in the presence of IL-6, can trigger IL-6 trans-signaling, inducing an autocrine activation loop (as measured by an increase in gp80 and gp130 content) and STAT3 phosphorylation. On the other hand, IL-6 trans-signaling has no effect on platelet degranulation or aggregation by itself, nor on thrombin-induced platelet aggregation. Our data add an important piece to the puzzle of thrombosis and inflammation: in the presence of IL-6, which can be produced by stressed endothelial cells, the platelet-derived IL-6 trans-signaling could be crucial for the evolution of inflammation within a damaged vessel.

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MUSCOLOSKELETAL DISORDERS AND OCCUPATIONAL STRESS OF VIOLINISTS

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Although musculoskeletal disorders are the most frequent cause of occupational diseases in musicians, very few studies have focused attention on a single category of instruments, in particular on the violin. This involves, in its practice, almost all the areas of the body, besides being in the category of strings which is the most numerous in an orchestra. A specific protocol, investigating postural and clinical profiles of the musculoskeletal apparatus as well as job stress, was utilized in a conservatory on graduates in the tenth year of violin study, who regularly participated in activities of orchestras or string quartets. The investigation revealed "target segments" of osteoarticular apparatus (jaw, vertebral spine, shoulders, elbows, hands and fingers, lower limbs) electively subjected to overuse, as well as muscle contracture of trapezoids and hyperkeratosis of fingers and clavicle. Although the work environment was comfortable, most violinists claimed to undergo intense rhythms and competitiveness. This study, highlighting subclinical occupational diseases in young musicians (violinists) suggests adequate prevention measures.

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ENTERO-COLPO-DEFECOGRAPHY *VS* SUPINE ENTERO-MRI: WHICH ONE IS THE BEST TOOL IN THE DIFFERENTIATION OF ENTEROCELE, ELYTROCELE AND EDROCELE?

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Pelvic floor disorders represent a significant cause of morbidity associated with a severe reduction of quality of life. It represents a very common clinical problem that afflicts women three to seven time more often than men. The purpose of this study was to assess the diagnostic tools available to define the imaging strategy in patients with pelvic floor dynamic dysfunctions and to investigate their abilities in the diagnosis of enterocele, elytrocele and edrocele. From January 2008 to May 2011, 614 patients with symptoms related to pelvic floor dynamic dysfunctions were enrolled in our retrospective study. After anamnesis and clinical examination, entero-colpo-defecography (ECD) and supine entero-magnetic resonance (SE-MR) exams were performed in all patients. This study showed that the diagnostic efficacy of ECD is higher than that of SE-MR in the detection of enterocele and edrocele. Furthermore, elytrocele can be visualized only with ECD considering the position of patient during SE-MR examination. In addition, in patients planned for surgery, SE-MR is more useful to clarify the intra-pelvic interaction of multiple organ prolapse and to better define the pelvic anatomy and functioning.

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LETTER TO THE EDITOR

COMPARISON OF EFFECT OF SEX HORMONE MANIPULATION DURING NEONATAL PERIOD, ON mRNA EXPRESSION OF Slc9a4, Nr3c2, Htr5b AND Mas1 IN HIPPOCAMPUS AND FRONTAL CORTEX OF MALE AND FEMALE RATS

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It has long been known that spatial memory and the ability to navigate through space are sexually dimorphic traits among mammals, and numerous studies have shown that these traits can be altered by means of sex hormone manipulation. Hippocampus, the main organ involved in this kind of memory, has specific signature genes with high expression level compared to other regions of the brain. Based on their expression levels and the role that products of these genes can play in processes like signal transduction, mediation of hormone effects and long term potentiation, these genes can be considered as genes necessary for routine tasks of hippocampus. Male and female rat pups were injected with estradiol and testosterone respectively. at early stage of their lives to examine the effect of sex hormone manipulation on mRNA expression of Slc9a4, Nr3c2, Htr5b and Mas1 using comparative quantitative real-time polymerase chain reaction. The results showed that expressions of these genes are strongly influenced by sex hormones in both the frontal cortex and hippocampus, especially in male hippocampus, in which expression of all genes were up-regulated. Htr5b was the only gene that was affected only in the males. Expression of Mas1 was contrary to expectations, showed stronger changes in its expression in cortex than in hippocampus. Nr3c2 was down regulated in all samples but up regulated in male hippocampus, and Slc9a4 also showed a huge up-regulation in male hippocampus compared to other samples.

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LETTER TO THE EDITOR

DISTRIBUTION OF EXTENDED SPECTRUM BETA-LACTAMASE RESISTANCE GENES AMONG NOSOCOMIAL IMIPENEM RESISTANT *A. BAUMANNII* STRAINS HARBORING *BLA*$_{\text{OXA-23}}$ CARBAPENEMASES ISOLATED FROM ILAM AND TEHRAN

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Antimicrobial susceptibility and ESBLs genes of 42 imipenem resistant *A. baumannii* carried out by DDST and PCR. The most antimicrobial agents against *A. baumannii* strains, harboring *bla*$_{\text{OXA-23-like}}$ carbapenemases, were meropenem (33.4%), piperacillin-tazobactam (23.9%), ceftazidime (14.3%) and gatifoxacin (19.1%), respectively. All the 42 isolates harbored the *bla*$_{\text{TEM}}$ gene, but the *bla* $_{\text{SHV and VEB}}$ genes were not present among all the isolates. With the exception of seven isolates, all the *A. baumannii* strains harbor *bla*$_{\text{TEM}}$ showed ESBL positivity in DDST. The result of this study show that resistance against antimicrobial agents, especially carbapenems, has increased and that *bla*$_{\text{TEM}}$ harboring *A. baumannii* strains can be help the *bla*$_{\text{OXA-like}}$ carbapenemase genes to code for resistance against carbapenem antibiotics.

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LETTER TO THE EDITOR

THERMAL WATER OF VETRIOLO, TRENTINO, INHIBITS THE NEGATIVE EFFECT OF INTERLEUKIN-1β ON NITRIC OXIDE PRODUCTION AND APOPTOSIS IN HUMAN OSTEOARTHRITIC CHONDROCYTE

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The thermal water of Vetriolo in Trentino, Italy (VW) has been known over 150 years for its therapeutic properties in the treatment of osteoarthritis (OA). This is a highly mineralized water, strongly acidic sulfate, rich in calcium, magnesium and iron and used for balneotherapy after dilution. The aim of our study was to investigate the possible *in vitro* effects of the VW in human OA chondrocytes cultivated in the presence or in the absence of Interleukin-1 beta (IL-1β). OA chondrocytes were cultivated in Deionized Water (DW) (DW-DMEM, controls), or in one of three different VW-DMEM media, in which DW had been totally (100%) or in part (25% or 50%) substituted with VW. All samples were analyzed before and after treatment with IL-1β at a concentration of 5 ng/ml. After 48 h, we evaluated the cell viability, the release of nitric oxide (NO) in culture medium, the inducible nitric oxide synthase (iNOS) expression, and the percentage of apoptosis and necrosis. Finally, we carried out a morphological assessment using a transmission electron microscope (TEM). Our data showed that VW alone at 25% or 50% concentration did not affect the viability of cultured OA chondrocytes, and determined a significant survival recovery rate in cultures stimulated with IL-1β. On the contrary, the VW alone at 100% of concentration reduced, in a significant ($P<0.05$) manner, the cells viability. NO levels were low both in DW-DMEM cultures and in those reconstituted with 25% or 50% of VW, and were significantly ($P<0.05$) increased in cultures with 100% of VW. VW at 25% or 50% concentration significantly ($P<0.001$) reduced the NO production induced by IL-1β. The data of the NO levels were confirmed by the immunocytochemistry assay for iNOS. Our experiments confirmed the pro-apoptotic effect of IL-1β and demonstrated a protective effect of VW at 25% or 50% concentration. These findings were confirmed by TEM. In conclusion, our study demonstrated that VW alone at 25% or 50% concentration modifies neither morphology nor NO production and neither iNOS expression nor apoptosis, but it inhibits the negative effects of IL-1β in chondrocytes cultures.

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LETTER TO THE EDITOR

HIGH DENSITY CHOLESTEROL LEVEL AS PREDICTOR OF CLINICAL RESPONSE TO ANTI-TNF-ALPHA THERAPY IN PSORIATIC PATIENTS

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Psoriasis is a common, chronic, inflammatory, and debilitating disease of the skin. Infliximab is a human/mouse chimeric anti-TNF-alpha antibody effective in the management of psoriasis. Availability of biomarkers for prediction of response, could optimize the therapeutic approach. The aim of this study was to identify predictors of clinical response to infliximab in psoriatic patients in the long-term treatment. Patients affected with psoriasis and suitable for treatment with infliximab were prospectively enrolled. Patients treated for a period longer than 96 weeks were included in the study and divided into high responders and low responders according to infliximab efficacy (PASI 90). A logistic regression analysis was used to explore independent association between high clinical response and possible biomarkers of prediction. A total of 112 patients were included for the analysis. Multiple regression analysis showed that high levels of HDL cholesterol and the short duration of psoriasis [OR 1.11 (CI 1.05-1.18) and OR 0.94 (CI 0.89-0.99)] predicted the most effective clinical response to infliximab. Our findings, which highlight a possible role for HDL cholesterol as clinical predictor for psoriasis treatment, are particularly noteworthy in the context of clinical strategies, but also suggest a possible role for lipid metabolism in aspects of psoriasis that deserves further investigation.

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LETTER TO THE EDITOR

KARYOMETRY AND QUANTITATIVE IMMUNOHISTOCHEMICAL ANALYSIS OF THE UROTHELIUM IN TISSUE SECTIONS: A FEASIBILITY STUDY BASED ON CHROMATIN REMODELER DAXX IMMUNOSTAINING

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The aim of this study was to investigate the feasibility of applying a software traditionally used in the field of engineering to pathology, in particular to tissue sections from normal urothelium (NU) immunostained for the chromatin remodeler DAXX (death domain-associated protein). The study included 5 cases of NU. Images were recorded with a Nikon digital camera. The nuclear area and the intensity of nuclear staining were analyzed with a software package developed in LabVIEW environment. The nuclear size is 14.8±6.5 square microns. The nuclei in the cells adjacent to the stroma are slightly smaller than in the intermediate cells by a factor of 0.86. The mean nuclear area of the nuclei in the superficial cell layer in NU is identical to the nuclei in the intermediate cell layers. For each nucleus intensity of nuclear staining is calculated based on the gray value of the individual picture elements in the green color plane. The mean and standard deviation of nuclear gray value are 106±15. The mean value in the nuclei adjacent to the stroma is slightly greater by a factor 1.02 and 1.04 compared to the intermediate and superficial cell layers. In conclusion, this exploratory study shows that karyometry and quantitative immunohistochemical analysis can be done accurately by using a digital camera commonly available to pathologists and an image analysis software routinely used in the field of engineering.

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