

COMMON VARIABLE IMMUNODEFICIENCY - NEW INSIGHT INTO THE PATHOGENESIS AND THE QUEST FOR A WORKABLE CLASSIFICATION

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In this editorial we argue that more and more complex classifications for patients with common variable immunodeficiency (CVID) fail to identify those patients at high risk of developing infections. We propose that the minimal requirement to identify such patients is the absolute numbers of total and memory B cells and the IgM response to immunization with polysaccharides. If these data should be confirmed, they will provide the basis for a good classification of a heterogeneous group of patients. This simple, workable classification may result in a clinically useful identification of patients prone to more aggressive infections.

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ROLE OF VITAMINS D, E AND C IN IMMUNITY AND INFLAMMATION

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Inflammatory responses are operationally characterized by pain, redness, heat and swelling at the site of infection and trauma. Mast cells reside near small blood vessels and, when activated, release potent mediators involved in allergy and inflammation. Vitamin D modulates contraction, inflammation and remodeling tissue. Vitamin D deficiency has been linked to multiple diseases and several data have demonstrated a strong relationship between serum vitamin D levels and tissue function. Therapy targeting vitamin D3 signaling may provide new approaches for infectious and inflammatory skin diseases by affecting both innate and adaptive immune functions. Mast cells are activated by oxidized lipoproteins, resulting in increased expression of inflammatory cytokines and suggesting that the reduction of oxidation of low density lipoprotein by vitamin E may also reduce mast cell activation. Vitamin C is also an anti-oxidant well-known as an anti-scurvy agent in humans. Vitamin C inhibits peroxidation of membrane phospholipids and acts as a scavenger of free radicals and is also required for the synthesis of several hormones and neurotransmitters. In humans, vitamin C reduces the duration of common cold symptoms, even if its effect is not clear. Supplementation of vitamin C improves the function of the human immune system, such as antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity. Vitamin C depletion has been correlated with histaminemia which has been shown to damage endothelial-dependent vasodilation. However, the impact of these vitamins on allergy and inflammation is still not well understood.

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METHYLATION PROFILE OF PROMOTER REGION OF p16 GENE IN COLORECTAL CANCER PATIENTS OF KASHMIR VALLEY

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Colorectal cancer (CRC) commonly known as bowel cancer is the third most common cause of cancer-related deaths in the western world and has been reported to show geographical variation in its incidence. Cancer development and progression is a complex process dictated by changes in expression and regulation of various genes which include tumor suppressor genes, DNA repair genes, translation regulatory genes and others. The aim of this case control study was to analyze the promoter hypermethylation at CpG islands of *p16* gene in CRC patients among the Kashmiri population and co- relate it with expression pattern of *p16*. Genomic DNA was isolated from surgically resected tumor and adjacent normal samples and was modified using bisulphite modification kit. Methylation-specific polymerase chain reaction (PCR) was setup for the analysis of the promoter hypermethylation of *p16* gene. The epigenetic analysis revealed that unlike other high risk regions, Kashmiri population has a different promoter hypermethylation profile of *p16* gene as 66% of the cases showed *p16* promoter hypermethylation in comparison to 20% of the normal cases which also showed promoter hypermethylation of *p16* gene. The association of promoter hypermethylation with colorectal cancer was found to be significant ($P=0.0006$). Occurrence of *p16* promoter hypermethylation was found to be unequally distributed in males and females with more frequency in males than in females but the difference was not statistically significant ($P=0.7635$). Similarly, frequency of *p16* promoter hypermethylation was found to be certainly higher in Stage III/IV (83.33%) compared to Stage I/II (56.25%) but the difference was not statistically significant ($P=0.0673$). Also, the degree of *p16* promoter hypermethylation increased with the increasing severity of the lesion but the difference was not again statistically significant ($P=0.6145$). Promoter hypermethylation correlated with the decrease in expression of the *p16* gene in CRC patients leading to the diseased phenotype. These results suggest that *p16* aberrant promoter hypermethylation in Kashmiri population contributes to the process of carcinogenesis in CRC and may be developed into a valuable tool for CRC diagnosis at early stages.

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PHENOTYPIC BEHAVIOR OF PBMC FROM IRRADIATED DOGS BASED ON FLOW CYTOMETRY

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The present paper investigates the phenotypic parameters of stimulation markers and cell immunosuppression markers in an animal model using flow cytometry analysis. Six dogs were exposed to 2, 4 or 6 Gy following a head and neck protocol. Samples of peripheral blood mononuclear cells (PBMCs) were collected before irradiation, representing standard values for all dogs (control), and at 2 h, 18 h and 30 d after irradiation. Such samples were separately assessed for surface markers with the monoclonal antibodies anti-CD5, anti-CD4 and anti-CTLA-4 by flow cytometry. A reduction in Tcell expression of CD5 and in the subpopulation expressing CD4 and an increase in CTLA-4 expression were found. No statistically significant differences were observed for the absorbed dose grouping, although the time kinetics were recorded. Radiation induced phenotypic differences between the lymphocyte lineages, reducing the CD5 and CD4 Tcell subpopulations and increasing CTLA-4 expression. The findings demonstrate the relevance of investigating the immunophenotype of irradiated subjects by examining the peripheral cell lineage.

Immunophenotypic characterization has been the leading method for the determination of cell lineages and of the degree of maturation under hematological conditions. The development of a large spectrum of monoclonal antibodies and the enhancement of flow cytometry techniques have occurred over the past 20 years, making the recognition of these cell lineages possible. Flow cytometry can recognize phenotypic, biochemical and molecular differences between cells. (1)

Ionizing radiation can produce structural changes in subsets of cells. Radiation can promote genetic changes that stimulate cytokines and growth factors that act on tissues. Radiation may also change the

phenotype of circulating lymphocytes. (2)

Applied flow cytometry is a quantitative and sensitive method to evaluate apoptosis induced by low-dose radiation *in vitro* in human peripheral blood lymphocytes. The time kinetics of apoptosis were investigated and showed a statistically significant difference between control and irradiated samples. Such a study illustrates the high sensitivity of the flow cytometry method when applied to irradiated cells. (3, 4). Additionally, the proinflammatory cytokines IL-6 and IL-8 may be involved in the inflammatory response of the vascular endothelium to exposure to ionizing radiation (5).

Further developments in flow cytometry

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GENETIC VARIABILITY IN COPPER-TRANSPORTING P-TYPE ADENOSINE TRIPHOSPHATASE (*ATP7B*) IS ASSOCIATED WITH ALZHEIMER'S DISEASE IN A CHINESE POPULATION

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H.P. Liu and W.Y. Lin contributed equally to this work. B.T. Wu and F.J. Tsai contributed equally to this work.

Previous experiments demonstrated that transgenic mice carrying both amyloid precursor protein and mutant *ATP7B* transgenes reduce amyloid plaques and diminish plasma A β levels. These experiments showed that a structural change of *ATP7B* may affect Alzheimer's disease (AD) susceptibility. In this study three missense SNPs in *ATP7B* gene (rs1801243, rs1801244, and rs1801249) were chosen to test whether they were associated with AD. We tested this hypothesis using a case control design. The experimental data showed that there was a significant deviation from Hardy-Weinberg equilibrium (HWE) for SNP rs1801249 (c.3419 T>C, Val1140Ala) in the case group ($p = 0.014$) but not in the control group and that there was an association between SNP rs1801249 and AD under a recessive model ($p = 0.003$). The data also showed that the genotype frequency distribution of the *ATP7B* c.1366 G>C polymorphism (rs1801244, Val456Leu) differed significantly between the AD patients and the normal subjects ($p = 0.012$). In addition, the frequency of the TGC haplotype of SNPs rs1801243, rs1801244, and rs1801249 was significantly higher in the AD patients compared with the normal subjects ($p = 8.49 \times 10^{-7}$). These observations suggested that genetic variations in the copper transporter gene *ATP7B* might contribute to AD pathogenesis in the Taiwanese population.

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COLCHICINE MODULATES EXPRESSION OF PRO-INFLAMMATORY GENES IN NEUTROPHILS FROM PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER AND HEALTHY SUBJECTS

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Colchicine (Col) is a microtubule depolymerizing drug, widely used for treatment of familial Mediterranean fever (FMF). Mechanisms by which Col exerts its beneficial effects are not yet completely understood, especially with respect to gene expression in polymorphonuclear neutrophils (PMNs), the main effector cells in acute inflammatory attacks of FMF. This study was, therefore, designed to elucidate possible modulatory effect of Col on expression of inflammation-related genes in circulating PMNs from 16 FMF patients in the remission period and 11 healthy subjects. *In vitro* effect of Col exposure (1 µg/ml) on expression of 8 selected genes was examined using quantitative real-time RT-PCR. Col up-regulated expression of IL-8 and IL-1β genes in FMF (13-fold and 2.7-fold, $p < 0.05$, respectively) and healthy (3-fold and 6.5-fold, $p < 0.05$, respectively) PMNs, and down-regulated caspase-1 in FMF neutrophils (3-fold, $p < 0.05$). In FMF PMNs treated with Col mRNAs of IL-8 (51-fold, $p < 0.01$) and c-FOS (7-fold, $p < 0.05$) transcripts were elevated compared to those from healthy subjects. By contrast, caspase-1 mRNA was decreased in FMF neutrophils compared to healthy cells (1.6-fold, $p < 0.05$). Hereby, we provide evidence that, at least *in vitro*, Col displays pro-inflammatory potential in respect to IL-1β and IL-8 genes. At the same time, our findings implicate suppression of caspase-1 expression by Col as a potential mechanism for its effects in FMF treatment.

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DIFFERENTIAL GENE-EXPRESSION ANALYSIS DEFINES A MOLECULAR PATTERN RELATED TO OLIVE POLLEN ALLERGY

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Analysis of gene-expression profiles by microarrays is useful for characterization of candidate genes, key regulatory networks, and to define phenotypes or molecular signatures which improve the diagnosis and/or classification of the allergic processes. We have used this approach in the study of olive pollen response in order to find differential molecular markers among responders and non-responders to this allergenic source. Five clinical groups, non-allergic, asymptomatic, allergic but not to olive pollen, untreated-olive-pollen allergic patients and olive-pollen allergic patients (under specific-immunotherapy), were assessed during and outside pollen seasons. Whole-genome gene expression analysis was performed in RNAs extracted from PBMCs. After assessment of data quality and principal components analysis (PCA), differential gene-expression, by multiple testing and, functional analyses by KEGG, for pathways and Gene-Ontology for biological processes were performed. Relevance was defined by fold change and corrected *P* values (<0.05). The most differential genes were validated by qRT-PCR in a larger set of individuals. Interestingly, gene-expression profiling obtained by PCA clearly showed five clusters of samples that correlated with the five clinical groups. Furthermore, differential gene expression and functional analyses revealed differential genes and pathways in the five clinical groups. The 93 most significant genes found were validated, and one set of 35 genes was able to discriminate profiles of olive pollen response. Our results, in addition to providing new information on allergic response, define a possible molecular signature for olive pollen allergy which could be useful for the diagnosis and treatment of this and other sensitizations.

MODULATION OF β_2 AND β_3 INTEGRINS IN EXPERIMENTAL COLITIS INDUCED BY IODOACETAMIDE AND ENTEROPATHOGENIC *E. COLI*

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Integrins can modulate the infiltration of inflammatory cells and the secretion of various inflammatory mediators, essential players in the pathogenesis of colitis. This study explores the role of β_2 and β_3 integrin signaling and their possible role in experimental colitis. A total of 160 adult male Sprague-Dawley rats were divided into 4 equal groups: methylcellulose, bacteria, iodoacetamide and iodoacetamide plus bacteria. Clinical symptoms and signs of colitis were checked daily and colonic tissues were biopsied on days 3, 14, 28, and 56 post induction. Histological studies along with histochemical analysis and polymerase chain reaction of β_2 , β_3 and $\alpha_v\beta_3$ were performed according to standard procedures. The symptoms and signs were consistent with previously reported data on active colitis. The highest expression of β_3 integrin was in the combined treatment mostly on platelets, endothelial and inflammatory cells. In the same group, the expression of $\alpha_v\beta_3$ integrin complex reached the highest score after 56 days in all colonic layers. β_2 integrin expression showed a 3-4-fold increase in the combined treatment group at all time points and kept increasing till day 56. It was mostly expressed in the mucosa and submucosa. In addition, the expression of both $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ integrins was also elevated 2- to 10-fold, respectively, in the same colitis groups throughout the duration of the experiment. In conclusion, the combined treatment of IA and Enteropathogenic *E. coli* led to a significant upregulation of all the tested integrins throughout the experimental duration. Such upregulation of integrins could have contributed to the increase and chronicity of inflammation.

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LYSOSOMES INVOLVED IN THE CELLULAR TOXICITY OF NANO-ALUMINA: COMBINED EFFECTS OF PARTICLE SIZE AND CHEMICAL COMPOSITION

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Nowadays, manufactured nano-particles of aluminum oxide (nano-alumina) have been widely used in many fields with the rapidly developed nano-technology, but their basic toxic data are scarce. It is believed that the smaller nano-particles are able to easily cross the bio-membrane and quickly reach cellular compartments rather than micro-size particles, thus showing more toxic effects. The aim of this study was to compare the toxicity of nano- and micro- particles of alumina for detecting particle size related toxicity, and to compare the toxicity of nano-alumina and nano-carbon with the same particle size for determining chemical composition related toxicity. The present study revealed that nano-particles of alumina were much toxic than micro-alumina particles, indicating a particle size related toxicity; and were much more toxic than nano-carbon particles as well, manifesting a chemical related toxicity. The mechanism might be concerned with the involvement of the lysosomes. In conclusion, toxicity of nano-alumina is a combination of the toxic effects of its particle size and chemical composition.

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DEVELOPMENT OF LIVER FIBROSIS DURING AGING: EFFECTS OF CALORIC RESTRICTION

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Liver is the central metabolic organ of the body and diet is considered one of the main environmental factors that can impact on aging liver. In the elderly stage liver function is relatively well conserved although there are a variety of not well defined morphological changes related to liver fibrosis which is commonly associated with an inflammatory state. The aim of this paper is to study these alterations during the physiological process of aging in Wistar rats and also test if caloric restriction (CR) could ameliorate them. As fibrosis is associated to hepatic stellate cell (HSC) function we also analyzed these cells during aging. Livers from five groups of male Wistar rats (3-, 8-, 24-months old *ad libitum* and 8- and 24-months caloric restricted rats) were used in this study. Histological analysis, expression of genes implicated in liver fibrosis and the status of inflammatory step-pathways as p38 mitogen-activated protein kinase (p38-MAPK), c-Jun N-terminal kinase (JNK) and the nuclear factor kappa B (NFκβ) isoforms, p50 and p65, in cytosolic and nuclear fractions were performed. During elderly, associated with morphological change of HSC, there is a progressive increase in collagen deposition due to an inhibition in collagen degradation. Higher expression of cytokines and the activation of inflammatory pathways are associated with aging. CR ameliorates these circumstances being more effective when it started in middle age. In conclusion elderly stage is associated to a mild fibrotic and inflammatory state in the liver which could be ameliorated after CR.

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LUPUS ERYTHEMATOSUS CELL PHENOMENON IN PEDIATRIC BRONCHOALVEOLAR LAVAGES: POSSIBLE MANIFESTATION OF EARLY RADIOADAPTIVE RESPONSE IN RADIATION-INDUCED ALVEOLITIS

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A ten-year (December 1992 - December 2002) evaluation of 225 pediatric bronchoalveolar lavage (BAL) differential cell counts showed appearance of the cells corresponding to the cytological entity - lupus erythematosus cell (LEC) in 47 specimens of which not a single case was associated with the coexistent autoimmune disease. There was a significant increase in the percentage of LEC in BAL samples of the examinees during the first 6 months after the bombing of targets in Serbia (July-December 1999) in comparison to the period 1992 to March 24, 1999, and after the bombing of targets in Serbia (2000-2002). Maintaining the character of occurrence of LEC in BAL as nonspecific (Zunic et al. 1996), the devastating power of alpha particles (originated from uranium decay) gives an opportunity to discuss this phenomenon more comprehensibly and perceive a new vista related to the pathogenesis of LEC phenomenon in BAL. Since the period after 1991 corresponds to the time after the first Gulf War, and later the bombing of targets in Bosnia, the possibility of occurrence of LEC in BAL as a manifestation of radiation alveolitis due to contamination by air transferred depleted uranium (DU) particles could not be excluded.

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LOSS OF HYDROPHOBIC MOTIF AND ACTIVATION LOOP PHOSPHORYLATION IS A CONSEQUENCE AND NOT THE MECHANISM OF S6 KINASE 1 INHIBITION BY RAPAMYCIN

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S6K1 regulation associates a central role with dynamics of sequential phosphorylations at the hydrophobic motif (T412) and activation loop (T252) of the enzyme, such that the hydrophobic motif phosphorylation supposedly brought about by mTOR- kinase, primes the enzyme for PDK1 dependent phosphorylation at the activation loop for its full activation. Accordingly loss of hydrophobic motif phosphorylation attributed to TOR- kinase inhibition, with resultant loss of activation loop phosphorylation is the hypothesis put forward to explain the mechanism of rapamycin inhibition. Our recent observation that rapamycin continues to inhibit S6K1 in the absence of either phosphorylation, together with the evidence that phosphorylation at activation loop may occur prior to that of hydrophobic motif raises serious questions about the proposed mechanism of rapamycin inhibition. Here, we show that rapamycin fails to effect preferential loss of either phosphorylation and the two instead exhibit equal sensitivity to rapamycin both in time and quantum. We further show that of activation loop and hydrophobic motif phosphorylations turnover in an interdependent manner so as to exhibit all or none pattern of loss to rapamycin. Using insect cell expression system, we further substantiate their interdependent turnover and provide evidence that the two phosphorylations are brought about in a coordinate and not sequential manner. These data together with the observation that both kinases that cause hydrophobic motif and activation loop phosphorylations in insect or mammalian cells are completely insensitive to inhibition by rapamycin, suggest that their loss is a consequence and not the mechanism of rapamycin inhibition in accordance with the model proposed herein.

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DISTRIBUTION OF COCAINE AND AMPHETAMINE REGULATED TRANSCRIPT IN URETERS AND URINARY BLADDER OF HYPERTENSIVE RATS

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Cocaine and amphetamine regulated transcript (CART), a neuropeptide of the central and peripheral nervous system plays an essential role in maintaining body homeostasis by regulating body temperature, orexia, digestive motility and blood pressure. Very few studies describe the relationship of hypertension with CART. Therefore, the present research was undertaken to identify, locate and determine the number of CART-immunopositive neuroendocrine cells (NE) and structures in the urinary bladder and ureter of rats with experimentally induced nephrogenic hypertension. The experiments were conducted on 20 Wistar rats in which hypertension was experimentally induced by applying a clamp on the left renal artery based on the two kidney, one clip experimental model (2K1C). After 6 weeks, fragments of the ureters and urinary bladder were sampled from rats with permanent hypertension. Immunohistochemical analyses revealed a salient effect of renovascular hypertension on the neuroendocrine system of rat ureters and urinary bladder. Differences in the number of neuroendocrine cells and in the density of CART-positive structures were identified between the hypertensive and normotensive (control) rats. Hypertension greatly increased the number of NE cells and the density of CART-immunoreactive (IR) structures in the analysed urinary system organs.

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ORTHODONTIC STRESS BCL-2 MODULATION AND HUMAN ODONTOBLAST SURVIVAL

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The first two authors contributed equally to this paper

This study assessed the effect of orthodontic traction on Bcl-2 expression and apoptosis in human dental pulp. It also explored, in absence of noxious stimuli the regeneration of odontoblasts during the entire life of the tooth. Twenty young patients, with Class II malocclusion and severe to moderate crowding, were referred for orthodontic assessment. Whole pulps were removed. Half the pulps were fixed, paraffin-embedded and processed for histology and immunohistochemistry using anti Bcl-2, Caspase 9 cleaved and Caspase 9 not cleaved antibodies. The rest of the samples, both orthodontically treated and not treated dental pulps, were immediately frozen at -80°C after the extraction and quantitative PCR was performed. Histology showed alterations in pulp microanatomy after 8 months of treatment. Immunohistochemistry depicted a decreasing expression of Bcl-2 in dental pulp over time in the non-treated while a very weak to absent Bcl-2 expression was detected in the orthodontically treated tissues. Active and non-active forms of Caspases, were expressed in both groups of dental pulp, however staining for the non active form was stronger than the corresponding cleaved form in all samples. The increased expression was detected mainly at nuclear level. Real time qPCR results correlated with those of immunohistochemistry and exhibited a decreasing expression of Bcl-2 in the treated samples. Orthodontic traction may inhibit the expression of Bcl-2, favoring the onset of apoptosis and leading us to conclude that the physical stress in the absence of noxious stimuli might make odontoblasts regeneration less likely.

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GLUCOCORTICOIDS UPREGULATE DECREASED IL-7 RECEPTOR EXPRESSION IN ASTHMATIC PATIENTS AND SIMIAN IMMUNODEFICIENCY VIRUS-INFECTED NON-HUMAN PRIMATES

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Signaling through interleukin-7 receptor (IL-7R) is essential for regulation of T-cell homeostasis and survival. Previously, we and others have found diminished IL-7R levels in simian immunodeficiency virus (SIV) - infected non-human primates and human immunodeficiency virus (HIV) - infected patients. To date, it remains unknown whether changes in IL-7R expression could also be linked to non-infectious inflammatory diseases such as asthma or anti-inflammatory drug use. Here, we investigated through flow cytometry the levels of IL-7R expression on CD4+ and CD4- T-cells in asthmatic patients in relation to disease severity, immune status and glucocorticoid (GC) use. In addition, we sought to evaluate the effects of *in vivo* and *in vitro* GC treatment on IL-7R expression in both asthmatic patients and SIV-infected non-human primates. We demonstrated that expression of IL-7R on peripheral blood CD4+ T-cells was significantly decreased in clinically stable GC-naïve mild and moderate asthmatic patients. Accordingly, the development of asthmatic reaction following bronchial allergen challenge performed in sensitized subjects was associated with a significant drop in levels of IL-7R on circulating CD4+ T-cells. In contrast, CD4+ T-cells from both, mild and moderate, but not severe asthmatics, treated with inhaled GC displayed levels of IL-7R similar to that seen in healthy controls. We did not find significant differences with serum or sputum interleukin-7 levels among healthy controls and GC-naïve and GC-treated asthmatic patients. Furthermore, both *in vitro* GC treatment and short-term oral GC administration to asthmatic patients resulted in a significant enhancement of IL-7R. Similarly, we demonstrated that GC-stimulated T-cells from SIV-infected non-human primates up-regulated IL-7R

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DISTINCTIVE GENE EXPRESSION PROFILES IN BALB/3T3 CELLS EXPOSED TO LOW DOSE COBALT NANOPARTICLES, MICROPARTICLES AND IONS: POTENTIAL NANOTOXICOLOGICAL RELEVANCE

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Size-dependent characteristics of novel engineered nanomaterials might result in unforeseen biological responses and toxicity. To address this issue, we used cDNA microarray analysis (13443 genes) coupled with bioinformatics and functional gene annotation studies to investigate the transcriptional profiles of Balb/3T3 cells exposed to a low dose (1 μ M) of cobalt nanoparticles (CoNP), microparticles (CoMP) and ions (Co²⁺). CoNP, CoMP and Co²⁺ affected 124, 91 and 80 genes, respectively. Hierarchical clustering revealed two main gene clusters, one up-regulated, mainly after Co²⁺, the other down-regulated, mainly after CoNP and CoMP. The significant Gene Ontology (GO) terms included oxygen binding and transport and hemoglobin binding for Co²⁺, while the GOs of CoMP and CoNP were related to nucleus and intracellular components. Pathway analysis highlighted: *i*) mitochondrial dysfunction for Co²⁺, *ii*) signaling, activation of innate immunity, and apoptosis for CoNP, and *iii*) cell metabolism, G1/S cell cycle checkpoint regulation and signaling for CoMP. Unlike ions, particles affected toxicologically-relevant pathways implicated in carcinogenesis and inflammation.

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MACITENTAN SLOWS DOWN THE DERMAL FIBROTIC PROCESS IN SYSTEMIC SCLEROSIS: *IN VITRO* FINDINGS

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Systemic sclerosis (or scleroderma) is an autoimmune disease characterized by skin and internal organ fibrosis, caused by microvascular dysfunction. The microvascular damage seems to be a consequence of an endothelial autoimmune response, followed by activation of the inflammatory cascade and massive deposition of collagen. Endothelin-1 (ET-1) contributes to the inflammatory and fibrotic processes by increasing the concentration of pro-inflammatory and pro-fibrotic cytokines, and it is considered one of the most relevant mediators of vascular damage in scleroderma. It is indeed found in very high concentration in serum of sclerodermic patients. Moreover, in these pathological conditions there is an increased expression of ET-1 receptors (ET_A and ET_B), which mediate the detrimental action of ET-1, and often a change of ET_A/ET_B ratio. The aim of the present study is to evaluate the *in vitro* effect of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist, and its major metabolite (ACT-132577) on alpha smooth muscle actin (α SMA) expression, evaluated on dermal fibroblasts from healthy subjects and on dermal fibroblasts from lesional and non-lesional skin from sclerodermic patients. The combination of macitentan and its major metabolite reduced the levels of α SMA after 48 h in sclerodermic fibroblasts from lesional skin. No relevant changes in α SMA levels were found in fibroblasts from non-lesional skin, whose behavior is similar to that of dermal fibroblasts from healthy patients.

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T-CELL SUBPOPULATIONS EXPRESS A DIFFERENT PATTERN OF DOPAMINERGIC MARKERS IN INTRA- AND EXTRA-THYMIC COMPARTMENTS

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An involvement of dopamine in regulation of the immune function has been assessed and dopaminergic system has been found widely represented in thymus. Nevertheless detail on the characterization of dopaminergic system in assisting thymocytes development and lymphocytes mature physiology are still lacking. The present study was designed to characterize dopamine plasma membrane transporter (DAT), vesicular dopamine transporters (VMAT)-1 and -2, and dopamine D1-like and D2-like receptors in rat thymocytes, splenocytes and peripheral blood mononuclear cells. Western blot and RT-PCR analyses, performed on these cells, showed an expression of dopamine transporters and receptors during thymocyte development (when of CD4 and CD8 markers are differently expressed). Furthermore FACS analysis, indicates that DAT and dopamine D1-like receptors are expressed at high levels in thymocytes, splenocytes, and peripheral lymphocytes. The percentage of CD4⁺ CD8⁺ (double-positive) thymocytes expressing dopaminergic markers was significantly higher compared to the percentage of double-negative ones. The percentage of CD8⁺ single positive cells expressing dopaminergic markers was significantly higher than that of CD4⁺ cells. The results suggest that the dopaminergic system plays a role in the thymus microenvironment during T-cell development. The more pronounced expression of dopaminergic markers in CD8⁺ subsets suggests that dopamine plays a role in development of cytotoxic T-cells. Our findings indicate dopaminergic system to have a role during the maturation and selection of lymphocytes, and support its involvement in the active phases of immune response.

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THE EFFECT OF PHOTON ACTIVATION THERAPY ON CISPLATIN PRE-TREATED HUMAN TUMOUR CELL LINES: COMPARISON WITH CONVENTIONAL X-RAY IRRADIATION

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Cisplatin is an antineoplastic drug widely used for the treatment of several solid tumours. However, the side effects related to cisplatin-based anticancer therapy often outweigh the benefits. Therefore, the identification of new anticancer strategies able to offer a better toxicity profile while maintaining the same level of efficacy as platinum-based treatments would be highly desirable. We assessed the efficacy of synchrotron radiation in triggering the Auger effect in human A549 non-small cell lung cancer and IGROV-1 ovarian cancer cells pre-treated with cisplatin. Cisplatin was chosen as the carrier of platinum atoms in the cells because of its alkylating-like activity and the irradiation was done with monochromatic beams above and below the platinum K-shell edge (78.39 keV). On cisplatin-treated cells, at concentrations allowing 80% of cell survival with respect to controls, no differences were observed in cell viability when they were irradiated either above or below the K-shell edge of platinum, suggesting that cisplatin toxicity can mask the enhancement of cell death induced by the irradiation. At lower cisplatin concentrations allowing 95-90% of cell survival, an enhancement in cellular death with respect to conventional irradiation conditions was clearly observed in all cancer types when cells were irradiated with beams either above or below the platinum K-shell edge. Our results lend additional support to the suggestion that the Photon Activation Therapy in combination with cisplatin treatment should be further explored in relevant *in vivo* models of glioma and non-glioma cancer models

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RELATIONSHIP BETWEEN DIFFUSION-WEIGHTED IMAGING AND BCL-2 EXPRESSION IN RABBIT MODELS OF HEPATIC VX2 TUMORS AFTER RADIOTHERAPY

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The paper aims to study diffusion-weighted imaging (DWI) and Bcl-2 gene expression in hepatic VX2 tumors after three-dimensional conformal radiotherapy (3D-CRT), we successfully developed 40 rabbit models with hepatic VX2 tumors. 3D-CRT was performed on 28 rabbit hepatic VX2 tumors, which were then randomly and evenly divided into four groups. The remaining 12 controls did not receive radiotherapy. Conventional and DWI was performed at 1, 5, 10, and 15 days following radiation therapy. We measured apparent diffusion coefficients (ADCs) in both a region of interest (ROI) of the VX2 tumor tissue and normal liver tissue and then calculated the ratio between them. RT-PCR was performed to detect the expression of the anti-apoptotic gene Bcl-2. On days 5 and 10, the ADC ratios of the radiotherapy groups were 1.322 ± 0.270 and 0.964 ± 0.341 , respectively. On days 5, 10, and 15, Bcl-2 gene expression in the radiotherapy group was 0.563 ± 0.284 , 0.421 ± 0.242 , and 0.314 ± 0.152 , respectively. For all three days, the gene expression values from the radiotherapy group were significantly lower than that in the control group ($P < 0.01$). Statistical analysis revealed that ADC ratio and Bcl-2 gene expression were significantly negatively correlated ($r = -0.493$, $P < 0.01$). Our results demonstrated that DWI sequence can reflect molecular changes at different time points for hepatic VX2 tumors following radiotherapy.

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INFLUENCE OF AGE AND PHYSICAL EXERCISE ON SIRTUIN ACTIVITY IN HUMANS

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The first two authors contributed equally to this paper.

Sirtuins are NAD⁺-dependent lysine deacetylases. Sirtuins acquired worldwide attention because of their ability to increase yeast, flies, worms and mice lifespan. Recently, this assumption has been challenged. However, their beneficial role on the quality of ageing is widely accepted. In this work we aimed to study how and if sirtuins expression and activity levels varies in function of age and, in the case of young subjects, of exercise. Fifteen blood donors of different ages and fifteen athletes of the Italian rowing male team were enrolled and peripheral blood mononuclear cells (PBMCs) isolated from blood samples. Our results show that sirtuins deacetylases activity measured in PBMCs increases from 18 to 40 years of age and then decreases during the following 20 years. Moreover, physical exercise in professional athletes can upregulate sirtuin activity. Thus, for the first time in humans, we demonstrate that sirtuin activity is a function of age and can be altered through physical exercise.

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RESVERATROL IN *CHLAMYDIA PNEUMONIAE*-INDUCED FOAM CELL FORMATION AND INTERLEUKIN-17A SYNTHESIS

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The involvement of *Chlamydia pneumoniae* in the pathogenesis of atherosclerosis has been suggested by numerous seroepidemiological, *in vivo* and *in vitro* studies. In particular, it has been shown that *C. pneumoniae* is able to promote the accumulation of low-density lipoproteins into macrophages, thus facilitating foam cell formation. The aim of our study was to investigate the effects of resveratrol on macrophage-derived foam cell formation induced by *C. pneumoniae*, examining its underlying biochemical mechanisms. Our results showed a relevant decrease in the number of foam cells, in the production of thiobarbituric acid reactive substances, superoxide anion and IL-17A while treating *C. pneumoniae* infected macrophages with resveratrol. Furthermore, the inhibition of Peroxisome Proliferator-Activated Receptors gamma by a specific antagonist (GW 9662), in presence of resveratrol and *C. pneumoniae*, enhanced intracellular lipid and cholesterol accumulation and the subsequent foam cell formation. In conclusion, the main result of our study is the evidence of an antiatherogenic effect of resveratrol on macrophage-derived foam cell formation and IL-17A production induced by *C. pneumoniae*.

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CONTRIBUTION OF ADENOSINE-PRODUCING ECTOENZYMES TO THE MECHANISMS UNDERLYING THE MITIGATION OF MATERNAL-FETAL CONFLICTS

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The interactions taking place between mother and embryo have been the focus of detailed studies in recent years, where pregnancy is considered as an *in vivo* transplant. The immune systems of the mother and the embryo together establish a condition of tolerance, which lasts throughout the pregnancy. Alongside immunogenetic components, a contribution is provided by the ectoenzyme network, a chain of surface molecules mainly operating in closed environments and potentially providing inhibitory or activator signals. One of the soluble products of the ectoenzyme network with immunosuppressive potential is adenosine, a purine nucleoside that plays multiple roles in almost all tissues and organs. The hypothesis behind the work was studied in patients with recurrent pregnancy loss (RPL), an event which remains unexplained in over 50% of cases. To this aim, we analyzed the expression of CD39 (ectonucleoside triphosphate diphosphohydrolase 1, ENTPD1) and CD73 (ecto-5'-nucleotidase, NT5E), the main pathway for adenosine generation, in samples obtained from women with RPL. The study included the evaluation of the expression of TNF- α (a pro-inflammatory cytokine) and of an alternative pathway of adenosine generation run by CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) and PC-1 (ectonucleotide pyrophosphatase/phosphodiesterase 1, ENPP1). The results of this study highlight the existence of a network of surface enzymes expressed at the maternal/fetal interface and addressed to the production of adenosine. Perturbation of this network may induce a rescue pathway driven by CD38 and ENPP1. Ectoenzyme and inflammation may be considered now key elements in orchestrating the events leading to the interruption of pregnancy in the RPL sample analyzed and at the same potentially becoming therapeutic targets.

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ADHESION AND GROWTH OF OSTEOBLAST-LIKE CELLS ON LASER-ENGINEERED POROUS TITANIUM SURFACE: EXPRESSION AND LOCALIZATION OF N-CADHERIN AND β -CATENIN

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Response of different types of cells on biomaterials is crucial for the applications of tissue engineering and regenerative medicine. It is recognized that cell behaviour depends largely on material surface characteristics. The purpose of this study was to define the biologic response of MG63 cells to the innovative patented surface SYNTHEGRA[®]. MG63 morphology and distribution on the three different titanium disk surfaces (sandblasted, smooth, and laser-treated) were evaluated by microscopy analysis after staining with hematoxylin and eosin. Cell adhesion was determined by crystal violet assay at 48 h while proliferation and cytotoxicity were performed by MTT assay at 24, 48, 72 and 240 h. The expression and localization of N-cadherin and β -catenin were studied by immunofluorescence and confocal microscopy. At 48 h the adhesion was similar in all titanium surfaces, no difference in cell viability were observed in all titanium disks when compared with controls, while the cell growth on laser-treated disks was significantly higher at 240 h than at 24 and 72 h. Morphological analysis show that cells are aligned along the grooves and inside the cavities. β -catenin signal appeared more diffuse and localized underneath the cell membrane, while N-cadherin signal was fainter in cells grown on SYNTHEGRA[®] surface. This work put into evidence the performance of newly designed laser-micromachined surface for adhesion, growth and distribution of human osteoblast-like cells. SYNTHEGRA[®] surface inducing modification of N-cadherin and β -catenin expression and localization, are suggestive of cells undergoing differentiation towards osteocytes and could be particularly suited for immediate load implant procedures.

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INTRARTICULAR TREATMENT OF OSTEOARTROPATY KNEE WITH POLYNUCLEOTIDES: A PILOT STUDY WITH MEDIUM-TERM FOLLOW-UP

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Knee osteoarthritis is a major cause of disability in the elderly. Many therapies are nowadays available, ranging from non-pharmacologic to pharmacological approaches like visco-supplementation, oral supplements or topical treatments, but a flawless treatment is still to be found. Visco-supplementation represents a valid treatment option for reducing pain associated with knee osteoarthritis and improving function in the affected joint. Many literature data report on the efficacy and safety profiles of hyaluronic acid in knee osteoarthritis, however the efficacy of intra-articular hyaluronic acid remains controversial, in fact while several clinical trials claimed a disease-modifying effect for hyaluronic acid, subsequent meta-analyses have cast doubts on this fact. The ideal intra-articular treatment for osteoarthritis should not only provide a mechanical protection of the cartilage surface, but also restore chondrocytes' homeostasis by restoring the physiological articular micro-environment and supplying nutrients. In this perspective an innovative medical product made up of polynucleotides (Condrotide) has been developed. The aim of this study is to test the 2-months efficacy in pain relief and improving function of intra-articular injections of Condrotide in patients with knee osteoarthritis or with grade III or IV chondropathy. Ninety-five subjects (33 men, 62 women), aged between 53 and 80, were included between May 2011 to July 2012. All subjects received intra-articular injections of Condrotide and were evaluated with the Knee injury and Osteoarthritis Outcome Score (KOOS), the NRS scale for pain assessment, the measurement of the range of motion (R.O.M.). In all subjects a significant improvement was found in KOOS score after 60 days. The mean global NRS pain decreased in both groups and there was also a R.O.M. improvement. These results show that the intra-articular administration of nucleotides in subjects with both severe knee arthritis and chondropathy can be recommended since is able to reverse in the short and medium term symptoms and function with a significant improvement in quality of life.

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THE EFFECT OF SWIMMING ON ORAL ECOLOGICAL FACTORS

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The aim of this study was to evaluate the oral health status in young swimmers, involving an assessment of salivary cariogenic bacteria, of S-IgA concentration, before and after training sessions. One hundred and eighteen swimmers and 48 sedentary individuals were selected. Before training sessions (T1), a clinical monitoring was performed and the following parameters were recorded: DMFT, Plaque Index (PII), Gingival Index (GI). At T1 and after training sessions (T2), stimulated saliva was collected and subjected to microbiological and immunological analysis. The athletes trained 2 h x 5 days/week and showed a good state of oral health related to a low prevalence of parafunctional behavior, decay presence, lower GI values, compared to controls. The swimmers' total bacterial count and the load of *S. mutans*, *S. sanguis*, *L. fermentum* and *A. gerencseriae* underwent a statistically significant increase at T2. *S. mutans*, *S. mitis* and *L. acidophilus* mean values were significantly higher in swimmers than in controls. Swimmers' S-IgA average value decreased significantly at T2. Therefore, the single physical exertion is a period characterized by the most intensive intraoral growth of cariogenic bacteria and a time of less intensive salivary functions and physiologic response as a decrease in the level of S-IgA.

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LETTER TO THE EDITOR

FLUORESCENCE *IN SITU* HYBRIDIZATION ANALYSIS OF CCND3 GENE AS MARKER OF PROGRESSION IN BLADDER CARCINOMA

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The first and second author contributed equally to this paper.

The aim of this study was to assess patterns of *CCND3* gene amplification in bladder cancer and correlate gene status with recurrence-free and progression-free survival. A sequential cohort series of 102 primary bladder tumor samples in which there was enough tissue material to assess *CCND3* gene status by fluorescent in situ hybridization (FISH) was the study group. *CCND3* gene FISH amplification present in 31.4% of bladder carcinomas, was related to tumor progression ($p=0.021$) and lower time to progression (mean \pm SD; 25.75 \pm 15.25 months) as compared to 33.29 \pm 11.0 months in the *CCND3* not amplified group ($p=0.05$). By immunohistochemistry, Cyclin D3 labeling index was higher in the *CCND3* amplified group (mean \pm SD, 76.69 \pm 27.51) than in not amplified (mean \pm SD, 21.57 \pm 7.02) ($p<0.0001$). The univariate survival analysis showed *CCND3* gene amplification to be associated to a shorter progression-free survival ($p=0.020$) together with WHO histological grade ($p=0.001$) and pT stage category ($p<0.0001$). Cox's regression analysis selected *CCND3* amplification as an independent predictor of progression-free survival ($p=0.030$, RR3.561, 95% CI 1.128-11.236) together with pT category ($p<0.0001$, RR5.834, 95% CI 2.364-14.395). Our FISH analysis suggests that *CCND3* gene amplification is a marker of aggressiveness and might be a predictor of tumor progression in bladder urothelial carcinoma.

LETTER TO THE EDITOR

ANGIOTENSIN II INHIBITS ADH-STIMULATED cAMP: ROLE ON O_2^- AND TRANSPORT-RELATED OXYGEN CONSUMPTION IN THE LOOP OF HENLEG.B. SILVA^{1,2}, L.I. JUNCOS³, S.T. BAIGORRIA³, and N.H. GARCIA^{2,4}

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Dehydration and acute reductions of blood pressure increases ADH and Ang II levels. These hormones increase transport along the distal nephron. In the thick ascending limb (TAL) ADH increases transport via cAMP, while Ang II acts via superoxide (O_2^-). However, the mechanism of interaction of these hormones in this segment remains unclear. The aim of this study was to explore ADH/Ang II interactions on TAL transport. For this, we measured the effects of ADH/Ang II, added sequentially to TAL suspensions from Wistar rats, on oxygen consumption (QO_2) -as a transport index-, cAMP and O_2^- . Basal QO_2 was 112 ± 5 nmol O_2 /min/mg protein. Addition of ADH (1nM) increased QO_2 by 227%. In the presence of ADH, Ang II (1nM) elicited a QO_2 transient response. During an initial 3.1 ± 0.7 minutes after adding Ang II, QO_2 decreased 58% ($p < 0.03$ initial vs. ADH) and then rose by 188% ($p < 0.03$ late vs initial Ang II). We found that Losartan blocked the initial effects of Ang II and the latter blocked ADH and forskolin-stimulated cAMP. The NOS inhibitor L-NAME or the AT2 receptor antagonist PD123319 showed no effect on transported related oxygen consumption. Then, we assessed the late period after adding Ang II. The O_2^- scavenger tempol blocked the late Ang II effects on QO_2 , while Ang II increased O_2^- production during this period. We conclude that 1) Ang II has a transient effect on ADH-stimulated transport; 2) this effect is mediated by AT1 receptors; 3) the initial period is mediated by decreased cAMP and 4) the late period is mediated by O_2^- .

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LETTER TO THE EDITOR

HRCT IN SYSTEMIC SCLEROSIS: CORRELATION BETWEEN RESPIRATORY FUNCTIONAL INDEXES AND EXTENSION OF LUNG FAILURE

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The purpose of the study was to identify the correlation between functional lung parameters to the extent of lung involvement evaluated by High Resolution Computed Tomography (HRCT) in systemic sclerosis (SSc), using a modified score scale. Forty-two patients with established clinical diagnosis of systemic sclerosis were retrospectively selected from the hospital information system and were prospectively included in the study protocol undergoing chest radiography, HRCT and functional lung testing. Lung involvement was assessed by HRCT, lesions were assessed in the individual segments and an additional severity score was introduced by assigning 3 points for bilateral lesions. The total new HRCT score was statistically related to severity of functional lung parameters. Thirty-six out of 42 patients showed an interstitial lung involvement by HRCT: Ground Glass (GG) n=36/42 of which n=27/36 were bilateral; IPM n=30/42, of which 24/30 were bilateral; SL n=33/42 of which 18/33 were bilateral; HC n=6/42 of which 6/6 were bilateral; SC n=6/42 of which 3/6 were bilateral. 18/42 had a total score between 0-10, 6/42 between 11-20, 12/42 between 21-30, 6/42 >31. Fifteen out of 42 had restrictive deficit. The results of functional respiratory testing were: FVC < 80% in 12/42 patients (28.5%), TLC < 80% in 15/42 patients (35.7%), DLCO < 80% in 38/42 patients (90.4%) and DLCO/VA < 80% in 21/42 patients (50%). The total score was statically related with FVC and TLC and with DLCO and DLCO/VA showing a significant negative correlation found between the total HRCT score of extent of lung damage and lung-function parameter (TLC: $r = -0.65$, $P = 0.00000264$; FVC: $r = -0.50$; $P = 0.000575$; DLCO: $r = -0.74$, $P = 2.02E^{-8}$; DLCO/VA: $r = -0.68$, $P = 0.0000005$). All Pairwise Multiple Comparison Procedures showed a significant difference between the two rank sums that enclosed the comparison for DLCO/VA vs SCORE and DLCO vs SCORE. In conclusion, our modified score scale gives interesting additional data to evaluate the extension of interstitial lung involvement in SSc. It is inversely proportional to spirometry and DLCO and DLCO/VA. The bilateralism of the lesions is directly proportional to the lung damage.

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*LETTER TO THE EDITOR***ANAPHYLACTIC REACTION AFTER THE CONCOMITANT INTRAVENOUS ADMINISTRATION OF CORTICOSTEROIDS AND GASTROPROTECTIVE DRUGS: TWO CASE REPORTS**

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Corticosteroids are therapeutic drugs widely used in cases of allergic, inflammatory and autoimmune diseases, but sometimes allergic hypersensitivity reactions have been reported as a rare adverse effect of the corticosteroids themselves. Moreover, glucocorticoids can induce gastric lesions; that's why they are sometimes administered intravenously together with some drugs such as proton pump inhibitors (PPI) or inhibitors of histamine-2 receptors (antiH2) working as gastric protectors. Although it is difficult to establish which drug was responsible in case of hypersensitivity reactions, as hypersensitivity reactions following to the use of PPI or anti-H2 have been already described in literature. Here we describe two cases of immediate-type hypersensitivity triggered from the administration of a corticosteroid plus a gastroprotective agent and the diagnostic check up required in both these patients.

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LETTER TO THE EDITOR

**ANATOMICAL FEATURES OF CEPHALOTHORACOPAGUS VARIATIONS:
CT AND MRI**

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Conjoined twins have fascinated human mankind for a long time. Until recently, their description was limited to the dissection of non-viable cases, the description of external features and of bones by x-ray imaging. The introduction of ultrasonographic techniques gave the first in utero images of conjoined twins, though the spatial resolution did not allow detailed descriptions. Subsequently, CT and MRI techniques allowed more precise definition of organs without any dissection, thus the need of formal interpretation of similar new images. As a matter of fact, few monstrosities have been studied by CT and MRI techniques. To this day very few cases still lack any CT/MRI documentation. Here we present a very rare type of cephalothoracopagus twins (joined at the head and the thorax). They have been accurately examined by CT and MRI imaging to study visceral structures. Pathophysiology and genetic aspects are also reviewed. These data offer precious details for accurate comprehension of imaging studies, and for theoretical studies concerning the information of several anatomical structures.

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LETTER TO THE EDITOR

**MARSUPIALIZATION OF RADICULAR CYST IN A 9-YEAR-OLD CHILD: REPORT OF
A CASE AND REVIEW OF THE LITERATURE**

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The following report describes the treatment of a 9-year-old child affected by a radicular cyst. The case was treated through the extraction of the impacted primary tooth followed by marsupialization. The residual cystic cavity was filled with a removable device in order to speed the healing process, facilitate the eruption of the permanent teeth and avoid orthodontic treatment. This technique is suitable as conservative treatment for patients affected by radicular cyst.

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LETTER TO THE EDITOR

ACUTE ABDOMINAL AORTIC THROMBOSIS CAUSED BY PAROXYSMAL ATRIAL FIBRILLATION

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Acute abdominal aortic thrombosis is a rare and potential fatal event, which occurs in adult subjects. We present the case of a 72-year-old-man, who referred to the emergency Department of our hospital because of persistent severe abdominal and perineal pain. Doppler ultrasounds and computerized tomography angiography revealed the acute thrombosis of the abdominal aorta. Immediate revascularization through aortic thrombo-endoarterectomy resolved the disease.

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