EDITORIAL

ROLE OF MACROPHAGE IN TUMOR MICROENVIRONMENT: PROSPECT IN CANCER IMMUNOTHERAPY

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Current evidence suggests an increasing role of macrophages in inflammation and tumor progression. Most tumors contain an abundant number of macrophages as a major component of their leukocyte infiltrate, which co-exist with tumor cells at the tumor microenvironment. Upon activation with soluble tumor antigens, macrophages release a distinct repertoire of growth factor, cytokines, chemokines and enzymes that inhibit growth of the tumor. However, the anti-tumor immune response induced by macrophages does not always ensue. Tumor cells themselves are capable of down-regulating macrophage phenotype and functions and anti-tumor immune responses in the tumor-bearing host. The present review aims to elucidate the role of macrophages in tumor growth and progression, invasion, metastasis, and angiogenesis at the site of tumor growth. Moreover, the effect of tumor microenvironment on the phenotype and function of macrophages, which are altered due to the continuous exposure of various soluble and non-soluble tumor promoting factors secreted by tumor cells, and implication of macrophages in cancer immunotherapy have been discussed in detail.
The pathology report should include clinically relevant information as well as provide clinically useful information derived from the macroscopic examination and microscopic evaluation of the radical prostatectomy (RP) specimens. The reporting pathologist should pay particular attention to the evaluation of the prognostic factors proven to be of prognostic importance and useful in clinical patient management, including histological type, grade and volume of cancer, the extent of local invasion and stage of cancer as well as the surgical margins status.

The first two authors contributed equally to this work
IMPACT OF IMMUNITY IN AUTISM SPECTRUM DISORDERS

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Autism spectrum disorders (ASDs) are childhood psychopathologies characterized by having difficulties in social interaction, verbal and non-verbal communication as well as sensor motor movements. Evidence suggests that in ASDs environmental toxicant exposure, genetic and mitochondrial dysfunction are involved associated with abnormal immune response with allergic problems and elevated serum IgE. ASDs present the major cytokine and chemokine dysfunction in CNS and is mediated by an increase of pro-inflammatory cytokine levels in the brain, such as TNF, IL-1, IFN-γ, IL-6, IL-8 and others. Mast cells, which are also implicated in ASDs, are worsened by stress and produce proinflammatory cytokines and can be stimulated by neurotensin in the brain and gut, contributing also to the inflammatory response. However, the exact etiology of ASDs remains largely unknown.
The influence of p38 mitogen-activated proteinkinase (MAPK) expression in the development and progression of periodontal disease is currently under investigation. The aim of the present study is to investigate whether the p38 MAPK expression in gingival tissues correlates with IL-1β levels in gingival crevicular fluid (GCF). Twenty patients with generalized aggressive periodontitis (GAgP), 15 patients with generalized chronic periodontitis (GCP) and 10 healthy subjects (H) were enrolled in the study. Clinical data, gingival tissue biopsies and GCF samples were collected. The expression of p38 was investigated by immunohistochemistry. The levels of IL-1β in GCF were measured using ELISA. Mean clinical parameters and GCF volumes were statistically higher in patients with GAgP and GCP compared to H subjects. Higher levels of IL-1β were found in both periodontitis groups. The p38 expression was significantly increased in inflamed gingival tissues. There were no statistically significant differences in levels of IL-1β and p38 expression between subjects with GAgP and GCP. Our data support the hypothesis that MAPK signaling pathway is an additional player in the pathogenesis of periodontitis. This is the first report to evaluate the involvement of p38 MAPK in patients with GAgP and GCP which might be, in part, considered of value in understanding disease mechanisms.

IMMUNOEXPRESSION OF p38 MITOGEN-ACTIVATED PROTEINKINASE IN PATIENTS WITH AGGRESSIVE AND CHRONIC PERIODONTITIS

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The influence of p38 mitogen-activated proteinkinase (MAPK) expression in the development and progression of periodontal disease is currently under investigation. The aim of the present study is to investigate whether the p38 MAPK expression in gingival tissues correlates with IL-1β levels in gingival crevicular fluid (GCF). Twenty patients with generalized aggressive periodontitis (GAgP), 15 patients with generalized chronic periodontitis (GCP) and 10 healthy subjects (H) were enrolled in the study. Clinical data, gingival tissue biopsies and GCF samples were collected. The expression of p38 was investigated by immunohistochemistry. The levels of IL-1β in GCF were measured using ELISA. Mean clinical parameters and GCF volumes were statistically higher in patients with GAgP and GCP compared to H subjects. Higher levels of IL-1β were found in both periodontitis groups. The p38 expression was significantly increased in inflamed gingival tissues. There were no statistically significant differences in levels of IL-1β and p38 expression between subjects with GAgP and GCP. Our data support the hypothesis that MAPK signaling pathway is an additional player in the pathogenesis of periodontitis. This is the first report to evaluate the involvement of p38 MAPK in patients with GAgP and GCP which might be, in part, considered of value in understanding disease mechanisms.
TARGETING THE IL-10 PATHWAY BY RNA INTERFERENCE HAS BENEFICIAL EFFECTS ON THE DEVELOPMENT OF EXPERIMENTAL LUPUS

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Results from patients with systemic lupus erythematosus (SLE) and from mice suffering from a lupus-like disease suggest that the IL-10 pathway is involved in pathogenesis, and that this cytokine could represent a target for managing SLE development. In this study, we constructed JC virus-like particles (VLP) expressing IL-10-specific short hairpin RNAs (shRNAs) that efficiently silenced IL-10 gene expression. In mice, a single injection of this preparation dramatically reduced serum levels of IL-10. We tested the preventive effect of this vector expressing anti-IL-10 shRNAs in female (NZBxNZW) F₁ mice. Weekly intraperitoneal injections decreased the incidence and severity of proteinuria, and prolonged lifespan, with reduced IL-10 production. Our data demonstrate that the IL-10 pathway plays a chief role in lupus pathogenesis. It indicates that JC virus-like particles represent a potent vector for delivering interfering RNA in vivo. They suggest that RNA interference targeting IL-10 is an effective strategy to silence the IL-10 pathway, and possesses a therapeutic potential that could be useful in the management of SLE and, possibly, other immune-mediated disorders.
This study was an attempt to overexpress the extracellular elastase from *Pseudomonas aeruginosa* in *Escherichia coli* and characterize the level of purified enzymes of recombinant bacterium. The gene encoding an elastase natively produced by *Pseudomonas aeruginosa* was cloned and overexpressed in *Escherichia coli* using pET-32a system and the resultant recombinant elastase was purified and compared with the native elastase gene. The 1497 bp gene was amplified and subcloned in pET-32a and subsequently transformed into *E. coli* BL21. The media assay, SDS-PAGE and Western blotting were carried out to analyze the results, and the extracellular enzyme was purified to detect enzyme activity of recombinant *E. coli*. Nucleotide sequencing of the DNA insert from the clone revealed that the protease activity corresponded to an open reading frame consisting of 1497 bp coding for a 53.69-kDa protein. The clear zones around the recombinant colonies on skim milk agar as well as sharp band on 53-kDa size on SDS-PAGE and Western blotting confirm the correct expression of elastase enzyme. Bacterial culture containing pET-32a-lasB showed high enzyme activity around 670 μg elastase ml⁻¹. The results showed that elastase has potential to be produced industrially and be applied in medicine, food, etc. divisions.
High mobility group box 1 (HMGB1), known as a pro-inflammatory cytokine and chromatin-binding molecule, plays an important role in the carcinogenesis and metastasis of various tumors. The present study aimed to investigate the expression of HMGB1 in human osteosarcoma and its clinical relevance. At first, human osteosarcoma tissues and their corresponding adjacent non-cancerous tissues (ANCT) from forty consecutive cases were collected. The expression of HMGB1 was detected by immunohistochemical assay through tissue microarray procedure and the correlation of HMGB1 expression with clinicopathologic factors was evaluated. Secondly, through small hairpin RNA (shRNA)-mediated HMGB1 knockdown in MG-63 osteosarcoma cells, we observed the changes of the biological behaviors of the osteosarcoma cells. As a consequence, the rate of positive expression of HMGB1 was significantly higher in osteosarcoma tissues than in the ANCT (60% vs 15%, $P < 0.01$). HMGB1 expression had significant positive correlation with Enneking staging ($P = 0.034$) and distant metastases ($P = 0.003$), but had no correlation with the factors including age and gender of the patients, or histology and location of the tumor (each $P > 0.05$). Knockdown of HMGB1 down-regulated the expression of p-AKT, p-PI3K, PCNA, MMP-9 and CyclinD1, while it up-regulated the expression of cleaved caspase-3. More importantly, HMGB1 knockdown inhibited the proliferative activities and invasive potential, and induced apoptosis and cycle arrest in MG63 osteosarcoma cells. Taken together, our results indicate that HMGB1 was highly expressed in human osteosarcoma tissues, and the patients with higher HMGB1 expression in osteosarcoma tissues were more likely to have progression and metastasis of the disease. Knockdown of HMGB1 could inhibit the proliferation and invasion of osteosarcoma cells and induce its apoptosis through down-regulation of PI3K/AKT signaling pathway. HMGB1 could be a potential therapeutic target for osteosarcoma.
Elevated fibroblast growth factor 23 (FGF-23) is independently associated with increased inflammatory markers in chronic kidney disease. Lanthanum carbonate (LaCa) reduces FGF-23. We studied the effects of LaCa on inflammatory profile of hemodialysis patients, and the relationship with changes in FGF-23. This prospective study was performed under habitual clinical practice conditions. Twenty-six hemodialysis patients with serum phosphate > 5 mg/dl receiving calcium-based phosphate binders were switched to LaCa. Ten patients with phosphate ≤ 5 mg/dl under calcium-based phosphate binders were enrolled as a control group for comparison. Serum calcium, phosphorus, calcium-phosphate product (CaxP), intact parathyroid hormone and the inflammatory profile [including serum high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-10, as well as mRNA expression levels of TNF-α and IL-6 in peripheral blood mononuclear cells] were analyzed. Serum FGF-23 significantly decreased in patients switched to LaCa (P < 0.01), with a concomitant reduction in serum hsCRP (-10.9%, P < 0.01), TNF-α (-6.7%, P < 0.05) and IL-6 (-8.1%, P < 0.01). mRNA expression levels of TNF-α and IL-6 in PBMC also decreased by 7.8% (P < 0.05) and 10.3% (P < 0.01), respectively. Multivariate regression analysis demonstrated that variations in FGF-23 were the only independent determinant of the changes in serum and mRNA expression levels of inflammatory parameters. In conclusion, LaCa posses anti-inflammatory actions, which are significant and independently associated with the reduction of FGF-23. FGF-23 may regulate inflammatory cytokine gene expression at the transcriptional level. Whether these effects have influence on clinical outcomes warrants consideration.
THE EFFECT OF TUMOR NECROSIS FACTOR-α-INDUCED PROTEIN 8 LIKE-2 ON IMMUNE RESPONSE OF CD4⁺ T LYMPHOCYTES IN MICE AFTER THERMAL INJURY

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The status of cellular immunity has been shown to be associated with the occurrence and development of sepsis. Accumulating evidence has demonstrated that tumor necrosis factor-α-induced protein 8 like-2 (TIPE2) plays an important role in maintaining homeostasis of immune function. The present study, with the use of a controlled in vivo approach, demonstrated the effect of TIPE2 on cell-mediated immunity of CD4⁺ T lymphocytes in thermal injury murine model. One hundred and twenty-eight male mice were randomly allocated into four groups, which were sham burn group (n=48), burn group (n=48), burn with lentivirus-RNAi-TIPE2 transfection group (n=16), burn with negative control transfection group (n=16), and they were sacrificed at the designated time points. CD4⁺ T lymphocytes were isolated from the spleen using MACS microbeads. Phenotypes were analyzed by flow cytometry analysis, and cytokines were determined using ELISA kits. We found that the expression of TIPE2 was markedly increased in CD4⁺ T lymphocytes in mice at 24, 48 and 72 hours postburn. Down-regulation of TIPE2 by lentivirus-RNAi-TIPE2 attenuated the suppressive effect of CD4⁺ T lymphocytes, which was associated with profound elevation of nuclear factor of activated T cell (NF-AT) activity. These results demonstrate that TIPE2 appear to be involved in the immune regulation of CD4⁺ T lymphocytes, and the decrease in TIPE2 expression on CD4⁺ T lymphocytes in vivo can enhance peripheral T lymphocyte function after thermal injury. These data might provide a valid strategy to prevent the development of immunosuppressive state resulted from major burns.
This study aims to describe the levels of circulating cytokines produced by Th lymphocytes (IFN-γ, IL-4, IL-10, IL-17A), as well as the levels of cytokines produced by monocytes/macrophages (TNF-α, IL-1β, IL-12), in patients with chronic Staphylococcus aureus infections before treatment and following completion of autovaccine treatment. The study was carried out on adult individuals, including 25 healthy subjects (group 1, control, not treated), 50 patients with chronic suppurative dermatitis (group 2) and 40 patients with chronic infections of the upper respiratory tract (group 3). Blood serum cytokine levels were measured by enzyme–linked immunosorbent assay (ELISA). S. aureus was detected in cultures of suppurative dermal exudates or of pharyngeal smears. For every individual patient an autovaccine was prepared, containing a suspension of inactivated S. aureus bacteria (1.5 x 10^8 bacteria/ml) isolated from the patient. The autovaccine was administered subcutaneously for a period exceeding 3 months, for a total of 18 injections. The average level of IFN-γ and IL-17 was 2–2.5 times higher in the infected patients. This was not accompanied by an increase in TNF-α or IL-12 levels. A treatment with autovaccine eradicated S. aureus infection in 42 (84%) patients of group 2 and in 14 (35%) patients of group 3. A significant increase (two-fold) in IL-17A was observed in treated patients. Also, following the treatment with autovaccine, all patients demonstrated a significant increase in the levels of IFN-γ, TNF-α and IL-12. These studies showed for the first time that efficiency of the autovaccine treatment in patients with chronic S. aureus infection depends on an adequate secretory response of TH17 cells.

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BEE VENOM ATTENUATES EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS THROUGH DIRECT EFFECTS ON CD4⁺CD25⁺FOXP3⁺ T CELLS

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to substantial disability through deficits of sensation and of motor, autonomic, and neuro-cognitive function. Many clinical and pathological features of experimental autoimmune encephalomyelitis (EAE) show close similarity to MS. Bee venom (BV) has been used in the practice of oriental medicine and evidence from the literature indicates that BV plays an anti-inflammatory or anti-nociceptive role against inflammatory reactions associated with arthritis and other inflammatory diseases. The purpose of the present study was to determine whether BV could suppress immune cell differentiation and infiltration into spinal cord on EAE mice commonly used as a model for MS. BV treatment increased the population of CD4⁺CD25⁺Foxp3⁺ T cells and inhibited CD4⁺ T-cell proliferation in vitro. In vivo, BV treatment increased the population of CD4⁺CD25⁺Foxp3⁺ T cells. Furthermore, BV administration reduced the severity of EAE while concurrently decreasing INF-γ producing CD4⁺ T cells, IL-17A producing CD4⁺ T cells and inflammatory cytokine production including INF-γ, IL-17A, TNF and IL-6. BV-treated animals exhibited less infiltration and preserved morphology compared to saline-treated animals. Interestingly, the therapeutic effects of BV on EAE disappeared when CD4⁺CD25⁺Foxp3⁺ T cells were depleted by using anti-CD25 antibody. Our research suggests that BV could be a potential therapeutic agent for anti-inflammatory effects in an animal model of EAE.
ENHANCING THE THERAPEUTIC EFFECTS OF ETHYL PYRUVATE ON GASTRIC CANCER THROUGH KNOCKDOWN OF YAP1 EXPRESSION

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Yes-associated protein (YAP) plays a critical role in tumor formation and malignancy of many cancers and has been shown to be the important therapeutic target. Ethyl pyruvate (EP), a stable lipophilic pyruvate derivative, is a potent inhibitor of high mobility group box-B1 (HMGB1) release and exerts significant anti-inflammatory activities. Previously, we reported the high expression of YAP1 and the antitumor effects of EP in gastric cancer (GC). However, whether small hairpin RNA (shRNA)-mediated knockdown of YAP1 expression enhances the antitumor effects of EP on GC is elusive. After GC SGC-7901 cells infected with lentivirus-mediated YAP1 shRNA vector were treated with 20mmol/L EP, the expression levels of HMGB1, receptor for advanced glycation endproducts (RAGE) and Protein kinase B (AKT) were identified by Real-time PCR and Western blot assays. Cell proliferative activities and independent growth were examined by MTT and colony formation assays, and their migration and metastasis were evaluated by wound-healing and Transwell assays. Cell apoptosis and cycle distribution were assessed by flow cytometry. As a result, EP coupled with YAP1 shRNA significantly decreased the expression levels of HMGB1, receptor for advanced glycation endproducts (RAGE) and Protein kinase B (AKT) were identified by Real-time PCR and Western blot assays. Cell proliferative activities and independent growth were examined by MTT and colony formation assays, and their migration and metastasis were evaluated by wound-healing and Transwell assays. Cell apoptosis and cycle distribution were assessed by flow cytometry. As a result, EP coupled with YAP1 shRNA significantly decreased the expression levels of HMGB1, receptor for advanced glycation endproducts (RAGE) and Protein kinase B (AKT), inhibited the proliferative activities and migration and metastasis capabilities, and induced apoptosis and cycle arrest in GC cells compared with the single EP treatment. Taken together, knockdown of YAP1 enhances the inhibitory effects of EP on GC cells through inhibition of the HMGB1-RAGE and AKT pathways, and this may provide an attractive strategy for the treatment of GC.
Asthma is characteristic with chronic airway inflammation and remodeling. Azithromycin (AZM), the 15-member macrolide, is known to present an anti-inflammatory effect and is increasingly being used in the treatment of chronic inflammatory pulmonary diseases. We hypothesize that low-dose azithromycin can inhibit allergen-induced airway remodeling except allergic airway inflammation in rat model. Male SD rats underwent intraperitoneal ovalbumin sensitization on days 1 and 6 followed by an intranasal challenge on day 7-13. On day 14, airway inflammation and remodeling were assessed by quantifying leukocytes in the airway, expression of multiple inflammatory mediators in BALF, histological examination in lung and TGF-β1 mRNA and protein levels by qRT-PCR, immunohistochemistry and Western blotting. Treatment with low-dose azithromycin at the dose of 25 mg/kg significantly reduced ovalbumin-dependent airway inflammation, including accumulation of neutrophils, lymphocytes and eosinophils, secretion of IL-2, IL-4, IL-13 and TNF-α. Moreover, airway remodeling was significantly abrogated by azithromycin in this model. The mucus cell hyperplasia, thickening of the peribronchial smooth muscle layer, secretion of ET-1,IL-2, IL-4, IL-13 and TNF-α, and increasing mRNA and protein expressions of TGF-β1 in lung tissue were all significantly decreased in azithromycin-treated rats. These findings demonstrate the protective effect of low-dose azithromycin on allergic airway remodeling in rat and suggest low-dose azithromycin may have beneficial effects in treating allergic airway inflammation.
Multipurpose solutions (MPSs) are the leading method for cleaning and disinfecting soft contact lenses (CLs). During recent years, numerous clinical studies have evaluated the MPS damage to the ocular surface. This study examined the cytotoxic and the inflammatory effects of MPSs and hydrogen peroxide disinfection system (H2O2) compared to appropriate controls on human corneal epithelial (HCE) cells. Primary cultured HCE cells were exposed to eight different commercially available MPS products (MPS A, ReNu MultiPlus®; MPS B, Opti Free® EverMoist; MPS C, Solo-care Aqua®; MPS-D, Complete®; MPS-E, Unica Sensitive®; MPS-F, Options Multi®; MPS-G, Biotrue®; MPS-H, COMPLETE® RevitaLens). Morphological changes and cytotoxic effects were examined with FITC-Annexin V/ PI and MTT assays. The protein contents of the inflammatory cytokines interleukin (IL)-1β, TNF-α, IL-6 and IL-8 were examined by multiplex fluorescent bead immunoassay (FBI), and the mRNA expression was examined by real time PCR. Lipopolysaccharide (LPS) with 500 ng/ml CD14 and 500 ng/ml LBP (LPS complex), polyinosinic: polycytidylic acid (Poly I:C) and un-neutralized H2O2 served as positive controls, respectively. Phosphate-buffered saline (PBS) was added as a negative control. The study demonstrated that most of the MPSs induced varying degrees of cytotoxicity to HCE cells, and increased production of pro-inflammatory cytokines compared to the negative control. In addition, several MPS increased the mRNA level of inhibitory factor-κBα (I-κBα). Among the various MPSs, MPS-H induced the highest protein contents of the pro-inflammatory cytokines (14.37±2.2-fold for TNF-α, 41.39±2.5-fold for IL-1β and 5.24±0.6-fold for IL-6) compared to the negative control (p<0.05). In contrast, no significant differences were noted between the neutralized H2O2 and the negative control. We conclude that most of the currently used MPSs induce significant damage and inflammatory response in corneal epithelial cells. MPS-induced inflammation was mediated through NF-κB signal transduction. This study demonstrates for the first time inflammatory responses at the molecular level in primary HCE cells following exposure to a large series of commercially available and commonly used MPSs. These findings strongly suggest that certain MPSs may be partially involved in the pathogenesis of contact lens intolerance. Therefore, we recommend that practitioners advise patients as to the preferable disinfecting contact lens solutions, and to consider using the hydrogen peroxide disinfection systems instead.
PRELIMINARY EXPLORATION ON ANTI-FIBROSIS EFFECT OF KAEMPFEROL IN MICE WITH SCHISTOSOMA JAPONICUM INFECTION

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This study is to explore the effectiveness and mechanism of kaempferol on treatment of hepatic fibrosis induced by schistosoma egg. Thirty-six healthy male balb/c mice were randomly divided into 6 groups, including negative group, positive group, and 4 different dosages of kaempferol treatment groups. Each mouse was infected with 20 schistosoma Cercariae japonicum, except the ones in the negative group. Four weeks later, every infected mouse was administrated with 500mg/kg/day praziquantel for 2 days, and all kaempferol groups were followed by a 4-week administration of kaempferol with 5, 10, 15 and 20mg/kg/day respectively, while both control groups were administrated with normal saline. All the mice were sacrificed on the 59th day after infection. The liver tissues were taken for Masson staining to detect collagen and real-time quantitative PCR to detect the mRNA expression of IL-13, collagen 1 and MMP-2. As a result, Masson stain showed that the optical density of the interested region in the positive group was significantly higher than that in the negative group (P<0.01), and the optical density in all kaempferol groups was significantly lower than that in the positive group (P<0.05 or P<0.01). Real-time PCR showed that the mRNA expression of IL-13 in the positive group was significantly higher than that in the negative group (P<0.01), and the expression of IL-13 in the 20mg/kg and 15mg/kg kaempferol groups was significantly lower than that in the positive group, respectively (P<0.05). The mRNA expression of collagen 1 in the positive group was significantly higher than that in the negative group (P<0.01), and mRNA expression of collagen 1 in the 20mg/kg kaempferol group was significantly lower than that in the positive group (P<0.05). There were no significant differences between the positive and negative groups on mRNA expression of MMP-2. The mRNA expression of MMP-2 in all kaempferol groups was significantly higher than that in the positive group (P<0.05 or P<0.01). In conclusion, kaempferol can ameliorate schistosoma egg-induced hepatic fibrosis via regulating the IL-13 signal pathway. Kaempferol is very likely to be an IL-13 targeted anti-fibrosis medicine.
Type II collagen (CII) protein is the main component of hyaline cartilage. The clinical importance of CII in arthritis, aging, and osteoarthritis is significant, but its ability to induce specific immune tolerance has not been extensively studied previously. We have recently proven that CII is capable of inducing Anterior Chamber Associated Immune Deviation (ACAID) when injected into the eye. Here, we hypothesized that ACAID-mediated tolerance could be induced in Balb/c mice that receive an intravenous administration of CII-induced in vitro-generated ocular-like antigen-presenting cells (APCs) or T regulatory cells (Tregs). Delayed hypersensitivity (DTH) assays were used to examine this hypothesis. In mice injected with CII-specific ACAID APCs, the specific regulatory activities resided in the spleen cells, splenic T cells, and ACAID CD8+ T cells, as proven by local adoptive transfer (LAT) assays. Conversely, there was a lack of regulatory activity in the CD4+ CD25+ T cell compartment of the recipient mice. Thus, ACAID CD8+ Tregs generated in vitro could be directly responsible for the expression of CII-driven ACAID-mediated tolerance and could be used as potential therapeutic tools in the treatment of CII-associated autoimmune diseases.
Polycystic Ovary Syndrome (PCOS) is characterized by an extreme variety of phenotypes and controversial metabolic implications. Hepatic Steatosis (HS) and low-grade chronic inflammation (LGCI) might be common findings in PCOS. We conducted a cross-sectional study to evaluate the LGCI and HS in young women with PCOS according to their Body Mass index (BMI), Insulin Resistance (IR), and PCOS phenotypes. Sixty young premenopausal PCOS women and 20 age-matched controls participated. Primary outcome measures were the presence/severity of HS; LGCI index evaluated as spleen longitudinal diameter (SLD) by UltraSound, C-Reactive Protein (CRP) and Interleukin (IL)-6 levels; BMI and the Homeostasis Model Assessment (HoMA) of IR. The second outcome measures were testosterone, Sex Hormone-Binding Globulin (SHBG) levels, and Free Androgen Index (FAI). The presence of HS and LGCI was not significantly different between NW and O/O patients, while there were significant differences particularly when the PCOS-women were grouped according to IR or to PCOS phenotypes. At multiple regression adjusted for BMI, HoMA-IR and the spleen size were the major determinants of the severity of HS ($\beta= 0.36$, p=0.007, and $\beta= 0.28$, p=0.034, respectively). At multiple regression SLD represented the unique predictor of FAI ($\beta=0.32$; p=0.018). In young women with PCOS, HS was detected independently from obesity and was well predicted not only by IR but also by spleen size, with variable expression of the liver-spleen axis across the different PCOS subtypes. A possible role of the spleen in determining LGCI also in women with PCOS is emphasized.
In aging, there is a gradual decrease in muscle mass (sarcopenia) and muscle strength which contributes to a decline in physical functions, increased disability, frailty, and loss of independence. Physical activity can reduce functional decline due to aging. Randomized controlled trials (RCT) are needed to determine the effectiveness of different exercise stimuli on muscle strength and balance in the sarcopenic elderly. Forty male volunteers diagnosed with sarcopenia (CDCP) (70.9 ± 5.2 yrs) were enrolled in this study. A randomized, controlled trial, with blind assessment, was designed to study the effect of global sensorimotor, high intensity focused vibrational (intensity: 300Hz) and resistance training (intensity: 60-80% of maximum theoretical force, 10-12 repetitions for 3 sets) stimuli on muscle strength and balance confidence. The subjects were randomly assigned to three different training programs or a control group which was encouraged to maintain their habitual activity level. The training was performed for 12 weeks in all groups: 2 sessions/week in Gsm and Ret groups; 1 session/week for the first 8 weeks and 3 sessions/week for the last 4 weeks in Vam group. The main outcome was maximal force contraction of the lower limbs, and secondary outcomes were static and dynamic balance confidence. All the training regimens increased isometric strength. Both the sensorimotor and the vibrational training increased stability with a reduction of sway area and of ellipse surface (p<0.01). Gait analysis showed a significant increase in the length of the half-step in all three groups (respectively 108%, p <0.01; 92% p< 0.01; 65% p <0.05). All the training programs implemented in the present investigation increase muscle strength. In addition, sensorimotor and vibrational training intervention aims to transfer these peripheral gains to the functional and more complex task of balance, in order to reduce the risk of falls.
Malignant mesothelioma (MM) is a highly fatal tumor of inner body membranes, the extensive growth of which is supported by both a weak immunogenicity and the ability to reprogram surrounding immune cells towards tumor-supporting phenotypes. Interleukin-17 (IL-17) is a major inflammatory cytokine which is now accepted as the paradigmatic cytokine of many autoimmune diseases; however, its role in tumor immunology has only been partially unraveled, and no data exist regarding its possible involvement in MM. Thus, in this work we evaluated the ability of MM to induce IL-17 production in immune cells and the effects of IL-17 on MM growth and invasiveness. Our data show for the first time that macrophages and CD4+ T-cells are polarized by MM to produce IL-17, and that this cytokine exerts multiple tumor-supporting effects on both cell growth and invasiveness. These data provide novel evidence of the crosstalk occurring between MM and immune cells and suggest potential targets for the development of new pharmacological approaches for MM treatment.
C-REACTIVE PROTEIN LEVEL AND ITS RELATIONSHIP WITH SUICIDE RISK AND ALEXITHYMIA AMONG NEWLY DIAGNOSED, DRUG-NAİVE PATIENTS WITH NON-AFFECTIVE PSYCHOSIS

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The aim of the present study was to evaluate C-Reactive Protein (CRP) levels in newly diagnosed drug-naïve patients with non-affective psychosis, testing the hypotheses that in such patients serum CRP levels would be higher than in healthy controls and related to more severe psychopathology, suicide risk and alexithymia. CRP levels of 30 adult patients and 30 sex- and age-matched healthy controls were evaluated. Patients were tested with the Scale of Suicide Ideation (SSI), the Toronto Alexithymia Scale (TAS-20), the Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS) and the Calgary Depression Scale for Schizophrenia (CDSS). Higher suicide risk patients showed higher CRP levels than lower suicide risk patients and healthy controls. Moreover, such patients showed higher SAPS, SANS and CDSS scores than lower suicide risk patients. In linear regression model, CRP was significantly associated with higher SSI and TAS-20 scores. The results of the present study support the notion that CRP, suicide risk and alexithymia are strictly linked in newly diagnosed, drug-naïve patients with non-affective psychosis, independently of depressive symptoms or general psychopathology. Limitations are discussed.
TH17-DRIVEN INFLAMMATION IS PRESENT IN ALL CLINICAL FORMS OF MULTIPLE SCLEROSIS; DISEASE QUIESCENT IS ASSOCIATED WITH GATA3-EXPRESSING CELLS

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Multiple Sclerosis (MS) presents in a variety of clinical forms associated with a diverse grade of neurological impairment, different prognosis and, possibly, multiple pathogenic mechanisms. Thus, whereas relapsing-remitting (RR) MS appears to be largely driven by inflammatory processes, neurodegeneration, partially independent from inflammation, drives primary progressive (PP) and secondary progressive (SP) MS. An extensive analysis of neuroinflammation in the different forms of MS was performed by evaluating immunophenotypic and functional parameters in MBP-stimulated T lymphocytes of 103 MS patients (26 benign (BE) MS, 30 RRMS, 33 SPMS and 14 PPMS) and 40 healthy controls (HC). Results showed that: i) IL-17-producing and RORC/γt-expressing CD4+ T cells (TH17 lymphocytes), as well as IL-6 expressing CD14+ cell were augmented in all patients; ii) IL-22-expressing cells were increased in all forms of MS with the exception of PPMS; iii) TGF-β-expressing B cells were increased only in RRMS; and iv) GATA3-, NFATc-1, IL-13-, and IL-25-expressing cells (TH2 lymphocytes) were augmented in RRMS and BEMS patients alone. Data herein indicate a pivotal pathogenic role of TH17-driven inflammation in all clinical forms of MS and suggest that control over disease (RRMS and BEMS) is associated not with lack of inflammation per se, but rather with the activation of immune-mediated anti-inflammatory mechanisms. These results could help the design of novel diagnostic and therapeutic approaches.
LETTER TO THE EDITOR

AN UNUSUAL CASE OF INFECTIOUS MONONUCLEOSIS PRESENTING WITH ADVANCED LYMPHADENOPATHY AND ASCITES

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We report a case of infectious mononucleosis initially presented with lymphoma-like features. Examinations revealed abdominal ascites, splenomegaly, elevated lactic dehydrogenase, extensive lymphadenopathy from neck to the mediastinum, and a high¹⁸F-fluoro-2-deoxy-D-glucose uptake pattern on positron emission tomography scan. The impression of lymphoma could not be ruled out based on the clinical manifestations, most importantly the diffuse necrosis with focal monotonous pattern and a high Ki-67 proliferation index found on pathological examination. Our presentation emphasizes the potential challenge in misdiagnosis of advanced infectious mononucleosis. Knowledge of its unusual clinical features is therefore essential to avoid misdirected interventions when it mimics diseases like lymphoma.
CONTACT ALLERGY TO DISPERSE RED DYE: A NEW SENSITIZER

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Recently an increasing prevalence of contact allergy to dyes has been described, but the diagnosis often fails because of a lacking anamnesis and the absence of these allergens in most patch test standard series. Herein, we report the case of a male patient affected by an unusual hand contact dermatitis to disperse red dye.
LETTER TO THE EDITOR

KYRLE’S DISEASE: TREATMENT WITH MINOCYCLINE AND TOPIC TACALCITOL

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Kyrle’s disease is a rare perforative skin dermatosis. It was first described in 1916 by J. Kyrle, under the name of hyperkeratosis follicularis et parafollicularis in cutem penetrans. It refers to a disorder of keratinization, which usually appears as scattered or grouped hyperkeratotic papules on the extremities and the trunk characterized by extrusion of keratotic material into an epidermal invagination.
LETTER TO THE EDITOR

INFLAMMATION AND NEUROTTRANSMISSION OF THE VESCICO-UTERINE SPACE IN CESAREAN SECTIONS

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Collagen IV and laminin play a key role in regulating stiffness, elasticity and flexibility of the vescico-uterine space (VUS) tissue. The neurotensin (NT), the neuropeptide tyrosine (NPY) and the protein gene product 9.5 (PGP 9.5) possessing vasorelaxation and tissue vascularization activities, play key roles in cervical ripening, scar innervations and pain control. We propose that the integrity of these substances in VUS tissue is compromised after Cesarean section (CS), since wound healing disturbances and pelvic pain, as well as pregnancy and delivery complications, are related with lower uterine segment dysfunctions after CS. Therefore, the contents of collagen IV, laminin, NT, NPY and PGP 9.5 nerve fibres from the VUS tissue samples obtained during the first CS and the repeated CS were comparatively studied. VUS specimens were collected from 104 patients during CS and evaluated by immunohistochemistry. Collagen IV and laminin were mostly found in the vascular membrane bounds and their images were quantitatively evaluated by Quantimet Leica analyzer software. Differences of collagen IV, laminin, NT, NPY and PGP 9.5 values in VUS tissue between the first CS and the repeat CS samples were calculated by Student’s t-test. Reduced laminin and increased collagen IV values were observed in the VUS scar tissue after the repeated CS in comparison with those of VUS intact tissue obtained during the first CS. Significantly higher values of nerve fibres, containing NT, NPY and PGP 9.5 were in VUS tissue between the first CS and the repeat CS samples were calculated by Student’s t-test. Reduced laminin and increased collagen IV values were observed in the VUS scar tissue after the repeated CS in comparison with those of VUS intact tissue obtained during the first CS. Significantly higher values of nerve fibres, containing NT, NPY and PGP 9.5 were registered in intact VUS tissue samples, respectively 5±0.7, 7±0.6 and 5±0.9 CU, than those of VUS scar tissue samples obtained during the repeated CS, respectively 3±0.6, 2±0.4 and 3±0.7 CU (p<0.05). The authors observed increased collagen IV and reduced laminin values after the repeated CS which might be the key signs of inflammatory damage of VUS scar tissue by CS. These findings were strengthened by the registration of decreased NT, NPY and PGP 9.5 values in the same samples, which are important neurotransmitters and are responsible for optimal wound healing, pain control and lower uterine segment functions.
LETTER TO THE EDITOR

THE ELUSIVE BUT PATHOGENIC PEPTIDOGLYCAN OF CHLAMYDIAE

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Chlamydia species cause a broad spectrum of diseases in humans including severe chronic sequelae related to persistent forms. Despite the lack of detectable amounts of peptidoglycan, several studies suggest the presence of small quantities of peptidoglycan or its derivative at least in some stages of the growth cycle. Based on recent discovery in Chlamydiae of the aminotransferase pathway for biosynthesis of meso-diaminopimelic acid, we demonstrated the up-regulation of the gene (cp0259) encoding L,L-diaminopimelate aminotransferase in chlamydial persistent forms. This finding may be important in the search for target molecules to diagnose and treat Chlamydia-associated chronic diseases.
LETTER TO THE EDITOR

HELCOBACTER PYLORI HP0175 PROMOTES THE PRODUCTION OF IL-23, IL-6, IL-1β AND TGF-β

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Helicobacter pylori infection induces a chronic gastric inflammatory infiltrate. This study was undertaken to evaluate the type of the innate immune responses elicited by the secreted peptidyl-prolyl cis-trans isomerase of H. pylori (HP0175). The cytokine production induced by HP0175 in neutrophils, and monocytes was evaluated. HP0175 was able to induce the expression of IL-23 in neutrophils, and monocytes, and IL-6, IL-1beta and TGF-beta in monocytes. These findings indicate that HP0175 is able to promote the activation of innate cells and the production of a cytokine milieu that may favour the development of Th17 response.
Type A aortic dissection (TAAD) is a severe cardiovascular disease with high mortality rates. Current evidence suggests inflammation as the main mechanism of its complex pathophysiology. Accordingly, in this study the eventual presence of inflammatory cells in aorta specimens and any contribution of these cells in both apoptosis and metalloproteinase levels were assessed. The potential relationship between plasma inflammatory molecules and TAAD was also detected. In addition, implication in TAAD susceptibility of ten common and functional single nucleotide polymorphisms (SNP)s of six candidate genes (CCR5, TLR4, ACE, eNOs, MMP-9 and -2) was determined. Thus, histo-pathological and immunoistochimical aorta examination, TUNEL testing, genotyping of ten SNPs were performed. Levels of plasma inflammatory molecules were also determined using ELISA technique. A significant inflammatory infiltrate was observed in the examined aortas. Consistent with these data, significantly higher plasma levels of systemic inflammatory mediators characterized the cases. In addition, a high risk genotype significantly associated with TAAD susceptibility was identified. Thus, inflammation producing MMPs, cytokines and death mediators seem to be the shared pathological mechanism for TAAD in the population examined.
LETTER TO THE EDITOR

DOES HELICOBACTER PYLORI INFECTION INCREASE THE LEVELS OF EXHALED NITRIC OXIDE?

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It has been suggested that H. pylori infection upregulates iNOS expression and synthesis of nitric oxide (NO). In order to extend the scope, exhaled NO in H. pylori-infected patients with chronic gastritis was investigated. Exhaled oral NO level was measured with Niox Mino® analyzer, twice before and six-seven months after successful H. pylori eradication therapy in 26 patients with gastritis and in 16 healthy non-atopic subjects. Exhaled NO was significantly increased in H. pylori-infected patients with chronic gastritis as compared with the healthy subjects. Following eradication the levels were significantly reduced compared to the basal level before the therapy and did not differ significantly from those of the healthy subjects. It seems that H. pylori-associated gastritis is accompanied by an increased level of exhaled NO, resulting probably from the locally increased NO production.
LETTER TO THE EDITOR

CONSERVATIVE SURGICAL APPROACH FOR REDUCTION OF MACROCHEILITIS CAUSED BY MASSIVE INJECTION OF LIQUID SILICONE

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Cosmetic lip augmentation, regardless of the filling agent, is nowadays one of the most requested aesthetic procedures. Liquid silicone injections were used in the past, but after reports of severe late complications their use has been discontinued, ending with a permanent ban in most western countries. In this report we describe clinical presentation, diagnostic pathways and surgical reconstruction of six patients presenting with macrocheilia due to previous liquid silicone augmentation. Patients showed chronic inflammation of the lower third of the face, lip eversion, various degrees of asymmetry and functional impairment of the lips. All patients underwent preoperative soft tissue High Frequency Ultrasound (HFUS) and Magnetic Resonance Imaging (MRI) of the of the face to obtain evidence of the filler material and to ascertain its diffusion within the soft tissues of the perioral region. Conservative surgery was carried out to remove foreign material and to restore symmetric aesthetically pleasing lips. Histology confirmed the siliconoma diagnosis. HFUS and RMI allowed to clearly identify the silicone within the soft tissues. The conservative surgery restored the harmonious relationship between the lips, with an improvement in lip functionality at long term follow-up. Healing was complete and uneventful in all of the patients.
LETTER TO THE EDITOR

INTRA VENOUS IMMUNOGLOBULIN THERAPY WHEN PLASMAPHERESIS FAILS IN THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH SEVERE ADAMTS 13 DEFICIENCY IN CHILDHOOD: A CASE REPORT

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Thrombotic thrombocytopenic purpura (TTP) is a disorder of the blood-coagulation system, causing extensive microscopic clots to form in the small blood vessels throughout the body. TTP is quite a rare pathology in childhood, being more frequent among adults. Often it is hardly to distinguish from other haematological pathologies in children both for its uncommon incidence and for the presence of clinical forms that are heterogeneous and difficult to classify. We report the case of an 11-year-old girl suffering from TTP, in whom the study of metallo-protease ADAMST 13 showed a low value (< 10%) with positive anti-ADAMTS 13 Ig G and inhibitor, strengthening the hypothesis of autoimmune genesis. The girl was initially treated with cycles of plasmapheresis with both poor compliance and benefit for the girl and later treated with IV Immunoglobulin. This last treatment resulted in a rapid improvement of the symptomatology and no reappearance of the clinical signs at four-year follow-up.
LETTER TO THE EDITOR

LACK OF SYSTEMIC SIDE EFFECTS OF LONG-TERM INHALED FLUTICASONE PROPIONATE USE IN A COHORT OF ASTHMATIC CHILDREN


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Inhaled corticosteroids (ICS) are established as first-line therapy for persistent asthma in children. Fluticasone propionate (FP) has been used because it has equivalent efficacy when used at half-dose of older-generation ICS and has a comparable safety profile. However, concerns persist about the potential risk of adverse effects of long-term FP therapy on childhood growth, bone, adrenal function and immune system. To evaluate the potential adverse effects of FP, we analyzed growth, glucidic metabolism, hypothalamic-pituitary-adrenal axis, bone metabolism, bone mass density and immune system in a cohort of 19 children (average 102±18 months), with asthma who were in treatment with FP (average duration: 14 months, range: 11-17 months). Of these, 11 children homogenous for control of asthma symptoms, and compliance to therapy, were selected for a prospective study during which they were treated with FP 250 mg/day for further 6 months (total period of treatment average duration: 22 months, range: 18-23 months). In all children, no alterations of growth, glucidic metabolism, hypothalamic-pituitary-adrenal axis, bone metabolism, bone mass density, immune system nor severe exacerbation of the disease were observed. Our study, showing that FP was able to control the symptoms of asthma and confirming the lack of systemic side effects at the recommended doses, supports its long-term use in children with asthma.
LETTER TO THE EDITOR

CD3 AND CD20 EXPRESSION IN TITANIUM vs ZIRCONIA PERI-IMPLANT SOFT TISSUES: A HUMAN STUDY

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The aim of this study was to investigate the presence of an inflammatory infiltrate in the peri-implant soft tissue of single-implant crowns supported by either zirconia or titanium abutments in healthy subjects. Serial sections from formalin-fixed, paraffin-embedded blocks from peri-implant mucosa of 25 patients were immunohistochemically analyzed for CD3 and CD20 lymphocyte marker expression. The results showed that levels of T cells (CD3) were higher around zirconia than titanium abutments (p<0.05). On the contrary, the levels of B cells (CD20) were found higher around titanium abutment in comparison with the zirconia abutment. These differences were statistically significant (p<0.05).
Frontal fibrosing alopecia (FFA) and lichen planopilaris (LPP) are classified as scarring alopecia. Most authors consider FFA as a clinical variant of LPP on the basis of their similar histological findings; other authors think these pathologies are two different entities. We studied 48 cases of FFA and 86 cases of LPP. Clinical diagnosis was histologically confirmed and all patients underwent videodermoscopy. Moreover, histological study, identifying the main targets of these diseases, results helpful to confirm the diagnosis. FFA selectively affects vellus-like hair in the frontoparietal region and is characterized by a mild skin atrophy and a total loss of follicular openings. In LPP an involvement of total preterminal, terminal and vellus-like follicles, partial or total loss of follicular openings, diffuse hair thinning and twisting, perifollicular erythematous or violaceous papules and mild/severe spinous follicular hyperkeratosis with scalp sclerosis are the features observed. Videodermoscopy improves diagnostic capability, appearing to be helpful to underline FFA and LPP features, confirmed by histologic studies which identify and show different intensity of inflammatory process. Therefore, the two diseases could be considered two different entities on the basis of the different clinical features and the different targets, that can be related to a different pathogenetic mechanism.