ROLE OF TH17 IN THE PATHOGENESIS OF CUTANEOUS INFLAMMATORY DISEASES

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Th17 cells are a new T-cell subtype characterized by the capability of producing IL-17. They are reported to be involved in a wide range of cutaneous immune-mediated conditions and, particularly in this review, we sought to elucidate the Th17 role in the pathogenesis of some common inflammatory diseases including psoriasis, allergic contact dermatitis and atopic dermatitis.
INTERLEUKIN-9 AND MAST CELLS

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Mast cells are granulated hematopoietic cells derived from stem cells that reside in nearly all tissues and are involved in protection of a host from bacterial infection with a protective and pathogenic activity. Mast cells are important for both innate and adaptive immunity in tissues which are in close contact with the environment. These cells express proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor which are necessary for innate immunity. Mast cells also produce interleukin-9 and enhance mast cell expression of several cytokines including IL-1β, IL-5, IL-6, IL-9 and IL-13. In addition, IL-9 can induce mast cell production of TGF-beta which can have proinflammatory downstream effects. IL-9 can function as either a positive or a negative regulator of immune responses and can have a detrimental role in allergy and autoimmunity. Furthermore, IL-9 contributes to disease by promoting mast cell expansion and production of IL-13 which in turn contributes to airway hyperresponsiveness. Here, in this editorial we review the interrelationship between IL-9 and mast cells.
The aim of this study is to test the activity of a marine bioactive compound containing high-purity caviar-derived DNA, collagen elastin and protein extracts from sturgeon (LD-1227, Caviarlieri, Laboratoires Dom, Switzerland) to exert neuroprotective properties in an experimental setting while also being potential triggers of neurogenesis in a separate *in vitro* study. Supplementation with high-DHA mixture of LD-1227 was applied for 30 days to stress model rats. Both supplementations significantly mitigated the histological brain damage when analyzing hippocampal subregions and corticosterone level. However, LD-1227 was most significantly efficient in preventing SOD, Catalase and ascorbic acid decrease in brain tissue. Both supplementations significantly stimulated neurogenesis *in vitro* and neuron markers in particular but oligodendrocyte markers and glia increased only in LD-1227-enriched medium. Taken together, these data suggest that LD-1227 is able to significantly protect the brain structure redox system to higher degree than DHA. Moreover, from *in vitro* study it appears that marine bioactive compound, through it wide array of small unsaturated fatty acids, phospholipids and neurotransmitter precursors, is likely to influence neuronal and glial lineage to act differently from a DHA-rich mixture.
In the present study, we examined the effect of a marine bioactive compound containing high-purity caviar-derived DNA, collagen elastin and protein extracts from sturgeon (LD-1227, Caviarlieri, Laboratoires Dom, Switzerland) on ILβ-induced activation and production of TNFα and MMP-13 in human osteo-arthritis (OA) chondrocytes and intracellular signaling factors. Human chondrocytes were derived from OA cartilage and stimulated with ILβ. Gene expression of TNFα, MMP-13, MMP-1 and Col10A1 was measured by quantitative RT-PCR. TNFα protein in culture medium was determined using cytokine-specific ELISA. Western immunoblotting was used to analyze the MMP-13 production in the culture medium and the activation of NF-κB. DNA binding activity of NF-κB p65 was determined using a highly sensitive and specific ELISA. MMP-13 activity in the culture medium was assayed by gelatine zymography. LD-1227 significantly decreased ILβ-stimulated gene expression and production of TNFα, MMP-1, MMP-13 and Col10A1 in human chondrocytes. The inhibitory effect of LD-1227 on the ILβ-induced expression of these genes was mediated at least in part via suppression of NF-κB p65. These data show that LD-1227 can inhibit ILβ-induced proliferation and inflammatory reactions via inhibited activation of the transcription factor NF-κB pathway in human chondrocytes derived from OA patients. These novel pharmacological actions of LD-1227 on ILβ-stimulated human OA chondrocytes provide suggestions that this marine biology compound may inhibit cartilage degradation by suppressing ILβ-mediated activation and the catabolic response in human chondrocytes.
There is growing interest in the role of neurotrophins in the pathophysiology of schizophrenia. Neurotrophins are a large family of dimeric polypeptides that promote the growth and the differentiation of developing neurons in the central and peripheral nervous systems as well as the survival of neuronal cells in response to stress. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) concentrations are here reviewed in relation to medication-naive early psychotic patients and in medicated chronic schizophrenic patients. Most data point to decreased plasma and serum NGF and BDNF concentrations in naive drug and in medicated schizophrenic patients compared to healthy controls. Higher BDNF levels were observed in patients with the paranoid subtype of schizophrenia. Low serum BDNF levels were associated with reduction in hippocampal volume (HV) at the onset of schizophrenia. Evidence on the correlation between BDNF levels and positive and negative schizophrenic symptoms were ambiguous. There are contrasting results on a possible correlation between increase in BDNF concentrations and treatment with antipsychotics. Antipsychotic treatment can elevate NGF values, specifically atypical. Growth factors might be good candidates as prognostically and diagnostically useful markers in schizophrenia.
Th17 cells are potent pro-inflammatory effectors crucial for defense against extracellular bacteria. However, in this context and in the context of autoimmune disorders Th17 cells have been demonstrated to be key contributors to destructive pathological mechanism. A number of trials report TGF-β to be involved in Th17 cell development. Nevertheless, to date, the role that TGF-β plays in Th17 cell generation remains unclear. In this paper we highlight the role of TGF-β in Th17 cell development in the mouse. The effects of likewise T cell specific over-expression of TGF-β or inhibition of TGF-β signal transduction in these cells on Th17 cell development were investigated by means of transgenic mouse models. The T cell specific insensitivity to TGF-β does not prevent Th17 cell development \textit{ex vivo} or \textit{in vitro} in the murine system. In contrast, stimulation of T cells over-expressing TGF-β actually results in decreased Th17 cell numbers in comparison to the wild type. Thus, our data indicate that TGF-β signaling in T cells is dispensable or even inhibitory for generation of Th17 cells in the mouse. Moreover, we could show TGF-β to inhibit a LPS driven Th1 cell development suggesting the cytokine to act as an indirect effector in Th17 cell differentiation.

\textbf{TGF-β SIGNALING IN T CELLS IS NOT ESSENTIAL FOR TH17 CELL DEVELOPMENT IN THE MOUSE}

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The sympathoneural system has a profound influence on the heart function. Sympathetic neurons are the major contributors to the huge rise of circulating noradrenaline (NA) level in response to stressful stimuli. Treadmill training in rats is forced exercise which has the propensity to induce both psychological and physical stress. The aim of this study is to examine how chronic forced running (CFR) affects the expression of catecholamine biosynthetic enzymes (tyrosine hydroxylase (TH), dopamine-β-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT)) and cAMP response element-binding (CREB) in stellate ganglia, as well as the concentrations of catecholamines, adrenocorticotropic hormone (ACTH) and corticosterone (CORT) in the plasma of rats. Also, we investigated how the additional acute immobilization stress changes the mentioned parameters. The rat training program consisted of 12 weeks running on a treadmill (20 m/min, 20 min/day). We found that CFR increases TH and DBH mRNA and protein levels in stellate ganglia, which is followed by increased NA concentration in the plasma. CFR reduces the level of PNMT mRNA, while the level of PNMT protein remains unchanged in stellate ganglia. The increased expression of TH and DBH genes positively correlates with the expression of CREB in stellate ganglia and with plasma ACTH level, while reduced level of PNMT mRNA in stellate ganglia correlates with reduced plasma CORT level. The additional acute immobilization stress increased gene expression of catecholamine biosynthetic enzymes in stellate ganglia, as well as catecholamines, ACTH and CORT levels in the plasma. The results presented here suggest that the continuous increase of the noradrenaline biosynthetic enzyme expression in stellate ganglia due to CFR may play a role in growing risk of cardiovascular diseases.
Obese subjects often present a low-grade chronic inflammation in the white adipose tissue, which seems to play an important role in the initiation and development of obesity-related diseases. It has been reported that this inflammatory process may be due to a hypoxic state occurring within this tissue. Oxygen is used in current medicine as a treatment for several conditions. The aim of this study is to analyze the effects of 95% O\textsubscript{2} on specific metabolic variables and on the expression of some genes on murine adipocytes. 3T3-L1 adipocytes were exposed during 48 h to different treatments: 95% O\textsubscript{2} hyperoxia (HPx group), CoCl\textsubscript{2} (CoCl\textsubscript{2} group), hyperoxia with CoCl\textsubscript{2} (HPx+CoCl\textsubscript{2} group) and 1% O\textsubscript{2} hypoxia (Hx group). Cell viability, intracellular ROS content, glucose utilization, lactate and glycerol concentrations were measured. Also, mRNA expression of HIF-1\alpha, GLUT-1, ANGPTL4, PPAR-\gamma, adiponectin, IL-6 and MCP-1 genes was analyzed. Importantly, 95% O\textsubscript{2} decreased cell viability and increased intracellular ROS production. Also, glycerol and lactate release were significantly increased and decreased, respectively, in HPx treated cells. This treatment also provoked a down-regulation of GLUT-1, ANGPTL4, PPAR-\gamma and adiponectin, IL-6 and MCP-1 genes. Importantly, 95% O\textsubscript{2} increased ROS levels and lipolytic activity, while it reduced lactate production. In addition to the effects on inflammation, the changes in GLUT-1, ANGPTL4 and PPAR-\gamma genes lead to suppose that hyperoxia may be beneficial for the hypertrophied adipose tissues of obese subjects and for improving insulin sensitivity.
Animal models of burn play a crucial role in studying the mechanisms of burn wound progression and the factors that regulate various stages of healing. In this study, using a rat model, we assessed the effect of Botox in the healing process through parameters like transepidermal water loss (TEWL), histological alterations, transforming growth factor β (TGF-β) and tumor necrosis factor alpha (TNF-α). Fifty Sprague-Dawley rats were inflicted with 5 cm² second degree burn and divided into 2 groups; one group was injected intralesionally with Botox and the other with saline. Daily observation and transepidermal water loss measurement were performed. Biopsies were taken on days 0, 3, 8, 14, and 28 for histology and polymerase chain reaction, testing TGF-β and TNF-α. The results showed no significant difference in TEWL except for slightly better preservation of moisture with Botox. Histology revealed relatively better and faster regeneration with Botox, delayed lower grade inflammation, and increase in fibroblasts. TNF-α had an acute increase of 21-fold then tapered down while TGF-β levels increased on day 3 after TNF-α, peaked on day 8 and then started to decrease until complete healing. Botox improved the healing process and the cosmetic appearance of burn scar.
ASSOCIATION ANALYSIS OF DOPAMINERGIC GENE VARIANTS (COMT, DRD4 AND DAT1) WITH ALZHEIMER’S DISEASE

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Defects in dopaminergic transmission play important roles in the disturbance of synaptic plasticity and even in advanced cognitive behavior. However, the relationship between genes involved in the regulation of dopamine levels and predisposition for Alzheimer’s disease (AD) remains unclear. The potential association of dopamine-modulating gene polymorphisms with AD was evaluated. We performed a case-control study with 120 patients and 86 healthy controls. Two catechol-O-methyltransferase (COMT) single-nucleotide polymorphisms (SNPs) (rs2020917 and rs4646312), two dopamine D4 receptor (DRD4) SNPs (rs3758653 and rs916455), and four dopamine transporter (DAT1) SNPs (rs2937639, rs6347, rs12516948 and rs11133762) were investigated. The T allele at the DRD4 SNP (rs3758653) was found to be significantly associated with AD. Our results also showed that haplotype frequencies, observed from the analyzed SNPs, were distributed significantly differently in AD patients vs control subjects. Moreover, a strong association was observed between the A allele at rs6347 of DAT1 and moderate stage of dementia. These observations suggest that genetic variations in the dopamine-modulating genes, COMT, DRD4 and DAT1, may contribute to AD pathogenesis in the Taiwanese population.
OBESE VISCERAL ADIPOSE TISSUE GRAFTED IN LEAN MICE CAN ALTER GLUCOSE HOMEOSTASIS AND ENERGY EFFICIENCY

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Fat transplantation experiments have previously shown regulatory properties of lean adipose tissue on glucose homeostasis in the whole animal. In the current study, we addressed whether obese visceral white adipose tissue grafted in lean mice could alter glucose homeostasis. Obese visceral fat (VF) tissue was effective in increasing body weight gain and energy efficiency but not energy intake, when transplanted into the epididymal VF depot in lean recipient mice. These changes were accompanied by impaired glucose and insulin tolerance tests, showing altered glucose homeostasis. None of these effects were observed when transplants were grafted subcutaneously. These effects show that both physiologic state of donor VF (obese vs lean) and graft location (epididymal vs subcutaneous) in the recipient animal are critical to express deleterious effects of VF on glucose homeostasis in the whole organism.
Cocaine- and amphetamine-regulated transcript (CART) was identified in the central and peripheral nervous system, including the gastrointestinal tract of rodents and pig. CART was also expressed in neuroendocrine cells of the rats stomach antral mucosa. The knowledge of the presence and functional role of CART peptide in the human alimentary tract is very limited due to difficulties in obtaining human samples (especially from healthy individuals). The presence of CART peptide in the gastrointestinal tract of the human was investigated immunohistochemically. CART-immunoreactive (IR) neural structures were observed in all studied fragments of alimentary tract. CART-like immunoreactive nerve fibers were numerous within the muscle in layers of muscularis externa and in the myenteric plexus of all gastrointestinal segments (from esophagus to colon), while they were moderate or few in density in other layers of gastrointestinal tract. CART-like immunoreactive nerve fibers were numerous within the muscle in layers of muscularis externa and in the myenteric plexus of all gastrointestinal segments (from esophagus to colon), while they were moderate or few in density in other layers of gastrointestinal tract. The present study reports for the first time a detailed description of the CART distribution pattern within the human alimentary tract. Our findings may hopefully provide some contribution towards a more complete and comprehensive understanding of the function and role of the CART peptide in the alimentary system.
THE EFFECT OF PGE ADMINISTRATION ON THE ACTIVITY OF OXIDATIVE SYSTEM IN ERYTHROCYTES AND PLATELETS DURING ISCHEMIA REPERFUSION INJURY AND ON POSTOPERATIVE RENAL FUNCTION IN PATIENTS UNDERGOING OPEN ABDOMINAL AORTIC ANEURYSM RECONSTRUCTION

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Postoperative decline of renal function remains a common and unpredictable complication after abdominal aortic aneurysm (AAA) reconstruction. The oxidative stress that occurs during perioperative ischemia/reperfusion injury (I/R) may contribute to the development of this complication. In this study, the influence of intraoperative prostaglandin E (alprostadil) administration on erythrocyte and platelet antioxidants as well as postoperative kidney function modulation were verified. AAA patients were randomly divided into control and study/alprostadil groups. Blood samples were collected directly before aortic clamping and 5 min after aortic declamping. Superoxide dismutase, catalase, glutathione, glutathione peroxidase (GPx), and glutathione transferase (GST) were measured using spectrophotometry. During I/R, the activity of catalase (57.14±30.65 vs 128.35±91.94 U/mg protein; P < 0.009), GPx (0.21±0.18 vs 0.35±0.21 mU/g protein; P = 0.028), and GST (217.49±101.39 vs 310.66±88.86 mU/g protein; P = 0.0006) significantly increased in the control group. GST activity before the aortic clamping was significantly lower in the study/alprostadil group (2.84±2.28 vs 3.48±2.30 U/g Hb; P = 0.05). The activity of the selected antioxidants proved to be of a diagnostic value for predicting postoperative decline in renal function. In conclusion, during I/R after AAA reconstruction, activation of various erythrocyte and platelet antioxidants occurs. Perioperative administration of alprostadil is associated with disruption of this activation.
PERCEPTION OF OCCUPATIONAL RISK BY RURAL WORKERS IN AN AREA OF CENTRAL ITALY

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The aim of this study is to analyze the subjective perception of risks for rural workers in Abruzzo, an area of central Italy. A group of 273 workers were asked to fill in a questionnaire which included, apart from general information, questions relative to six different types of risks normally found in the field of agriculture. The types of risks considered were: falling from a height, manually moving loads, overturning/accident whilst driving an agricultural tractor, noise and vibration, use of pesticides, the risk of being cut/injured. The workers were requested to assess, on a scale of 1 to 3, both the probability of an accident taking place and the consequent damage which could result from each of the risks considered. The assessment of the risks provided by the workers was related to the objective assessment of the risks carried out by the study group, also on the basis of objective data provided by INAIL (Italian insurance company) indexes, to highlight the eventual under/over estimations of risk. Furthermore, the possible correlation was evaluated between having received specific training regarding work safety and the workers’ perception of the risk. The results showed that approximately 11% of the workers do not consider their job as being dangerous; the risk perceived by the workers is higher for accidents that cause an immediate injury compared to those which cause professional illnesses, except the risk deriving from noise/vibrations. A direct correlation was found between considering one’s job as being dangerous and having attended courses on accident prevention.
NANOTECHNOLOGY AND VASCULAR NEUROSURGERY: AN IN VIVO EXPERIMENTAL STUDY ON MICROVESSELS REPAIR USING LASER PHOTOACTIVATION OF A NANOSTRUCTURED HYALURONAN SOLDER

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Sealing tissues by laser in neurosurgical procedures may overcome problems related to the use of conventional suturing methods which can be associated with various degrees of vascular wall damage. Despite the significant experimental and clinical achievements of the past, a standardized clinical application of laser-welding technology has not yet been implemented. The main problem is related to the use of common organic chromophores. A substantial breakthrough in the laser welding of biological tissues may come from the advent of nanotechnologies. In this paper we describe an experimental study, to confirm the feasibility of an innovative laser-assisted vascular repair (LAVR) technique based on diode laser irradiation and subsequent photoactivation of a hyaluronan solder embedded with near infrared (NIR) absorbing gold nanorods (GNRs), and to analyze the induced closing effect in a follow-up study performed in animal model. Twenty New Zealand rabbits underwent closure of a 3-mm longitudinal incision performed on the common carotid artery (CCA) by means of 810 nm diode laser irradiation, in conjunction with the topical application of an optimized GNR composite. Effective closure of the arterial wound was accomplished by using very low laser intensity (30 W/cm²). The average CCA occlusion time was as low as 50 sec. Animals underwent different follow-up periods (2, 8, 30 days). After follow-up, they were re-anesthetized, the patency of the treated vessels was tested (Doppler analysis) and then the irradiated vessels were excised and subjected to histological evaluations. Morphological examinations of the samples documented the integrity of the vascular wall. No host reaction to nanoparticles occurred. Collagen and elastic fibers returned to their normal architecture 30 days after treatment. A Scanning Electron Microscopy (SEM) examination and immuno-histochemical analysis demonstrated a full re-endothelization of the vessel walls. We thus confirmed that a laser-based approach is technically easy to perform, and provides several advantages, such as a simplification of the surgical procedure, a reduction in the operative time, and the suppression of bleeding. The use of GNRs improves the selectivity of welding and minimizes the surgical trauma to vessels, resulting in an optimal healing process.
Mechanisms associated with reactivation of hepatitis B virus (HBV) in patients with occult HBV infection (OBI) remain unclear. In some cases immunosuppression is an enhancer of viral replication. However, not all patients with OBI who undergo immunosuppression experience reactivation. This study explores the role of viral heterogeneity as a determinant of occult HBV reactivation. HBV genotype, mutation patterns and quasispecies were assessed by sequencing the PreS/S region of 16 patients with OBI undergoing chemotherapy, 3 of whom experienced a OBI reactivation. The latter were also assessed at the time of reactivation. Phylogenetic analysis identified low nucleotide and amino acid diversity rates. There were no differences in the viral quasispecies, or common mutation patterns, detected between patients who underwent reactivation of OBI, and those who did not. Furthermore, upon reactivation, the quasispecies evolved towards a loss of most of the variants present during the initial OBI stage, probably representing the fittest version of the virus. The genetic variability of HBV alone did not account for the transition from occult to overt infection, which appears to be governed principally by the host’s immune response.
The study was performed to evaluate the effectiveness of lumbar paravertebral injections of a gas mixture of Oxygen and Ozone in patients with lumbar radiculopathies caused by L4-L5 or L5-S1 disk herniations compared to a pharmacological therapy based on non-steroidal anti-inflammatory drugs. Lumbar radiculopathy caused by disc herniation is widely spread. Many therapeutic options are available before steering patients to the surgery. Low back pain and sciatica represent some of the most frequent causes of antinflammatory-analgesic drugs overuse. Recent findings have shown that medical Ozone can be used in the treatment of radicular syndrome caused by herniated intervertebral discs. Although widely spread, there are insufficient published data supporting the effectiveness of this approach in clinical practice. We studied 38 affected patients with acute L5 or S1 radiculopathy. The patients were randomly divided in two groups: A) 20 patients treated with lumbar paravertebral injections of Oxygen and Ozone; B) 18 patients treated pharmacologically with antinflammatory-analgesic drugs. All patients underwent a clinical and neurological examination at baseline (T1) and after 1 (T2), 2 (T3), 4 weeks (T4) and after 3 (T5) and 6 months (T6). An MRI and EMG examination were performed at baseline and after 6 months. The intensity of pain and the outcome of treatments were evaluated in all patients with the Visual Analogue Scale and with the Oswestry Disability Index. We found a reduction of pain and discomfort soon after one week with oxygen-ozone injections compared with pharmacological treatment, but this difference of response became statistically significant after two weeks (50% vs 16.6%) and is confirmed after 3 and 6 months, when 80% of patients treated with injections turned out pain free compared with half of the patients treated pharmacologically. No statistical difference were found in MRI and EMG examinations. No adverse effects were found in any patient of group A. We hypothesize that oxygen-ozone injections in paravertebral regions can induce a direct reduction of root inflammation with a corresponding reduction of pain. The paravertebral injections of oxygen-ozone represent a rapidly effective therapy, easily practicable and secure, in patients with lumbar radiculopathies secondary to disc herniation.
Even though muscle injuries are very common, few scientific data on their effective treatment exist. Growth Factors (GFs) may have a role in accelerating muscle repair processes and a currently available strategy for their delivery into the lesion site is the use of autologous platelet-rich plasma (PRP). The present study is focused on the use of Platelet Rich Fibrin Matrix (PRFM), as a source of GFs. Bilateral muscular lesions were created on the longissimus dorsi muscle of Wistar rats. One side of the lesion was filled with a PRFM while the contralateral was left untreated (controls). Animals were sacrificed at 5, 10, 40 and 60 days from surgery. Histological, immunohistochemical and histomorphometric analyses were performed to evaluate muscle regeneration, neovascularization, fibrosis and inflammation. The presence of metaplasia zones, calcifications and heterotopic ossification were also assessed. PRFM treated muscles exhibited an improved muscular regeneration, an increase in neovascularization, and a slight reduction of fibrosis compared with controls. No differences were detected for inflammation. Metaplasia, ossification and heterotopic calcification were not detected. This preliminary morphological experimental study shows that PRFM use can improve muscle regeneration and long-term vascularization. Since autologous blood products are safe, PRFM may be a useful and handy product in clinical treatment of muscle injuries.
Early and predictive acute kidney injury (AKI) markers may be decisive for the clinical outcome of heart surgery. Hence, this study set out to evaluate the biological variability of urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels in adult cardiac surgery patients, to test their feasibility as a biomarker of early AKI in a routine laboratory setting. uNGAL levels were measured with an automated immunoassay in urine samples from patients undergoing cardiac surgery using cardiopulmonary bypass, at the time of admission (T0) and 4 hours (T1) and 24 hours (T2) after surgery. Patients without post-operative AKI did not show significant differences in urine NGAL levels after surgery. In contrast, patients developing AKI displayed a significant increase \((P=0.011)\) in uNGAL levels compared to T0. This increase was detectable at an earlier time point (T1, 4 hours) with respect to serum creatinine (T2, 24 hours). Confirming its utility as a biomarker, at T1 the uNGAL levels were significantly higher in AKI patients than in non-AKI patients \((P=0.021)\). A receiver operating characteristic curve analysis of the uNGAL assay gave a sensitivity of 55.3 (95% confidence interval [CI], 26.59-78.73), a specificity of 72.9 (95% CI, 55.88-86.21), and a cut-off value for AKI prediction of 55.2. These results support the notion that urinary NGAL is an earlier marker of AKI than serum creatinine. However, the cut-off value of the assay was too low to consider it as a positive or negative diagnostic marker in AKI patients with moderate degree of severity. Likewise, its sensitivity and specificity were not high enough for it to be considered better than the others currently in use.
Multidrug resistance (MDR) to anticancer chemotherapy is often mediated by the overexpression of the plasma membrane drug transporter P-glycoprotein (Pgp) encoded by multidrug resistance gene (MDR1). Various chemosensitizing agents are able to inhibit Pgp activity but their clinical application is limited by their toxicity. Furthermore, hepatotoxicity related to chemotherapy causes delays of treatment in cancer patients and often requires supplementation of anti-tumour therapy with hepatoprotective agents. In this in vitro study, we investigated the effectiveness of an endogenous hepatoprotective agent, S-adenosylmethionine (SAMe), and a natural hepatoprotective compound, Cynarin (Cyn), to inhibit Pgp activity in order to evaluate their potential use as chemosensitizing agents. Human doxorubicin (doxo) resistant uterine sarcoma cells (MES-SA/Dx5) expressing high levels of Pgp were treated with two hepatoprotectors at various concentrations (1, 5 and 10 µM) that are clinically achievable, in the presence or absence of three different concentrations of doxo (2, 4 and 8 µM). In order to evaluate the effects of both hepatoprotectors, we measured the intracellular accumulation and cytotoxicity of doxo, the cellular GSH level, ROS production and catalase (CAT) activity. We found that treatment with 2, 4 and 8 µM doxo in the presence of SAMe or Cyn significantly increased the doxo accumulation and cytotoxicity on MES-SA/Dx5 cells, when compared to control cells receiving doxo alone. Moreover, treatment with SAMe or Cyn significantly increased GSH content (> 80% and >60%, respectively) and CAT activity (>60% and 150%, respectively) in resistant cancer cells, while ROS production was below the values of corresponding untreated control cells. Our in vitro findings provide a rationale for the potential clinical use of these hepatoprotectors both as chemosensitizing agents, to reverse Pgp-mediated MDR, and as antioxidants to protect normal cells from chemotherapy-induced cytotoxicity.
The aim of this study is to assess in vitro the proliferation and the morphological changes of primary osteoblast-like cells (HOst) seeded on titanium dish grade 4 and 5 with different roughness and different titanium grade: machined (M), sandblasted (SBT), laser-treated with pitches of 20-µm diameter and 30-µm interpore distance. The titanium disks were divided into two groups: group A (titanium grade 4) and Group B (titanium Grade 5), respectively. Proliferation rate of attached cells was evaluated at different time (24, 48, 72 h and 1 week) by the quantitative colorimetric MTT assay. Our results showed a cell growth decrease evident in M titanium surfaces in both Groups A and B, while the cells seeded on the SBT and laser disks displayed an increase of cells growth, more evident in laser titanium surfaces in groups A and B. Morphological changes of the biocomplex cells/titanium was assessed by light, scanning and confocal microscopy. In fact, the microscopic analysis helped to clarify the behavior of the cells in contact with the titanium surfaces, in particular the M surface induced significant morphological changes, which were less evident in the SBT surfaces. Laser-engineered porous titanium surfaces promoted viability and proliferation of the osteoblasts. In particular, hemispherical porosity of 20 µm could be responsible for the higher HOst activation, in terms of cells proliferation, adhesion and morphological features.
Pathogenic or non-pathogenic bacteria from flora may play a key role in inflammatory bowel disease (IBD) pathogenesis. However, a specific infectious agent causing IBD has not been identified. This study assessed the impact of enteropathogenic $E.\ coli$ (EPEC) on the modulation of IL-1β, IL-6, TNF-α, COX-2, BAX and Bcl-2 expression, in sustaining inflammation of a rat colitis model. Two hundred male Sprague-Dawley rats (4 groups) were inoculated weekly or bi-weekly for 70 days, with (a) 1% methylcellulose (MC), (b) 6% iodoacetamide (IA) in 1% MC, (c) 4x10^8 CFU of EPEC, and (d) IA+EPEC. After a month, treatment was stopped in half of the animals in each group. IL-1β, IL-6, TNF-α, COX-2, BAX and Bcl-2 expression were measured in colonic mucosa scrapings. IL-1β, IL-6, TNF-α, and COX-2 were significantly increased in colonic mucosa of the IA+EPEC group and to a lesser but significant level in the IA group compared to controls, or EPEC alone, both in continued and discontinued treatment groups. Additionally, the BAX/Bcl-2 ratio decreased, indicating less apoptosis in the IA+EPEC group which exhibited more necrosis. These effects increased with experiment duration. This work provides new arguments favouring the role of bacteria in IBD pathogenesis.
CORRELATION BETWEEN VIRAL LOAD, PLASMA LEVELS OF CD4 - CD8 T LYMPHOCYTES AND AIDS-RELATED ORAL DISEASES: A MULTICENTRE STUDY ON 30 HIV+ CHILDREN IN THE HAART ERA

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This experimental retrospective multicenter study carried out on 30 seropositive children treated with Highly Active Antiretroviral Therapy (HAART), between the ages of 18 months and 14 years, in the clinical categories Centers for Disease Control (CDC) classification 1993 A (mildly symptomatic), B (moderately symptomatic) and C (severely symptomatic) aims to: 1) clinically and immunologically demonstrate the therapeutic benefits of HAART; 2) monitor the frequency of AIDS-related oral diseases in seropositive children with HAART therapy; 3) monitor the plasma levels of total CD4, CD4%, CD8%, CD4-CD8 lymphocytes and viral load from 1997 to 30 April, 2011. The statistic methods used are the analysis of covariance and the Bonferroni Test. More than 100 AIDS-related oral diseases were found in the study samples, the most frequent being: oral candidiasis, oropharyngeal candidiasis, HSV-1 herpetic esophagitis, herpetic gingivostomatitis (RHOG), recurrent aphthous stomatitis (RAS), parotid swelling, oral hairy leukoplakia (OHL), Herpes simplex 1 (HSV-1), linear gingival erythema (LGE), necrotizing gingivitis (NUG), facial lipodystrophy, facial-cervical lymphadenopathy (FCL), xerostomia, dysgeusia, hyposmia, oral mucosa hyperpigmentation (OMP). The Bonferroni test showed a significant difference between the mean plasma values (mpVTL) of total CD4, CD4 percentage, CD4-CD8 T lymphocytes and Viral Load (VL) of the various oral diseases found in the study samples. The therapeutic benefits of HAART are: immune reconstitution; reduction of the HIV/AIDS-related stomatology diseases; prevention and cure of the AIDS correlated neoplasias; reduction in maternal-fetal transmission of the HIV virus. The negative effects of HAART in relation to odontostomatolgy are: increase in oral lesions from HPV; xerostomia; dysgeusia/ageusia, hyposmia, perioral paresthesia; hyperpigmentation of oral mucosa; facial lipodystrophy, recurrent aphthous stomatitis (RAS). No case of immune reconstitution inflammatory syndrome or human papillomavirus (HPV)-related oral diseases were found in this study.
POSTOPERATIVE PAIN MANAGEMENT AT TIRANA UNIVERSITY HOSPITAL CENTER “MOTHER TERESA”, TIRANA, ALBANIA

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There is no or little evidence on postoperative pain assessment and treatment in Albanian hospitals. This study is based on our every day work and aims to highlight our experience. We conducted a descriptive drug utilization study which implied data collection over 6 months. Evidence of the enrolled patients was kept by maintaining records and the completed structured questionnaires. Postoperative pain was assessed through a five-category verbal rating scale (VRS). Metamizole was the most prescribed and administered analgesic drug as single therapy and in combination therapy, and acetaminophen was the least prescribed drug. The compliance between the prescribed dosages and those administered was higher in patients treated with a single analgesic compared to multiple therapies. A few patients reported adverse events (4.2%). There is much variability in postoperative pain management methods used by medical staff within the Tirana University Hospital. In Albania to date there is no standard protocol for postoperative pain treatment. This study shows that there are no essential differences in patients’ outcomes in terms of efficacy of analgesic treatment. This leads to the conclusion that a postoperative protocol/guideline for pain management should be prepared, based on our local study findings and also on international experience. Moreover, the guidelines should consider use of balanced analgesia.
The aim of this *ex vivo* study was to evaluate bacterial penetration after filling root canals using 3 different techniques. Three experimental groups of 25 teeth each, obturated with lateral-warm-vertical condensation of gutta-percha, Microseal technique and EndoREZ® system, respectively, were tested in a split chamber model system using *Enterococcus faecalis* and monitored for 180 days to determine bacterial penetration. A statistical analysis was performed using the Kaplan-Meier method. Median survival time was 25 days for Microseal system, 41 for lateral-warm-vertical condensation and 81 for EndoREZ®. Significant differences were demonstrated between Microseal and EndoREZ® (*p*<0.001) and between Microseal and lateral-warm-vertical condensation technique (*p*<0.05). No statistically significant differences were observed between EndoREZ® and lateral-warm-vertical condensation. After 180 days of assessment, 20% of the EndoREZ® samples resisted bacterial penetration and furthermore, the EndoREZ® system has the potential to be a filler system compatible with other currently used systems.
Piercing is the practice of puncturing some parts of the body to apply ornamental objects. The presence of oral and perioral piercings are a risk factor for many acute and chronic complications, such as chipping of the dental enamel, periodontal lesions and infection. The aim of this study is to assess the prevalence of lip and tongue piercing complications in the dental and periodontal tissues in a sample of young adults. Twenty-five adult patients were examined (test group: 11 males and 14 females with an average age of 23.4±3.6 years) who had had a minimum of one labial or tongue piercing for at least 1 year and were compared with 25 subjects (control group: 11 males - 44%, and 14 females - 56%) without any lingual or labial piercing. A questionnaire was compiled for each patient and a clinical examination was performed. The following parameters were examined by the same operator: abnormal toothwear, tooth chipping or cracking, clinical attachment loss (CAL), probing pocket depth (PD) and gingival recession (GR, classified by using Miller’s classification). The data were analyzed using χ² or Fisher’s exact test for small numbers and non-parametric Mann–Whitney or Kruskal–Wallis tests to examine for differences in continuity; the level of significance was p< 0.05. According to the results found in the present study the prevalence of abnormal toothwear and tooth chipping was higher in the subjects with labial or tongue piercing. Moreover, patients with tongue or labial piercing exhibited a higher GR in comparison to control subjects without any oral piercing. No differences were observed between the two groups as regards CAL and PD. A significant association between the duration of piercing and dental defects was found in the group of patients with piercings with greater prevalence of tooth and periodontal defects in the group of 13 subjects who had had the piercings for a period ≥ 4 years.

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ADMA, SDMA, L-ARGININE AND NITRIC OXIDE IN ALLERGIC PEDIATRIC BRONCHIAL ASTHMA

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Published data regarding asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), L-arginine (L-ARG) and nitric oxide fraction in exhaled air (FeNO) in pediatric bronchial asthma are limited. Many question remain open about plasma concentration of these substances. The aim of this study is to evaluate ADMA, SDMA, L-ARG and FeNO concentration in allergic pediatric mild asthmatic patients in respect to healthy subjects. In this case-control study 60 children (50 asthmatics and 10 healthy) underwent a complete clinical visit, baseline respiratory function, allergy tests and biochemical analyses. The statistical significance of the different concentrations between the two groups were studied using one-way analysis of variance (ANOVA). A p value < 0.05 was considered statistically significant. The mean plasma ADMA (0.58 vs 0.68 µmol/L), SDMA (0.40 vs 0.45 µmol/L) and L-ARG (52.2 vs 74.13 µmol/L) concentration were significantly lower (p<0.001) in the asthmatic patients in respect to healthy subjects (control group). The concentration of FeNO was significantly higher in the asthmatic subjects in respect to the control group (9.18 vs 4.2 µmol/L; p<0.001). Low plasma concentrations of ADMA, SDMA, L-ARG and high concentration of FeNO are associated with bronchial asthma and indicate an important role in airway disease through NO metabolism.
LETTER TO THE EDITOR

PRION SEARCH AND CELLULAR PRION PROTEIN EXPRESSION IN STRANDED DOLPHINS

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The recent description of a prion disease (PD) case in a free-ranging bottlenose dolphin (Tursiops truncatus) prompted us to carry out an extensive search for the “disease-associated” isoform (PrPSc) of the cellular prion protein (PrPC) in the brain and in a range of lymphoid tissues from 23 striped dolphins (Stenella coeruleoalba), 5 bottlenose dolphins and 2 Risso’s dolphins (Grampus griseus) found stranded between 2007 and 2012 along the Italian coastline. Three striped dolphins and one bottlenose dolphin showed microscopic lesions of encephalitis, with no evidence of spongiform brain lesions being detected in any of the 30 free-ranging cetaceans investigated herein. Nevertheless, we could still observe a prominent PrPC immunoreactivity in the brain as well as in lymphoid tissues from these dolphins. Although immunohistochemical and Western blot investigations yielded negative results for PrPSc deposition in all tissues from the dolphins under study, the reported occurrence of a spontaneous PD case in a wild dolphin is an intriguing issue and a matter of concern for both prion biology and intra/inter-species transmissibility, as well as for cetacean conservation medicine.
ExtraMedullary Plasmacytoma (EMP) is a rare plasma cell tumor. It can occur in the upper aerodigestive tract and presents as a large nodule causing local compressive symptoms. A 79-year old woman presented to Otorhinolaryngology Department with progressive hearing loss and no other symptoms. Following PET/TC examination due to the suspicion of a lymphoproliferative disease, the patient underwent tonsillectomy and the diagnosis of solitary EMP was formulated. In addition to that, the histological examination of the tonsillar tissue revealed large colonies of filamentous bacteria, showing abundant sulphur granules and Splendore-Hoeppli phenomenon; these evidences indicating the presence of a chronic Actinomycosis infection. Immunohistochemical analysis demonstrated a marked IL-6 immunoreactivity of the neoplastic plasma cells. Interestingly, a marked IL-6 immunoreactivity was also found in the tissue surrounding the Actinomyces colonies. In the present study we report for the first time a solitary EMP associated with Actinomyces. It is tempting to speculate that the unsuspected and untreated Actinomycosis infection, through chronic IL-6 production, could contribute to the neoplastic transformation of plasma cells.