EDITORIAL

ROLE OF VITAMIN D IN CHILDREN WITH RESPIRATORY TRACT INFECTION

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It has recently been shown that vitamin D (VitD) plays an important role in host defences, inflammation and immunity. We reviewed PubMed and selected all of the studies published over the last 15 years concerning VitD deficiency and VitD supplementation in children with respiratory tract infections. Our analysis showed that VitD seems to be very important because of its part in the complexity of the immune system. However, there are few pediatric studies and most have various limitations. First of all, the literature mainly refers to studies concerning the prevalence of VitD insufficiency and deficiency in specific pathologies. Secondly, it is extremely difficult to identify a common specific range of normal, insufficient and deficient VitD levels. Thirdly, the available studies of VitD supplementation often combined VitD with the use of other micronutrients, thus obscuring the role of VitD itself. Finally, different doses have been used for VitD supplementation. These observations clearly highlight the fact that further studies are needed to evaluate the impact of VitD deficiency and insufficiency in terms of the epidemiology and outcomes of pediatric respiratory tract infection, and whether VitD supplementation favours a positive outcome.
Congenital HCMV infection is the most frequent congenital infection, with an incidence of 0.2-2.5% among all live births. About 11% of infected newborns show symptoms at birth, including hepatosplenomegaly, thrombocytopenia, neurologic involvement, hearing impairment and visual deficit. Moreover, 5-25% of the asymptomatic congenital HCMV-infected neonates will develop sequelae over months or even years. The relevant social burden, the economic costs of pre-natal screening, post-natal diagnosis, follow-up and possible therapy, although still limited, are the major factors to be considered. Several types of vaccines have been explored in order to develop an effective and safe HCMV vaccine: live attenuated, subunit, vectored, peptide, DNA, and subviral ones, but none are available for use. This review illustrates the different vaccine types studied to date, focusing on the possible vaccination strategy to be implemented once the HCMV vaccine is available, in terms of target population.
IL-36 RECEPTOR ANTAGONIST WITH SPECIAL EMPHASIS ON IL-38

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IL-36 is another family member of IL-1 and induces the production of proinflammatory cytokines and activates MAPK and NFκB pathways. IL-36 is a common mediator of innate and adaptive immune response and is inhibited by IL-36 receptor antagonist (RA). IL-36RA acts on IL-36 receptor ligand which exerts proinflammatory effect \textit{in vivo} and \textit{in vitro}. IL-38 binds to IL-36 receptor as does IL-36RA and has similar biological effects on immune cells. IL-38 is also a member of IL-1 cytokine and shares some characteristics of IL-1RA, binding the same IL-1 receptor type I. IL-38 plays a role in the pathogenesis of inflammatory diseases, exerting protective effect in some autoimmune diseases. Both IL-38 and IL-36RA have an anti-inflammatory biological effect, however in some cases have contrary effects.
Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation, bone erosion, and cartilage destruction in the joints. It is increasingly being realized that inflammation might play an important role in inducing bone damage in arthritis. However, there is limited validation of this concept in vivo in well-controlled experimental conditions. We addressed this issue using the adjuvant arthritis (AA) model of RA. In AA, the draining lymph nodes are the main sites of activation of pathogenic leukocytes, which then migrate into the joints leading to the induction of arthritis. We tested the temporal kinetics of mediators of bone damage [e.g., receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG) and osteopontin (OPN)] and inflammation (pro-inflammatory cytokines and chemokines) in the draining lymph node cells (LNC) at different phases of AA, and then examined their inter-relationships. Our study revealed that, together with cytokines/chemokines, some of the mediators of bone remodeling are also produced in LNC. Various cytokines/chemokines showed distinct kinetics of expression as well as patterns of correlation with mediators of bone remodeling at different phases of the disease. Pro-inflammatory cytokines such as TNF-α are known to play an important role in bone damage. Interestingly, there was a positive correlation between TNF-α and RANKL, between RANKL and each of the 3 chemokines tested (RANTES, MIP-1α, and GRO/KC), and between TNF-α and RANTES. Our results in the AA model lend support to the concept of osteo-immune crosstalk during the course of autoimmune arthritis.
HIGH CIRCULATING CHEMOKINES (C-X-C MOTIF) LIGAND 9, AND (C-X-C MOTIF) LIGAND 11, IN HEPATITIS C-ASSOCIATED CRYOGLOBULINEMIA

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(C-X-C motif) ligand 9 and (C-X-C motif) ligand 11 (CXCL9 and CXCL11), are potent chemoattractants for activated T cells, and play an important role in T helper 1 (Th1) cell recruitment in chronic hepatitis C. No study has evaluated CXCL9, together with CXCL11, circulating levels in patients with mixed cryoglobulinemia and hepatitis C (MC+HCV-p). The aim of the present study therefore was to measure serum CXCL9, and CXCL11 levels, in MC+HCV-p, and to relate the findings to the clinical phenotype. Serum CXCL9 and CXCL11 were measured in 71 MC+HCV-p and in matched controls. MC+HCV-p showed significantly higher mean CXCL9 and CXCL11 levels than controls (P < 0.001, for both), in particular, in 32 patients with active vasculitis (P < 0.001). By defining high CXCL9 or CXCL11 level as a value of at least 2 SD above the mean value of the control group (> 100 pg/mL): 89% MC+HCV-p and 5% controls had high CXCL9 (P < 0.0001, chi-square); 90% MC+HCV-p and 6% controls had high CXCL11 (P < 0.0001, chi-square). In a multiple linear regression model of CXCL9 vs age, ALT, CXCL11, only CXCL11 was significantly (r = 0.452, P < 0.0001) and independently related to CXCL9. Our study demonstrates in MC+HCV-p vs controls: (i) high serum CXCL9, and CXCL11, significantly associated with the presence of active vasculitis; (ii) a strong relationship between circulating CXCL9 and CXCL11. Future studies on a larger cohort of patients are needed to evaluate the relevance of serum CXCL9 and CXCL11 determination as clinico-prognostic marker of MC+HCV.
CD1d-ASSOCIATED EXPRESSION OF NF-κB AND CARDIAC DYSFUNCTION IN DIABETIC AND OBESE MICE

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In patients with obesity and diabetes mellitus, abnormal production of inflammatory factors may result in cardiovascular dysfunction. In the current study, we tested the impact of CD1d-mediated innate immune responses on the expression and activation of NFκB in the hearts of adipose diabetic (db/db) mice. Splenocytes from adult db/db and CD1d-knockout mice of both genders and their wild-type, C57BL/6 and Balb/C counterparts were examined for tumor necrosis factor (TNF)-α and TNF-α receptor type 1. The percentage of natural killer T (NKT) cells in CD3+ T cells was compared with that in nondiabetic control mice. Despite the absence of inflammatory infiltrates, the hearts of db/db mice showed alterations in TNF-α receptor-1 and NFκB activity, including increased expression of both the NFκB p52 and p65 subunits. In the hearts of CD1d-knockout mice, p52 expression was reduced, while p65 expression remained largely unchanged. On echocardiography, the ratio of E to A transmitral flow velocities (an indicator of diastolic function) was significantly decreased in db/db mice after they swam for 30 minutes. These results provide evidence for CD1d-mediated NFκB activation and diastolic dysfunction in the hearts of db/db mice. Therefore, CD1d-associated abnormalities of innate immune responses and TNF-α production in splenic tissue may contribute to NFκB activation and cardiac dysfunction in type 2 diabetes.
Asthma is a chronic airway inflammatory disease associated with airway hyperresponsiveness which affects subjects with genetic predisposition. An association has been reported between some polymorphisms in various cytokine genes and asthma. Most of them are single nucleotide polymorphisms (SNPs). These polymorphisms are detected in the protein coding sequence or in the promoter region thus influencing cytokine production. We investigated the involvement of SNP mapping in 5 cytokine genes in mild to severe asthmatics of Italian Caucasians. The frequency of alleles and genotypes, relatively to 10 allelic specificities of the cytokine genes, was defined in 57 asthmatics and in 124 control subjects by a Polymerase Chain Reaction-Sequence Specific Primer method.

TNF-α –308A and TNF-α –238A allele frequencies were higher in asthmatics than in controls (p<0.001). Significant differences in the frequency of IL-4 –590T allele and of IL-4Rα +1902A allele were also detected in asthmatics in comparison with controls (p<0.001 and p=0.005, respectively). Similarly, IL-1α -889C allele was present in 84.1% of asthmatics and in 70.2% of controls (p=0.013). Furthermore, the IL-4Rα +1902A/A and IL-1α -889C/C homozygous conditions and the TNF-α -308G/A, TNF-α -238G/A, IL-4 -590T/C and IL-10 -1082G/A heterozygous conditions were significantly associated with asthma (p<0.05). ACA haplotype of IL-10 was observed only in asthmatic patients. This study reports, for the first time, the frequency of 10 different single nucleotide polymorphisms in 5 cytokine genes in the Italian Caucasians. Furthermore, we also indicate that in our population some single nucleotide polymorphisms are associated with mild to severe bronchial asthma.
This study investigates the effects and possible molecular mechanisms of corilagin extraction on prevention of *Schistosoma japonicum* ova-induced granulomas and liver fibrosis. As a result, under a light microscope, when compared to a model group, the corilagin group showed smaller granulomas, less liver cell denaturation and less inflammatory cell infiltration, and the connective tissues were significantly decreased. By Masson staining, the liver sections from the corilagin group showed less collagen distributed around granulomas, decreased liver fibrosis in the portal tracts and less formed interlobular tissue. The expression of hydroxyproline, IL-13 in liver and GATA3 in spleen in the model group was significantly higher than that in the normal group (P<0.05 or 0.01), while the level of hydroxyproline, IL-13 and GATA3 in the corilagin group were significantly lower than that in the model group (P<0.05). In conclusion, corilagin extraction can decrease the level of Th2-associated profibrotic cytokine IL-13, and down-regulate the transcription of GATA3 mRNA in spleen cells, which alleviate the hepatic fibrosis caused by egg granuloma in *Schistosoma japonicum* infection.

"ACTIVITY OF CORILAGIN ON POST-PARASITICIDE LIVER FIBROSIS IN SCHISTOSOMIASIS ANIMAL MODEL"

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This study investigates the effects and possible molecular mechanisms of corilagin extraction on prevention of *Schistosoma japonicum* ova-induced granulomas and liver fibrosis. As a result, under a light microscope, when compared to a model group, the corilagin group showed smaller granulomas, less liver cell denaturation and less inflammatory cell infiltration, and the connective tissues were significantly decreased. By Masson staining, the liver sections from the corilagin group showed less collagen distributed around granulomas, decreased liver fibrosis in the portal tracts and less formed interlobular tissue. The expression of hydroxyproline, IL-13 in liver and GATA3 in spleen in the model group was significantly higher than that in the normal group (P<0.05 or 0.01), while the level of hydroxyproline, IL-13 and GATA3 in the corilagin group were significantly lower than that in the model group (P<0.05). In conclusion, corilagin extraction can decrease the level of Th2-associated profibrotic cytokine IL-13, and down-regulate the transcription of GATA3 mRNA in spleen cells, which alleviate the hepatic fibrosis caused by egg granuloma in *Schistosoma japonicum* infection.
This study investigates whether KMUP-1 improves hepatic ischemia-reperfusion (I/R) and hypoxic cell injury via inhibiting Nox2- and reactive oxygen species (ROS)-mediated pro-inflammation. Rats underwent ischemia by occlusion of the portal vein and hepatic artery for 45 minutes. Reperfusion was allowed for 4 h. Serum was used for analysis of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). DNA extracted from liver homogenate was analyzed by electrophoresis to observe the fragmentation. Lipid peroxidation (LPO) was evaluated by measuring thiobarbituric acid-reactive substances (TBARS). NO and ROS contents were measured using Griess reagent and 2′-7′-dichlorofluorescein, respectively. Proteins levels were visualized by Western blotting. Liver damage was observed under a microscope. Intravenous KMUP-1 (0.25, 0.5 and 1 mg/kg) reduced I/R-induced ALT and AST levels, DNA fragmentation, ROS and malondialdehyde (MDA) and restored the NO levels of I/R rats. KMUP-1 protected the liver architecture from worsening of damage and focal sinusoid congestion, increased endothelium NO synthase (eNOS), guanosine 3′, 5′cyclic monophosphate (cGMP), protein kinase G (PKG) and the B-cell lymphoma 2/Bcl-2-associated X protein (Bcl-2/Bax) ratio, attenuated phosphodiesterase 5A (PDE-5A) and cleaved caspase-3 expression in I/R-liver. In hypoxic HepG2 cells, KMUP-1 increased cGMP/PKG, restored peroxisome proliferator-activated receptor-γ (PPAR-γ) and decreased matrix metalloproteinases-9 (MMP-9), Rho kinase II (ROCK II), hypoxia-inducible factor-1α (HIF-1α) and vascular endothelium growth factor (VEGF). KMUP-1 protects liver from I/R-injury and hypoxic hepatocytes from apoptosis-associated free radical generation and pro-inflammation by restoring/increasing NO/cGMP/PPAR-γ, reducing ROS/Nox2 and inhibiting ROCKII/MMP-9.

Key words: oxidative stress, ischemia-reperfusion liver injury, hypoxic cell apoptosis, pharmacology
Allergic rhinitis (AR) is characterized by IgE-mediated immediate hypersensitivity and usually progresses to chronic nasal inflammation, with depression as one of its comorbidities. The importance of treating the depression in AR patients has been increasingly recognized. Desipramine is a representative of tricyclic-antidepressant agents. In the present study we investigate whether desipramine has therapeutic effects on AR inflammation. BALB/C mice were sensitized by intraperitoneal injection of ovalbumin (OVA), followed by repeated challenge with OVA intranasally. Desipramine was administered orally to treat the mice. The nasal symptoms (sneezing, nasal scratching etc.) of AR were evaluated to determine the severity of AR. Cytokines in the nasal lavage fluid (NALF), including interferon-γ (IFN-γ), interleukin 4 (IL-4) and serum OVA-specific immunoglobulin E (IgE) antibody were measured by ELISA. The regulatory T cells (T_{reg}) and T helper cells 17 (T_{h17}) were quantified by flow cytometric analysis. As a result, the repeated oral administration of desipramine attenuated the nasal symptoms (sneezing and nasal rubbing) in AR mice. Desipramine also suppressed the serum OVA-specific IgE and IL-4 levels, but had no effect on IFN-γ level. Moreover, desipramine treatment up regulated CD4^{+}CD25^{+}Foxp3^{+}T_{reg} cells, which were found down-regulated in established AR mice. Meanwhile, desipramine administration attenuated CD4^{+}IL-17^{+}T_{h17} cells, which were significantly increased in AR mice. These results suggest that the antidepressant drug, desipramine, also has anti-allergic action, which was possibly achieved by reducing allergen-specific IgE and T_{h2} cytokine production and maintaining a balance between T_{reg} and T_{h17} cells. Thus, this study provide the first evidence that desipramine may be utilized to treat allergic diseases, especially for those allergic patients with depression or depression patients with allergy.
REGULATORY T-CELL MODULATION BY GREEN TEA IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Regulatory T cells (Tregs) are considered to be key immunomodulatory cells of the immune system and are increased in chronic lymphocytic leukemia (CLL). Rai stage 0 identifies patients with early stage CLL for which there is no effective intervention at the present time and a “wait and see” policy is usually adopted. Some biological and clinical studies have reported that green tea constituents, such as epigallocatechin-gallate (EGCG), have antitumor effects on hematologic malignancies including CLL. We report data on a clinical trial in which green tea extracts were given orally to 12 patients with stage 0 CLL and 12 healthy subjects. Ten patients and 10 controls completed the 6-month scheduled therapy. Two patients and 2 controls stopped therapy within 1 month because of tachycardia and epigastralgia. Eight out 10 evaluable patients (80%) showed a reduction of lymphocytosis and absolute number of circulating Tregs, as well. One patient (10%) had a stabilization of lymphocytosis and a reduction of Tregs, and 1 patient (10%) showed an increase of both lymphocytosis and Tregs. Only the non-responding patient progressed after 5 months from the end of green tea administration and chemotherapy was given. Interestingly, both IL-10 and TGF-β serum levels declined throughout the green tea intake period, in both patients and controls. These data seem to indicate that green tea is able to modulate circulating Tregs in CLL patients with early stage of the disease. This can result in the control of lymphocytosis as well as in the prevention of disease progression.
Hyaluronic acid is a major component of many extracellular matrices that plays a role in the regulation of vasomotor tone and mucous gland secretion, and in the modulation of the inflammatory process in upper and lower airways. This pilot study was aimed at evaluating the effects of nasal washes with 9 mg nebulised sodium hyaluronate given for 15 days per month over 3 months in 75 paediatric patients with recurrent upper respiratory tract infections (URTI). Eligible patients were randomized to treatment with nasal washes containing 9 mg sodium hyaluronate plus saline solution or saline alone, according to an open-label, parallel group design, with blind observer assessment. Ciliary motility, which was assessed based on a 0-3 point rating scale (0 = absent, 1 = < 5 minutes, 2 = ≥ 5 and ≤ 10 minutes, 3 = > 10 minutes) was the primary study endpoint. The secondary efficacy variables included cytological (presence of neutrophils, eosinophils and mast cells), microbiological (presence of bacteria and mycetes), endoscopical (presence of adenoid hypertrophy and biofilm) and clinical (presence of rhinitis, post-nasal drip, nasal dyspnoea) parameters. The two treatment groups (mean age 7.5 years, 53% of males) were comparable for baseline data, except a higher mean age in the control group than in the treated group. Treatment with 9 mg sodium hyaluronate was associated with significantly greater improvements (p<0.001 between groups) in primary outcome ciliary motility [odds ratio (OR) 13.61; 95% CI 4.51-41.00 in the univariate regression analysis that examined the probability of improvement]. Treatment with 9 mg sodium hyaluronate was also significantly superior to saline alone in adenoid hypertrophy (p<0.001; OR 14.72; 95% CI 4.74-45.68), presence of bacteria (p = 0.026; OR 2.95; 95% CI 1.15-7.55), neutrophils (p = 0.002; OR 4.51; 95% CI 1.75-11.62), rhinitis (p = 0.040; OR 10.47; 95% CI 3.10-35.31), nasal dyspnoea (p = 0.047; OR 3.80; 95% CI 1.09-13.19) and biofilm (p = 0.049; OR 9.90; 95% CI 2.61-37.47). Advantages of 9 mg of sodium hyaluronate over control on post-nasal drip and presence of mycetes (although evident) did not reach the level of statistical significance. The superiority of the treated group over saline alone was confirmed in a multivariate logistic regression analysis that took into account age as confounding factor. The number of days of absence from school was significantly lower in the 9 mg sodium hyaluronate group compared to controls (p<0.001 between groups). A 3-month intermittent treatment with 9 mg sodium hyaluronate with nasal washes plus saline solution was associated with significant improvements in ciliary motility and in cytological, microbiological, endoscopic and clinical outcomes compared to saline, in children with recurrent URTI.
HYALURONAN PLUS SALINE NASAL WASHES IN THE TREATMENT OF RHINO-SINUSAL SYMPTOMS IN PATIENTS UNDERGOING FUNCTIONAL ENDOSCOPIC SINUS SURGERY FOR RHINO-SINUSAL REMODELING

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Hyaluronic acid is a major component of many extracellular matrices and plays a central role in the homeostasis of physiology in upper and lower airways. When topically administered following endoscopic sinus surgery, hyaluronic acid may be effective in functional recovery and in the prevention of recurrence of chronic rhinosinusitis. This pilot study was aimed at evaluating the effects of nebulised 9 mg of sodium hyaluronate given for 15 days per months over 3 months in 46 patients aged > 4 years who underwent functional endoscopic sinus surgery (FESS) for rhino-sinusal remodelling. Eligible patients were randomized to receive nebulised 9 mg sodium hyaluronate nasal washes plus saline solution or 5 ml saline alone (23 patients in each group), according to an open-label, parallel group design, with blind observer assessment. Treatment was administered by means of a nasal ampoule that allows nebulisation of particles with a median aerodynamic diameter > 10 micron, i.e. suitable for upper respiratory airways deposition. The efficacy variables included clinical (presence of nasal dyspnoea), endoscopical (ostium of paranasal sinuses, oedema, respiratory patency, synechiae, and appearance of nasal mucosa) and cytological (ciliary motility and presence of neutrophils, eosinophils, mast cells, bacteria, mycetes and bio film) measures. At the end of the study, patients expressed an opinion on the overall tolerability of treatment. The two treatment groups were comparable at baseline. Treatment with 9 mg of sodium hyaluronate was associated with significantly greater improvements compared to controls in nasal dyspnoea (p<0.001), presence of mycetes (p = 0.044), ciliary motility (p<0.001) and abnormalities in nasal secretions. A univariate logistic model, in which the odd ratio (OR) indicates the probability of success in the 9 mg sodium hyaluronate group compared to the control group, showed that the highest OR was observed for presence of nasal dyspnoea (OR = 21.36; 95% CI: 1.07 to 426.56), normal mucosa at endoscopy (OR: 9.62; 95% CI: 1.82 to 50.89), ciliary motility (OR: 7.27; 95% CI: 1.68 to 31.42) and presence of bio film (OR: 4.41; 95% CI: 1.26 to 15.40). Treatment with 9 mg sodium hyaluronate plus saline was well tolerated. A 3-month intermittent treatment with 9 mg sodium hyaluronate plus saline solution nasal washes following FESS for rhino-sinusal remodelling was associated with significant improvements in nasal dyspnoea, appearance of nasal mucosa at endoscopy and ciliary motility compared to saline alone.
Human pituitary tumor transforming gene 1 (PTTG1) is an oncogenic transcription factor that is overexpressed in many malignancies, especially cancers with metastatic potential, while transgelin-2 (TAGLN2) is an actin-binding protein shown to be a tumor suppressor. However, the expression and clinical significance of PTTG1 and TAGLN2 in pancreatic cancer remain unclear. The present study aimed to investigate the expression and clinical significance of PTTG1 and TAGLN2 in human primary pancreatic cancer. Seventy-five cases of human pancreatic cancer tissues were collected. The expression of PTTG1 and TAGLN2 protein was assessed using immunohistochemistry (IHC) through tissue microarray procedure. The clinicopathologic characteristics of all patients were analyzed. As a result, the expression of PTTG1 and TAGLN2 in cancerous tissues showed the positive staining mainly in the cytoplasm, and they were found in cancerous tissues with higher strong reactivity rate compared with the adjacent non-cancer tissues (ANCT) (56.0% vs 22.7%, \( P<0.001 \); 100% vs 84%, \( P=0.002 \)), elevating with the ascending order of tumor malignancy. Furthermore, the positive expression of PTTG1 was associated with the gender of pancreatic cancer patients, but did not correlate with their age, pathological styles, tumor size, tumor sites, TNM staging, perineural infiltration and distant metastasis (each \( P>0.05 \)). In addition, Spearman rank correlation analysis showed the positive correlation of PTTG1 with TAGLN2 (\( r=0.624, P<0.001 \)). Taken together, PTTG1 and TAGLN2 are highly expressed in human pancreatic cancer, and the positive expression of PTTG1 is associated with the gender of cancer patients, suggesting that it may represent a potential therapeutic target for the treatment of pancreatic cancer.
THE ROLE AND CLINICAL SIGNIFICANCE OF YES-ASSOCIATED PROTEIN 1 IN HUMAN OSTEOSARCOMA

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Yes-associated protein 1 (YAP1) is an oncogene that plays multiple roles in the tumorigenesis and progression of many malignances. The present study aimed to investigate the clinical significance of YAP1 expression in human osteosarcoma (OS) and explore the molecular mechanisms of YAP1 activity in OS MG-63 cells. The expression of YAP1 was assessed by immunohistochemical assay using a tissue microarray procedure. A loss-of-function approach was used to investigate the effects of small hairpin RNA-mediated knockdown of YAP1 on the expression of RUNX2, CyclinD1, and matrix metalloproteinase-9 (MMP-9) as well as the proliferative activities and invasive potential in OS MG-63 cells (evaluated by MTT and Transwell assays, respectively). The expression of YAP1 protein in OS tissues was significantly higher than that in ANCT, and was closely associated with gender \( (P = 0.013) \) and Enneking staging \( (P = 0.035) \), but it did not correlate with age, tumor location, or distant metastases of OS patients \( (P > 0.05, \text{ each}) \). Knockdown of YAP1 resulted in downregulation of the expression of RUNX2, CyclinD1, and MMP-9 and inhibited the proliferation and invasion of MG-63 cells. Our findings suggest that YAP1 is highly expressed in OS tissues, and increased expression of this molecule is correlated with the gender and Enneking staging of osteosarcoma patients. Knockdown of YAP1 may inhibit the proliferation and invasion of OS cells through downregulation of the RUNX2 pathway, thereby representing a potential therapeutic target for the treatment of cancer.
EVALUATION OF THE EXPRESSION AND ROLE OF IGF PATHWAY BIOMARKERS IN HUMAN SARCOMAS

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Recent studies have shown that insulin-like growth factor (IGF) signaling components have been involved in the pathogenesis and progression of different types of sarcomas. There has been some evidence to indicate the differential expression of IGF2 and insulin-like growth factor 1 receptor (IGF1R) in human sarcomas. The present study utilized immunohistochemistry (IHC) and in situ hybridization (ISH) to determine the expression of IGF2 and IGF1R in eighty-two cases of human sarcoma specimens and eight cases of non-tumor tissue (NTT). IGF2/IGF1R signaling was blocked by recombinant adenovirus-mediated IGF1R small hairpin RNA (shIGF1R), which was used to transfect into human osteosarcoma (OS) MG-63 cells. The expression of IGF2, IGF1R, matrix metallopeptidase-2 (MMP-2) and MMP-9 was detected by Real-time PCR. Cell migration was evaluated by wound healing assay. As a consequence, the expression of IGF1R and IGF2 was found in human OS with higher strong reactivity rate compared with the NTT (85.0% vs 50.0%, P=0.022; 95.0% vs 100.0%, P=0.042), elevating with the ascending order of tumor malignancy. Also, IGF1R had differential expression in different types of sarcomas (P=0.002), while IGF2 had no significant difference (P=0.105). Targeted blockade of IGF2/IGF1R signaling decreased the expression of IGF2, IGF1R, and MMP-2/-9, and diminished the migration capabilities of MG-63 cells. In conclusion, IGF1R is differentially-expressed in different types of human sarcomas, and targeted blockade of IGF1R pathway may inhibit human OS migration through down-regulation of MMP-2/-9 expression. IGF1R pathway may represent a significant therapeutic modality for the treatment of sarcomas.
KNOCKDOWN OF AXL RECEPTOR TYROSINE KINASE IN OSTEOSARCOMA CELLS LEDS TO DECREASED PROLIFERATION AND INCREASED APOPTOSIS

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Dysregulation of the Axl receptor tyrosine kinase (RTK) has been implicated in the development and progression of a variety of malignancies. Axl is known to activate strong anti-apoptotic signaling pathways that promote oncogenesis. However, the role of Axl plays in osteosarcoma (OS) remains elusive. The present study aimed to investigate the clinical significance and function of Axl in human OS. Forty cases of OS and corresponding adjacent non-cancerous tissues (ANCT) were collected. The expression of Axl was assessed using immunohistochemical assay through tissue microarray procedure. A loss-of-function experiment was performed to investigate the effects of small hairpin RNA (shRNA)-mediated knockdown of Axl on the expression of p-AKT, poly ADP-ribose polymerase (PARP) and Ki-67, the proliferative activities, indicated by MTT assay, and the apoptotic index in OS MG-63 cells. As a result, the expression of Axl was found in OS tissues with higher strong reactivity rate, compared with the ANCT (75.0% vs 20.0%, \( P=0.000 \)), but it did not associate with the age, gender, tumor size, TNM staging and distant metastases (each \( P>0.05 \)). Furthermore, knockdown of Axl inhibited the proliferative activities and induced apoptosis in MG-63 cells with decreased expression of p-AKT, and Ki-67 and increased expression of PARP. In conclusion, our findings suggest that Axl is highly expressed in most of the OS tissues compared with the ANCT, and knockdown of Axl inhibits proliferation and induces apoptosis of OS cells possibly through downregulation of the AKT pathway, suggesting that our findings may provide new insights into the potential therapeutic target for cancer.
Fibrinogen-based sealants have been used to improve hemostasis after total hip replacement (THR) with conflicting results. We therefore conducted a double-blind randomized controlled trial to determine whether the commercially available fibrin sealant Quixil is effective in reducing the volume of red blood cell transfusions, postoperative blood loss and postoperative hemoglobin drop. Patients with coxarthrosis scheduled for primary cementless THR, were enrolled in a single hospital setting and randomized to either a fibrin sealant group (n=35) or a negative control group (n=35). The surgeon was blind to group allocation until the moment of fibrin application, while the cardiologist determining the need for transfusions remained blind throughout the intervention. In the fibrin sealant group, less blood was lost in the first 48 hours (median, 125 vs 200 ml), fewer patients required allogeneic blood transfusion (1 vs 6 in the control group), and fewer total units of allogeneic blood were transfused (2 vs 12). These differences, however, were not significant partly due to confounding from the use of autologous transfusion of predeposited blood (according to a more liberal regime) and intraoperative autologous blood reinfusion in some patients of both groups. Excluding these last individuals from analysis, no remaining patient of the fibrin sealant group had an allogeneic blood transfusion that, instead, was carried out on 5 patients (23.8%) of the control group (p=0.048). Overall postoperative hemoglobin drop from baseline was significantly less in the fibrin-treated group on day 7 (mean, 3.5 vs 4.5 g/dl; p=0.02). No adverse events were associated with fibrin treatment. These results strengthen the evidence in support of the safety and efficacy of the use of fibrin sealant in improving hemostasis after THR. Clinical trial registration: EudraCT 2008-002024-28.
RAGE GENE POLYMORPHISM IN HEART FAILURE PATIENTS WITH AND WITHOUT ANGIOGRAPHIC EVIDENCE OF SIGNIFICANT CORONARY ATHEROSCLEROSIS

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Heart failure (HF) is a multifactorial disorder in which clinical, environmental and genetic components take part. For this reason it is possible that common gene variants could affect development, progression and response to pharmacological therapy. In recent years the role of AGEs in the pathogenesis of cardiovascular diseases has become recognized but little is known about the role of the AGE–RAGE system in heart failure. The aim of the present study was to identify possible relationship between -374 T/A RAGE gene polymorphism with heart failure. The population in this study consists of 386 subjects with HF, selected according to the presence of depressed Left Ventricular Ejection Fraction (LVEF) <45%, and 639 patients with CAD documented at coronary angiography. Within the population with HF there are 228 patients with disease secondary to non-ischemic cause and 158 with post-ischemic condition. The sample of AA genotype was significantly lower in patients with post-ischemic HF in respect to HF secondary to non-ischemic causes (p<0.001). A significant difference between the two groups was also observed regarding the allele frequency. In addition, differences in the allelic and the genotypic frequencies of homozygous genotypes were found between the HF patients free from evidence of coronary significant lesions and patients with at least one hemodynamically significant coronary lesion, both HF and CAD. In patients with at least one vessel compromised the presence of A allele and the homozygous AA genotype were significantly lower than in patients with lesion-free coronary. In conclusion, our research reveals that the -374 T/A polymorphism is related to the genesis of atherosclerotic coronary artery disease but not to its evolution. The protective role of AA genotype in respect to atheromatous disease is therefore confirmed also in the HF population with non-ischemic origin.
Inferior turbinate hypertrophy (ITH) is the main cause of nasal obstruction symptom. This study aimed at investigating whether a particular cellular pattern could be a predictive factor for failure of medical treatment for ITH in patients with rhinitis. Globally, 258 patients with chronic nasal obstruction due to ITH were evaluated by: visual analogue scale assessment of symptoms, skin prick tests, fiber-endoscopy, active anterior rhinomanometry, and nasal cytology. All patients were treated with drugs for 3 months and then re-evaluated.

The symptom improvement depended on the different cellular pattern. There was improvement in: 54 (51.4%) patients with allergic rhinitis, 72 (69.2%) with non-allergic rhinitis with neutrophils (NARNE), 15 (42.8%) with non-allergic rhinitis with eosinophils (NARES), and 9 (64.3%) with non-allergic rhinitis with mast cells/non-allergic rhinitis with eosinophils and mast cells (NARMA/NARESMA). The non-responders (108; 41.9%) were therefore directed towards surgical treatment. Both patients with allergic rhinitis and patients affected by NARES had a higher failure rate to medical treatment compared with NARMA and NARESMA groups (p<0.01). In conclusion, elevated number of eosinophils, in the nasal secretion of both allergic (allergic rhinitis) and non-allergic (NARES) patients with ITH, can be associated to a higher medical treatment failure rate.
LETTER TO THE EDITOR

GRAVES’ DISEASE, HYPOPARATHYROIDISM, SYSTEMIC LUPUS ERYTHEMATOSUS, ALOPECIA, AND ANGIOEDEMA: AUTOIMMUNE POLYGLANDULAR SYNDROME VARIANT OR COINCIDENCE?

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Data on coexisting Graves’ disease (GD), hypoparathyroidism, and systemic lupus erythematosus (SLE) are limited. The thyroid and parathyroid glands may be extra sensitive to irradiation damage in an underlying autoimmune condition. A 34-year-old black woman presented with tetanic-like cramps, easy skin bruising, fatigue, weight gain, nocturia and back pain. She was previously diagnosed with GD in 2001 and underwent radioiodine therapy (RAI) in 9/01 using 6 mCi. PostRAI (November 2001) she developed hypocalcemia and hypothyroidism (2/02). In 2007, SLE was diagnosed. In October 2009, s-calcium and PTH were still low at 7.1 mg/dl and 9 pg/mL, respectively, although the patient denied symptoms on vitamin D and calcium supplementation. To identify possible autoimmune damage of the parathyroids, we evaluated the presence of activating antibodies to the CaSR and also analyzed the DNA sequence of all 6 translated exons and flanking intronic sequences of her CaSR gene for a functionally significant CaSR mutation but neither was positive. The initial autoimmune damage to her thyroid and possibly parathyroid glands followed by irradiation of them seems to have contributed to her developing both hypoparathyroidism (11/01) and hypothyroidism (2002). The patient could potentially have had parathyroid autoantibodies in 2001 that disappeared by 2009 when she was tested for them. We consider that the multiple autoimmune conditions developed over the past decade of her life with the concurrent irradiation contributing to her brittle hypoparathyroidism. Select patients with GD and perhaps parathyroid autoantibodies with a slowly developing destructive impact on the parathyroid glands may then develop overt hypoparathyroidism with rather low dose RAI ablation. This patient adds to the evolving spectrum of polyglandular syndrome variants.
Adamalisyynes (ADAMs) play an important role in inter-membrane interactions, cell adhesion and fusion processes and protein shedding from the cell surface. Many reports indicate that members of the ADAMs family are overexpressed in human cancer. The aim of the present study was to evaluate ADAM28 and Insulin Like Growth Factor Binding Protein-3 (IGFBP-3) gene expression in colorectal carcinoma tissues with regard to the overweight or obese status of the patients using an oligonucleotide microarray technique. Fresh tissue specimens were obtained from colorectal cancer patients during surgical treatment. Eighteen specimens from tumour and 18 normal tissue specimens from colorectal cancer patients at clinical stages III and IV were analysed. The examined patients were divided into two groups; those with BMI ≥ 25 and those with normal BMI. The control group consisted of 18 specimens of non-neoplastic colon tissues, which were divided between overweight/obese and normal body weight patients. The gene transcriptional activity from the specimens was analysed using an oligonucleotide microarray technique. Microarrays and rinsing and marking solutions were prepared according to the procedure in the Gene Expression Analysis Technical Manual. The following conclusions were made: i) change of ADAM28 and IGFBP-3 genes expression are present in the normal tissue in overweight/obese patients with colorectal cancer only; ii) the observed molecular variability of ADAM28 and IGFBP-3 expression may be an initial process of cancer proliferation; iii) the histopathologically normal surgical margin in this group of patients was not equal to the molecular margin.
LETTER TO THE EDITOR

MELKERSSON-ROSENTHAL SYNDROME IN A PATIENT WITH PSORIATIC ARTHRITIS RECEIVING ETANERCEPT

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Melkersson-Rosenthal syndrome is a rare granulomatous neuro-mucocutaneous systemic disease that is characterized by relapsing peripheral facial paralysis, orofacial edema and fissured tongue. The disease etiology is still not well known, but it has been hypothesized that a possible role is played by various causal agents such as infectious diseases, genetic causes, allergic conditions, benign lymphogranulomatosis, various associations with other pathological conditions, particularly with immune-mediated diseases and food contact allergies. In this report we describe the case of a woman, 42 years old, with psoriatic arthritis who developed neurological episodes related to MRS after treatment with anti-TNF therapy. This finding further supports the hypothesis that TNF-α blockade, and particularly the use of the TNF-α receptor, could trigger the development of granulomatous lesions in predisposed patients. The case we report further sustains the importance for the clinician to take into account this potential adverse event in patients receiving anti-TNF-α therapies.
PERFORMANCES OF AN IMPROVED DEVICE FOR SKIN PRICK TESTS

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Every day allergists deal with skin prick testing. Following a recent paper showing that the intrevenous needle and the metal lancets are superior to the Stallerpoint® plastic lancet, the manufacturer has improved the device to reach better standards in terms of sensitivity, intra-patient reproducibility and inter-patient reproducibility, as demonstrated on 10 adult patients, comparing the results with skin tests performed with the intravenous needle. We evaluated the sensitivity of the device by calculating the ratio between the number of true-positive tests and the sum of true-positive and false-negative tests. To assess the reproducibility of the test, we calculated the interpatient and the intrapatient coefficient of variation between the mean diameters of the papules induced by the different techniques. The improved device shows performances similar to those obtained with the intravenous needle.
Infection of the oral cavity and dentures by Candida species are frequent in denture wearers. C. albicans is the most common pathogen; however, other emerging Candida species are also responsible for this condition. Few data are available about the occurrence of Candida species in the oral cavities of denture-wearing immigrants to Italy. In this study, we compare the Candida species found in the oral mucosa and on dentures from a population of denture wearing immigrants to Italy to a matched Italian group. Oral swabs were collected from dentures and the underlying mucosa of patients enrolled in the study and were then cultured to test for the presence of Candida species in each sample. Out of 168 patients enrolled (73 Italians and 95 immigrants), 51 Italians (69.8%) and 75 immigrants (78.9%) tested positive for the presence of Candida. Candida albicans was the most frequently observed species overall; however, we found a higher occurrence of C. glabrata among immigrants than among Italians. In addition, immigrants displayed a higher incidence of Candida – associated stomatitis and a lower mean age than Candida-positive individuals from the Italian group. Immigrants are more prone to longer colonization of the oral mucosa and dentures by Candida. In these patients, dentures must be checked periodically to prevent the presence of Candida.
LETTER TO THE EDITOR

SHORT-TERM TOLERABILITY OF MORNIFLUMATE IN PATIENTS WITH CUTANEOUS HYPERSENSITIVITY REACTIONS TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Morniflumate is the morpholinoethyl ester of niflumic acid, a non-steroidal anti-inflammatory drug, derived from nicotinic acid. We studied 112 patients who had experienced cutaneous reactions after using non-steroidal anti-inflammatory drugs. Only two of all the patients who underwent an oral challenge with morniflumate had a positive result to the test. By demonstrating the low incidence of reactions to morniflumate through oral challenges, we suggest that patients with non-steroidal anti-inflammatory drug hypersensitivity may tolerate this drug which would therefore be a useful alternative.
LETTER TO THE EDITOR

SYSTEMIC NICKEL ALLERGY: ORAL DESENSITIZATION AND POSSIBLE ROLE OF CYTOKINES INTERLEUKINS 2 AND 10

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Nickel ingested with food can elicit either systemic cutaneous or gastrointestinal symptoms causing a systemic nickel allergy syndrome (SNAS) that can be treated with tolerance by oral ingestion of the metal. It has been suggested that interleukins 2 (IL-2) and 10 (IL-10) are involved in the mechanisms underlying oral tolerance. We evaluated the clinical efficacy of oral desensitization therapy in SNAS consisting in the administration of nickel sulphate. Because nickel allergy prevalently affects women, only female subjects (N = 22) were recruited. Oral nickel desensitizing therapy was associated with low-nickel diet for three months. Before and after therapy, clinical conditions were evaluated, and circulating cytokines IL-2 and IL-10 were measured. After the two-year treatment, visual analogue scale (VAS) scores for symptoms were significantly reduced (P < 0.001). Patients were released by either cutaneous or gastrointestinal symptoms and by tolerating nickel-containing food. At the end of the treatment, nickel oral challenge test was negative in 18 patients, and IL-2 level in the serum was significantly reduced while IL-10 was increased, although this datum was not statistically significant. Our study confirms the clinical efficacy of nickel oral immunotherapy and focuses on the mechanisms triggered by oral tolerance indicating that reduction of IL-2 can be associated with success of oral nickel desensitizing therapy.
LETTER TO THE EDITOR

ULCERS CAUSED BY BULLOUS MORPHEA: SUCCESSFUL THERAPY WITH N-ACETYLCYSTEINE AND TOPICAL WOUND CARE

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Bullous morphea is an uncommon form of localized scleroderma. The pathogenesis is unknown and treatment of coexistent ulcers is difficult. The pathogenesis of bullae formation in morphea is multifactorial, but reactive oxygen species production appears to play a key role. We report a patient with bullous morphea with long-standing ulcers whom we successfully treated with N-acetylcysteine and topical wound care. N-acetylcysteine, an antioxidant sulfhydryl substance, promotes the healing of ulcers in patients with bullous morphea.
LETTER TO THE EDITOR

LATEX-FRUIT SYNDROME IN ITALIAN CHILDREN AND ADOLESCENTS WITH NATURAL RUBBER LATEX ALLERGY

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Approximately 30-50% of individuals with natural rubber latex (NRL) allergy show an associated hypersensitivity to particular plant-derived foods, which has been defined “latex-fruit syndrome” (LFS). In our population of 22 patients with IgE-mediated NRL allergy we found a relevant prevalence (36%) of LFS, which resulted significantly higher in the group of patients with more severe clinical manifestations of NRL allergy than in patients with contact symptoms due to NRL (78% vs 8%; p<0.005).
LETTER TO THE EDITOR

EXPRESSION OF CD7, CD20 AND CDX-2 IN A SECONDARY SIGNET-RING CELL TUMOR OF THE PROSTATE: A CASE REPORT

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As is well-known, signet ring cell carcinoma (SRCC) rarely appears as a histological finding in the prostatic tissue. Nevertheless, a differentiation should be made between a primary tumor and a metastatic disease. We describe the case of a 52-year-old man with lower urinary tract symptoms, serum total PSA of 0.2 ng/ml, elevated serum CEA and CA19-9 levels. Two years prior to presentation, he underwent total gastrectomy with histological findings indicating “poor differentiated adenocarcinoma with signet-ring cell”. A palpable nodule was found on digital rectal examination and for this reason he underwent 12-core transperineal prostate biopsy with a diagnosis of “poor differentiated adenocarcinoma with signet-ring cell and adipose tissue infiltration”. Immunohistochemical examinations revealed positivity for PAS, CK7 and CDX-2, focal positivity for CK20 and negativity for PSA and PSAP. The diagnosis of a prostatic secondary SRCC was possible given the positivity to CK7, CDX-2, focal positivity to CK20 and negativity to PSA.
LETTER TO THE EDITOR

A CASE OF CEPHALIC TETANUS IN A DEVELOPED COUNTRY

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Tetanus is a potentially life-threatening infection that results from contamination of skin wound by Clostridium Tetani spores. Although, it remains an important health problem in developing countries without strict national immunization programs, this condition is rare in the developed world. The most frequent presenting symptoms are trismus and dysphagia, due to the spasmodic contraction of the masticatory muscles. Then the disease usually diffuses with a descending pattern inducing a generalized contraction of the agonist and antagonistic muscles, which characterize a tetanic spasm. Mortality usually results from respiratory failure, cardiovascular collapse, or autonomic dysfunctions. Treatment usually requires the prompt admission to the intensive care unit to avoid the development of potential life-threatening complications. We report the case of a 78-year-old farmer, who was referred to us with progressive onset of lock-jaw and muscular stiffness of the facial region, that had occurred after he had scratched himself with a rose. The recognition of the presenting signs of cephalic tetanus allowed the prompt management of the infection. However, because of the rarity of this condition, the clinicians may be unfamiliar with the clinical presentation, and be unsuspecting of the diagnosis.
LETTER TO THE EDITOR

OVERUSE OF PRESCRIPTION AND OTC NON-STERoidal ANTI-INFLAMMATORY DRUGS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

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Non-steroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to have significant cardiovascular and gastrointestinal toxicity; high dose of intake and concomitant use of multiple compounds or corticosteroids are factors that increase the risk of NSAID toxicity. In this paper we described our experience on NSAIDs misuse (both prescribing and OTC formulations), particularly relevant in the setting of rheumatoid arthritis (39.5% of patients) and osteoarthritis (47% of patients). We also evaluated causes underlying NSAIDs misuse (e.g. not satisfactory pain control, other painful conditions, etc).