Intestinal inflammation is associated with various pathological diseases, such as gastritis Helicobacter pylori infection, Crohn’s and colitis in inflammatory bowel disease, and colorectal cancer. Thus, treatment with anti-inflammatory substances in these inflammation-associated diseases is critical. Increasingly compelling evidence indicates that glutamine is an anti-inflammatory compound candidate because it can influence the long-term outcome of the inflammatory diseases with a low-risk way. However, before recommending its use in clinical practice, it is important to elucidate the molecular mechanism by which glutamine exerts its roles in modulating intestinal inflammation. In this study, we review the current knowledge on the detailed regulation pathway used by glutamine in its proinflammatory regulation, with a special emphasis on intestinal inflammation. These regulation pathways include nuclear factor kappa B (NF-κB), signal transducer and activator of transcription (STAT), mitogen-activated protein kinases (MAPK), phosphoinositide-3-kinases (PI3K)/ PI3K-protein kinase B (Akt), activating protein-1 (AP-1), nitric oxide synthases (NOS)-nitric oxide (NO), peroxisome proliferator-activated receptor-γ (PPARγ), heat shock factor-1 (HSF-1)- heat shock proteins (HSP) and glutathione (GSH) - reactive oxygen species (ROS). Although some regulatory pathways, such as PI3K/ PI3K-Akt, GSH-ROS and AP-1, need to be further investigated, this review provides useful information to utilize glutamine as an immunonutritional or pharmaconutritional drug, not only for inflammation-associated diseases in the intestine, but also possibly for other inflammatory-associated diseases, i.e. arthritis, asthma, type 2 diabetes, etc.
PHARMACOLOGICAL IMPORTANCE OF SIMPLE PHENOLIC COMPOUNDS ON INFLAMMATION, CELL PROLIFERATION AND APOPTOSIS WITH A SPECIAL REFERENCE TO β-D-SALICIN AND HYDROXYBENZOIC ACID

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Simple phenolic (SP) compounds are natural products that exhibit multiple pharmacological functions. The best known of these compounds is β-D-salicin, the first discovered phenolic glycoside and salicylic acid, or 2-hydroxybenzoic acid (2-HBA). Both of these compounds have attracted the interest of scientists in various interdisciplinary fields, including chemistry, pharmacology and medicine. Although β-D-salicin is found in various plants, it is often associated with willow, as it was first discovered in this species of plant. While the presence of glucose in β-D-salicin improves the physicochemical properties of the benzyl moiety, β-D-salicin itself does not have anti-inflammatory or anti-proliferative activity until it is metabolised into 2-HBA in the gastrointestinal tract and blood stream. Likewise, the majority of 2-acetoxybenzoic acid (2-ABA), or acetoxysalicylic acid also undergoes metabolic hydrolysis into 2-HBA. 2-HBA has been shown to play a role in modulating both inflammation and cancer partly through the inhibition of cyclooxygenase-2 (COX-2). It is now clear that 2-HBA most likely acts on the transcription factor NF-κB, which regulates the transcription of COX-2 thereby suppressing inflammation and cell proliferation and promoting apoptosis. Other phenolates, also exhibit anti-inflammation and anti-proliferation activities like the 4-hydroxybenzoate zinc (4-HBZn) complex, which was previously shown to preferentially inhibit COX-2 compared to 2-HBA and ASA. This review aims to collect all the available information related to β-D-salicin and other SP compounds in order to promote a new perspective of this interesting class of compounds and encourage further research into their pharmacological and clinical properties.
EDITORIAL

USE OF TOPICAL OR SYSTEMIC STEROIDS IN CHILDREN WITH UPPER RESPIRATORY TRACT INFECTION

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Steroids have long been used to improve a number of clinical conditions because of their role in reducing inflammatory responses, but their use has always been limited because of their possible long-term side effects. The aim of this review is to establish whether steroids can have a positive effect on the outcome of some pediatric upper respiratory tract infections. We used PubMed to select all of the studies on topical or systemic steroids, and their therapeutic use in children with rhinosinusitis (RS), acute otitis media (AOM), otitis media with effusion (OME), acute pharyngitis (AP), or periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), published over the last 15 years. Although a generally significant improvement in signs and symptoms has been observed with the use of intranasal steroids in children with RS, it is not clear which molecule should be recommended, how long treatment should be continued, or whether the benefits are limited to allergic children. No high-quality studies on the use of topical or systemic steroids in AOM have been carried out, and the results of studies of OME are controversial. The potential positive effects of steroids in children with AP are too slight to justify their use, and their possible adverse effects (particularly in the case of repeated administration) have not been clearly evaluated. Oral corticosteroids seem to be effective in resolving the symptoms of PFAPA, although they do not prevent future fever cycles. These findings show that further randomised and controlled studies are required in order to approach upper respiratory tract infections correctly and avoid the risks associated with frequent steroid use.
Inflammation is a common albeit overlooked cause of local and systemic bone loss which results from an imbalance between bone formation and bone resorption. The Wnt pathway, which plays an essential role in the regulation of bone turnover, has been proposed as a potential molecular link between inflammation and inflammatory bone loss. We here recapitulate present knowledge about sclerostin, a Wnt pathway inhibitor, and bone damage in inflammation. A better understanding of sclerostin action and regulation might help in designing an effective treatment strategy in inflammatory bone loss.
Mast cells are essential not only for allergies but also for innate and acquired immunity, autoimmunity and inflammation, and they are recognized as a new type of immunoregulatory cells capable of producing different cytokines. Natural compounds have long been recognized to possess anti-inflammatory, antioxidant and anticancergetic activity. Quercitin is an inhibitor for mast cells and is a potent antioxidant, cytoprotective and anti-inflammatory compound and has a negative effect on intracellular regulator signal events initiated by FceRI receptor cross-linking and other activating receptors on mast cells. These observations candidate quercitin as a therapeutic compound in association with other therapeutic molecules. Capsaicin is a compound derived from peppers, especially capsicum, and is involved in stimulating circulation aiding digestion and relieving pain. Capsaicin receptor sub type I (VRI) is expressing in neurons and is present in a number of brain nuclei and in non-neuronal tissues, mediating inflammatory response. Capsaicin is involved in migraine, allergic symptoms, arthritis pain and gastric secretion. In this paper we review the biological effects of quercitin and capsaicin.
Cardiovascular diseases (CVD), due to accelerated atherosclerosis, are responsible for approximately 50% of mortality in End Stage Renal Disease (ESRD) patients undergoing haemodialysis (HD). Over the last decade, *Chlamydia pneumoniae*, a respiratory pathogen, has been involved in the pathogenesis of atherosclerosis and several reports have suggested the association between *C. pneumoniae* infection and CVD in HD patients. This report reviews the contribution of *C. pneumoniae* infection in cardiovascular diseases in ESRD patients, in light of recent studies on cardiovascular risk factors; we hypothesize that *C. pneumoniae*-infection may contribute to mineral bone disorder and, consequently, vascular calcification. However, further studies are needed to define the relationship between *C. pneumoniae* and bone and vascular disorders in HD patients.
RANTES GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A META-ANALYSIS

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A few recent studies have suggested that regulated on activation, normal T-cell-expressed and secreted (RANTES) polymorphisms (-403 G/A, -28C/G) are not associated with systemic lupus erythematosus (SLE). However, there still exist studies confirming this correlation. The objective of this study is to evaluate the relationship of RANTES and SLE using a meta-analysis. Pubmed, Embase, and Cochrane library databases were systemically searched. Data were extracted by two independent reviewers and pooled odds ratio (OR) with 95% confidence interval (CI) were calculated. Six studies were considered, including a total of 838 cases and 906 controls of -403 G/A, as well as 710 cases and 775 controls of -28C/G in this meta-analysis. The overall ORs and 95% CIs of -403A were 0.79, 0.64-0.97 (P=0.07); and 1.09, 0.64-1.87 (P=0.287) in dominant and recessive models, respectively. The overall ORs and 95% CIs of -28G were 0.64, 0.44-0.94 (P=0.379), and 0.63, 0.21-1.86 (P=0.580) in dominant and recessive models, respectively. No publication bias was found in this meta-analysis. This meta-analysis showed that RANTES-403 G/A and -28C/G were not associated with SLE.
Acupuncture is commonly used to relieve chronic pain worldwide. Accumulating evidence shows that peripheral opioid system plays an important role in inhibiting inflammatory pain. This study aimed to investigate the involvement of peripheral opioid system in electroacupuncture (EA) analgesia for prolonged inflammatory pain. Inflammatory pain was induced by an intraplantar injection of complete Freund’s adjuvant (CFA) into the right hind paw. EA (2/100 Hz, 2 mA) was applied to the ipsilateral Zusanli (ST36) and Kunlun (BL 60) acupoints for 30 min once everyday. Block studies on EA analgesia were performed on day 18 after CFA injection by using α-helical corticotrophin-releasing factor (CRF), a CRF antagonist, and naloxone methiodide, a peripherally restricted opioid receptor antagonist. Paw withdrawal latency (PWL) to a noxious thermal stimulus was measured as the pain behavioral change. Radioimmunoassay for beta-endorphin (beta-END), Met-enkephalin (Met-ENK), and dynorphin A (DYN A) in paw inflammatory tissue and immunohistochemistry study for mu, delta, kappa opioid receptors in dorsal root ganglion (DRG) were carried out. A subsequent validation experiment by locally delivered exogenous beta-END was also performed. We found that EA significantly increased the PWL of rats injected with CFA from day 4 to day 18. Locally administered α-helical CRF or naloxone blocked EA-produced analgesia. EA increased beta-END level in the paw inflammatory tissues, while CFA raised the local levels of Met-ENK and DYN A. The increased beta-END level by EA was fully reversed by α-helical CRF. Intraplantar injection of exogenous beta-END alleviated prolonged inflammatory pain. EA also up-regulated the expressions of mu, delta, kappa opioid receptors in rat L5 DRG. In conclusion, peripheral local beta-END and three subtypes of opioid receptors may be involved in EA analgesia for prolonged inflammatory pain.

INVOLVEMENT OF PERIPHERAL BETA-ENDORPHIN AND MU, DELTA, KAPPA OPIOID RECEPTORS IN ELECTROACUPUNCTURE ANALGESIA FOR PROLONGED INFLAMMATORY PAIN OF RATS


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HIGH AVIDITY ANTI-β2-GLYCOPROTEIN I ANTIBODIES ACTIVATE HUMAN CORONARY ARTERY ENDOTHELIAL CELLS AND TRIGGER PERIPHERAL BLOOD MONONUCLEAR CELL MIGRATION

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Anti-β2-glycoprotein I antibodies (aβ2GPI) represent a potential pathogenic candidate for coronary artery diseases. High avidity aβ2GPI (HAv aβ2GPI) are known to be associated with thrombotic and obstetric manifestations in patients with antiphospholipid syndrome, who are also susceptible to the development of premature atherosclerosis. However, there is little information about how human coronary artery endothelial cells (HCAEC) are affected by HAv aβ2GPI. The purpose of our study was to evaluate the pathophysiological effects of HAv aβ2GPI on HCAEC and determine their influence on cytokine expression and migration of peripheral blood mononuclear cells. Following the two hit hypothesis, we co-stimulated HAv aβ2GPI-treated HCAEC in the presence and absence of the acute phase protein serum amyloid A (SAA). HAv aβ2GPI induced in vitro HCAEC dysfunction, through the ERK1/2 signaling pathway, promoted the expression of chemokines (MCP-1, GROα and IL-8) and IL-6, which led to the attraction and migration of peripheral blood mononuclear cells. These effects were potentiated and intensified in conditions with SAA, indicating that HAv aβ2GPI, in the presence of physiological concentrations of acute-phase proteins represent pathogenic autoantibodies, which could lead to the development of premature atherosclerosis and/or thrombosis development.
ESSENTIAL OIL EXTRACTED FROM RHIZOMA OF *ATRACTYLODE LANCEA* INDUCES ONCOSIS IN HUMAN MKN-45 CANCER CELLS

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The aim of this study was to examine whether the essential oil extracted from rhizoma of *Atractylode lancea* has cytotoxicity to human MKN-45 cancer cells and its underlying mechanisms. The cytotoxicity of essential oil to cancer cells was examined by MTT assay. The effects of essential oil and disruption were monitored using whole-cell, time-lapse recording by microscopy. The effects of essential oil on cytoskeletal systems were detected by Western blotting and immunofluorescence. The effects of essential oil on cytokine secretion were measured by ELISA. The result showed that the cytotoxicity of essential oil was triggered rapidly by 2 μl/ml (1 h caused 50% maximum cytotoxicity) and involved secretion function perturbation. In addition, essential oil could induce membrane blebbing within 1 h of sustained application, which was blocked by polyethylene glycols (PEG) with molecular weights £3350, but not prevented by PEG with molecular weight³4000 and extracellular calcium chelator EGTA. Moreover, essential oil did not disrupt cytoskeletal systems as demonstrated with no degradation of microtubules and actin. In conclusion, essential oil extracted from rhizoma of *Atractylode lancea* can rapidly initiate acute injury and burst via oncosis and may offer a novel therapeutic strategy for cancer treatment.
INFLAMMATORY SIGNATURE AFTER LOW DOSE γ-RADIATION IN MICE BRAIN AND GUT: SWITCH FROM THERAPEUTIC BENEFIT TO INFLAMMATION

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Low dose γ-radiation (LDIR) has been used as curative/adjuvant/palliative treatment modality for a variety of medical conditions. However, LDIR has been casually linked to NFκB activation and inflammation. Here, we investigated the kinetics of cyto/chemokines and their influence on inflammation in normal tissues after LDIR. C57BL/6 mice exposed to LDIR (2-50cGy) and sacrificed after 1 h-8 days were examined for alterations in 95 cyto/chemokines in brain and gut (QPCR profiling) and selectively validated by assessing secreted levels (ELISA). Kinetics of LDIR-induced inflammation was assessed using DNA fragmentation and histomorphological changes in brain and gut. LDIR induced a dose-dependent upregulation of cyto/chemokines after 2-50cGy in both brain and gut. Two genes, Csf3 and Tnfα, were upregulated in a ‘dose- and tissue-independent’ manner. Transcriptional kinetics revealed induction of more genes both in brain and gut in early response time (1-48 h) after LDIR. Conversely, only few genes upregulated and more genes downregulated in these tissues after extended response (4-8 days) period. DNA fragmentation and histomorphological analysis revealed consistent dose-, time- and tissue-dependent inflammation after LDIR. Also, serum levels of TNF-α, VEGFA, IFN-γ, GM-CSF, MCP-1 reinstigates the inflammatory signature after LDIR. Together, these results suggest that LDIR significantly inflicts a dose- and tissue-dependent inflammation in normal tissues and this induced inflammation may equivocate over-time and, hence frequency of LDIR use may control the switch from therapeutic benefit to inflammatory response.
Periodontitis is a chronic inflammatory disease caused by the interaction of plaque-associated bacteria with host cells. Gingival epithelial barriers provide the first line of defense against plaque-associated bacteria, the primary cause of periodontitis. To investigate the role of physical barriers in the pathogenesis of periodontitis, dextran sulfate sodium (DSS), a tight junction (TJ)-disrupting chemical, was applied onto the gingival mucosa of mice in the absence or presence of Porphyromonas gingivalis, and alveolar bone loss was measured. The levels of the TJ proteins ZO-1 and JAM-1, the number of T cells, and the presence of bacteria within gingival tissue were examined by immunohistochemistry and in situ hybridization, respectively. In addition, oral bacterial communities were analyzed by pyrosequencing. Here, we show that both DSS and P. gingivalis induced alveolar bone loss accompanied by the reduced ZO-1 expression in the junctional epithelia. This reduction in ZO-1 expression was associated with increased levels of bacteria and T cells within the gingival tissues. Furthermore, bacterial invasion was strongly correlated with T-cell infiltration, which was associated with alveolar bone loss. Interestingly, both DSS and P. gingivalis shifted oral flora from Proteus-dominant community to Escherichia-dominant ones. Collectively, these findings suggest that a barrier-disrupting periodontal pathogen or chemical can induce periodontitis by facilitating bacterial invasion into tissues, leading to a subsequent inflammatory response. The association between compromised physical barriers and periodontitis was further supported by the reduction of ZO-1 expression in the periodontal lesions of patients with chronic periodontitis. Therefore, physical barriers may be a promising future target for the prevention and treatment of periodontitis.
Esculetin is a coumarin derivative with high antioxidant activity. In a rat experimental model of inflammatory bowel disease induced by trinitrobenzenesulfonic acid, esculetin at the dose of 5mg/Kg displayed intestinal anti-inflammatory activity; however, its mechanism of action needs to be elucidated. Our objective was to evaluate the effects of esculetin on the intestinal inflammatory process and to clarify the mechanism of action of this compound. We also compared its effects with prednisolone and sulphasalazine. Our results demonstrate that treatment with esculetin prevented an increase in malondialdehyde content, counteracted the depletion of glutathione content, reduced epithelial cell apoptosis, reduced the secretion of pro-inflammatory cytokines, such as IL-1β, IL-2 and IFN-γ, in vitro, and reduced the colonic levels of TNF-α and IL-1β in vivo. Additionally, esculetin treatment inhibited MPO and AP activities. These results demonstrated that esculetin produced a more effective intestinal anti-inflammatory effect than sulphasalazine because it was used at a 10-fold lower dose, and it produced effects similar to those created by prednisolone. We suggest that esculetin exerts its activity by inhibiting pro-inflammatory cytokine secretion and increasing the defences against reactive oxygen species. This leads to less migration and/or activation of inflammatory cells, resulting in the improvement of lesions and functions in the intestinal epithelium. This study confirms the intestinal anti-inflammatory activity of esculetin and demonstrates that this compound has both antioxidative and immunomodulatory properties. Therefore, esculetin may be an interesting new anti-inflammatory drug for the treatment of inflammatory bowel disease.
The immunosuppressive drug Rapamycin (RAPA) has been shown to promote expansion of CD4+ IL-10+ natural human regulatory T cells (nTreg) in vitro and in vivo. RAPA effects on inducible Treg (Tr1) are unknown, and this study explores in vitro responses of Tr1 to this drug. CD4+CD25neg T cells isolated from PBMC of normal donors were used to generate Tr1 cells. Expanded Tr1 cells were tested for surface markers, expression of survival proteins, resistance to apoptosis and the ability to suppress proliferation of autologous CD4+CD25neg responder T cells (RC) in functional assays. RAPA was found to promote the generation of human Tr1 cells from autologous CD4+CD25neg precursors in peripheral blood. Tr1 cells + RAPA mediated higher suppression (p<0.01) of RC proliferation than Tr1 cells cultured without RAPA. Tr1 cells + RAPA also expressed higher levels of FasL and granzyme B (p<0.002), produced more IL-10 and TGF-β1 and were more resistant to activation-induced cell death (p<0.02). RAPA up-regulated expression of the Bcl-2 family anti-apoptotic proteins in Tr1. In addition, stimulation of Tr1 by LPS + RAPA resulted in increased proliferation and resistance to apoptosis. RAPA favors in vitro generation of inducible human Treg (Tr1) from CD4+CD25neg precursor cells and significantly enhances their survival and suppressor functions.

RAPAMYCIN EXPANDS AND CONFERS RESISTANCE TO APOPTOSIS OF HUMAN INDUCIBLE REGULATORY T CELLS (TR1)

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Cardiovascular disease is one of the leading causes of death worldwide. Controlled prospective studies and randomized clinical studies have shown that inflammation plays a major role in the pathogenesis of atherosclerosis, and that a chronic inflammatory systemic reaction increases the risk of cardiovascular, and cerebrovascular attacks. In recent years, many researchers have focused on defining a correlation between cardiovascular and periodontal diseases. The aim of the present study was to observe the effects of periodontal causal therapy on the level of specific inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) levels, before and after non-surgical periodontal therapy. A total of 64 patients were enrolled in the present study. Among these, 26 patients were affected by cardiovascular disease and periodontal disease, (MCV-Perio test group), whereas 38 patients were only affected by cardiovascular disease, without periodontal disease, (MCV control group). The MCV-Perio group was then sub-divided into two additional groups: Treated MCV-Perio test group, treated with non-surgical phase I periodontal therapy; Not-Treated MCV-Perio test group, not treated with any periodontal therapy. A comprehensive periodontal treatment was carried out at baseline. The non-surgical therapy treatment was conceived according to Full Mouth Therapy (FMT) treatment protocol, consisting of various phases delivered in a very short time. Blood samples were collected at baseline and re-evaluated in order to assess periodontal and inflammation marker changes. All values were registered as an average ± standard deviation (x ± SD) and Wilcoxon-Mann-Whitney test was used. It is interesting to observe that the serum concentrations of IL-6 and hs-CRP were higher in the group with cardiovascular and periodontal disease compared to the group with cardiovascular disease alone. Non-surgical periodontal treatment determined a dramatic improvement in the levels of the systemic inflammatory markers. The results of the present study show that non-surgical periodontal therapy performed according to the Full Mouth Therapy protocol may prove beneficial in reducing the levels of inflammatory markers typically associated with heart disease. Because the two pathologies share a certain number of common risk factors, this may be a hindrance in the correct interpretation of the results. Therefore, further evidence, represented preferably with a randomized controlled clinical design is necessary to interpret the results correctly.
EFFECTS OF PLASMA FROM PATIENTS AFFECTED BY MILD COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE ON CULTURED ENDOTHELIAL CELLS

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There is accumulating evidence that Alzheimer’s disease (AD) can have vascular contribution. In particular, endothelial dysfunction may impair nitric oxide (NO) production and cause cerebral hypoperfusion. Blood flow impairment can be provoked also by an increased production of reactive oxygen species (ROS). The present study was performed in order to investigate the effect of plasma from subjects affected by AD and mild cognitive impairment (MCI) on human aortic endothelial cells (HAECs) in vitro, since endothelial dysfunction has been suggested to be an early event in patients affected by AD. Plasma samples were obtained from 27 AD patients, 15 MCI subjects, and 19 age- and sex-matched healthy subjects. After a short incubation period the following parameters were evaluated: NO release, superoxide dismutase (SOD) and Na⁺/K⁺-ATPase activities, membrane fluidity, and thiobarbituric acid-reactive substance (TBARS) production. Exposure to MCI plasma provoked a decrease in NO release, more pronounced in the presence of AD plasma. Our data on SOD and Na⁺/K⁺-ATPase activities showed a similar trend, since the lowest values were recorded after incubation with AD plasma. Endothelial membrane fluidity was deeply affected by the exposure to MCI plasma, and even more following incubation with AD plasma. Finally, enhanced TBARS production after incubation with MCI and AD plasma was observed. In conclusion, our results showed that MCI and AD plasma affects endothelial cells, thus highlighting the need for early treatment aimed at protecting the endothelium.
Periodontal disease is characterized by inflammation and bone loss. The balance between inflammatory mediators and their counter-regulatory molecules may be fundamental for determining the outcome of immune pathology of periodontal disease. Cytokines play crucial roles in the maintenance of tissue homeostasis, a process which requires a delicate balance between anabolic and catabolic activities. In particular, two families of growth factors—such as transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF)—are thought to play important roles in modulating the proliferation and/or migration of structural cells involved in inflammation and regulation of immune responses. The aim of this work was to analyze gingival samples and periodontal tissue specimens collected from thirty-eight patients with chronic periodontal disease and from forty healthy individuals, in order to detect the expression and distribution of TGF-β1 and VEGF between the two groups. TGF-β1 and VEGF expression levels were detected using immunohistochemical analysis and computer-assisted morphometric analysis. The findings presented here suggest that biomarkers such as TGF-β1 and VEGF have an important regulating role in the orchestration of the immune response, which in turn influence the outcome of disease establishment and evolution.
ADALIMUMAB MODULATES ANGIOGENESIS IN PSORIATIC SKIN

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Angiogenesis plays a key role in the pathogenesis of psoriasis. New blood vessel formation occurs early during plaque lesion development in psoriatic skin, and sometimes precedes disease recurrence. TNF-α, a well established mediator of inflammation in psoriasis, up-regulates the transcription of several pro-angiogenic chemokines that are over-expressed in psoriatic skin and serum, promoting microvascular modifications in psoriatic plaque. Adalimumab is a fully human monoclonal antibody that blocks the interaction between TNF-α and its cell surface receptor, thus inhibiting the TNF-α dependent inflammatory cascade. The aims of this study were to investigate several angiogenic parameters involved in the pathogenesis of psoriasis, and to evaluate the ability of adalimumab to modulate them. Fifteen patients affected by psoriasis received Adalimumab 40 mg EOW for twelve weeks and were evaluated at baseline (T₀) and after treatment (T₁₂) for the following parameters: i) new blood vessels formation in lesional skin assessed by intra-vital video-capillaroscopy analysis (IVCP) and histology; ii) VEGF and Factor VIII expression in lesional skin detected by immunohistochemistry; iii) serological levels of several angiogenic chemokines detected by luminex assay. At baseline, newly formed capillaries in psoriatic plaque correlated with skin expression of VEGF and factor VIII and with serum levels of angiopoietin-2, IL-8, PDGF-BB, VEGF, but not with serum levels of follistatin, TNF-α, G-CSF, HGF, FGF, PECAM, IFN-γ, and TGF-α. All patients responded to adalimumab, reached PASI 50, and 70% achieved PASI 75 after twelve weeks of treatment. Although adalimumab administration for twelve weeks caused a dramatic decrease of new blood vessel formation, confirmed by IVCP (p<0.05), histology and immunohistochemical (p<0.05) analysis, we did not observe a parallel significant reduction of angiogenic chemokines in the serum. However, a positive correlation between the density of newly formed blood vessels in lesional skin and the serum levels of angiopoietin-2, IL-8, PDGF-BB, and VEGF, was still persisting after treatment.
The aim of this study was to evaluate the efficacy of the treatment of chronic ulcers with unfocused shock waves. Between March 2009 and February 2012 we studied a group of 124 patients, aged between 28 and 80 years, with serious wounds arisen over three months and who met the inclusion criteria for treatment. The patients were randomly divided into groups A and B, both treated with unfocused ESWT but with an average energy density for each impulse equal to 0.10 mJ/mm$^2$ in group A (total energy equal to 1.7 mJ for each shot) and an average energy density for each impulse equal to 0.04 mJ/mm$^2$ in group B (total energy equal to 3.3 mJ for each shot). The pulses were administered at a frequency of 4 Hz in both groups. Wounds were classified according to: location, width, length, percentage of granulation tissue, necrotic tissue, fibrous tissue, presence of bacterial exudation and pain (assessed by VAS). Their evolution was monitored by photo capture. The patients were treated with a frequency of 1 session every 7 days for 7 weeks. During the treatment period, the possible occurrence of side effects was monitored. Before treatment the wounds in group A had an average area equal to 3.85 cm$^2$ and the average value of the VAS pain scale was equal to 5.8 (range 2-9); the wounds in group B had an average area equal to 3.4 cm$^2$ and the average value of the VAS pain scale was equal to 5.7 (range 3-9). At the end of the treatment protocol the mean area in group A decreased by 80% (final mean area 0.93 cm$^2$), and the average pain on VAS scale dropped by 79%; the mean area in group B decreased by 67% (final mean area 1.2 cm$^2$) and the average score on VAS scale dropped by 48%. None of the treated patients experienced adverse reactions to treatment. None of the treated wounds developed infection during treatment. In conclusion, shock waves can act on difficult wounds, stimulating the reparative physiological process; therefore it represents an effective and safe procedure to accelerate the healing process, reducing the operating costs and avoiding more complex interventions.
A number of clinical trials have reported beneficial effects after nut consumption. The aim of the present work was to investigate the effect of natural almond skins (NS) on an animal model of acute pneumonia. Mice were inoculated with a multidrug-resistant strain of \textit{Pseudomonas aeruginosa} (PA, $2 \times 10^7$ cfu’s in 50 µl of lactated Ringer’s solution) into their left lung. An oral administration of NS (30 mg kg$^{-1}$) was given 1 h and 12 h after intra-tracheal PA inoculation. Mice were killed at 24 h for analyses of injury and inflammation. We investigated the effect of NS on the lung histology associated with PA, cytokine production, myeloperoxidase (MPO) activity and mortality caused by PA. Treatment with NS was effective in reducing the PA infection with a significant decrease in inflammation and lung injury. Significant inhibitions of the pro-inflammatory cytokines TNF-α and IL-12 and MPO activity were detected in mice which received NS compared with vehicle-treated animals. Treatment with NS reduced the overall mortality over the observation period (10 days). Almond skins were effective reducing the lung injury caused by PA inoculation in mice and may be useful in the treatment of antibiotic-resistant strains alone or in combination with existing antibiotics.
Psoriasis is a hyperproliferative inflammatory disease that is considered to be involved with both gene and environmental factors, such as stress. Serotonin plays an important role related to stress, and thus, can be a candidate for relieving disease symptoms. We investigated the expression of the serotonin gene receptor of the 5-HT3AR subtype on mononuclear blood cells in psoriatic patients as compared to healthy individuals. We isolated Peripheral Mononuclear Cells (PBMCs) from blood samples followed by total cellular RNA extraction, cDNA synthesis, and real-time PCR using primer pairs specific for 5-HT3AR mRNA and beta-actin mRNA as an internal control. Finally RT-PCR products were sequenced. Results showed that the expression of 5-HT3AR was significantly reduced (P<0.001) in patients compared to the healthy individuals group. However, there were no related nucleotide changes in the sequencing analysis of gene coding region. Our results raise the possibility of using 5-HT3A receptor specific drugs in the treatment of psoriasis.
The aim of the study was to evaluate possible involvement of environmental factors in the incidence of preeclampsia. A retrospective observational study on the seasonal variation of severe preeclampsia, derived from the intensive obstetric care unit files over a 48-month period, was undertaken. Obstetrics were studied and all deliveries and number of severe preeclamptic patients were recorded. The extracted data were then divided into four groups, based on the four main seasons of the year. The rates of severe preeclampsia, occurring in each season, were compared. Although there is a trend of higher incidence during summer, statistical difference was not significant (unpaired t-test: p=0.1250 for preeclampsia, p=0.1250 for total deliveries, and paired t-test: p=0.0027 for severe preeclampsia, p=0.0002 for total deliveries), perhaps due to the small numbers of the studied groups. In this study we found a prevalence of preeclampsia during summer when the weather is warmer than the other seasons. This finding may provide new possible mechanisms in the pathogenesis of preeclampsia.
LETTER TO THE EDITOR

WHAT IS ERYTHEMA ANNULARE CENTRIFUGUM? A FAMILIAL CASE

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We report a case of erythema annulare centrifugum present since birth in three generations in an Albanian family. The proband is a 45-year-old white Caucasian man; his mother (deceased), a 38-year-old sister and a 16-year-old niece presented with the same phenotype. To our knowledge this is the third case of familial annular erythema since its original description in 1966 by Beare et al. Autosomal dominant inheritance of the disorder is suggested.
LETTER TO THE EDITOR

ERYTHEMA MULTIFORME MAJOR AFTER WHOLE BRAIN RADIOTHERAPY: A CASE OF EMAR SYNDROME?

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We report the case of a woman with a 4-year history of metastatic breast carcinoma presenting a large erosive area on her scalp plus erosive lesions on the lips and in the mouth and erythematous plaques with vesicles on the trunk and upper limbs. In this case, contrary to other reports, the most important trigger for this syndrome was radiotherapy rather than the systemic medications administered. Therefore we propose the term EMAR (erythema multiforme associated to radiotherapy) to describe this case.
Thyroid Associated Ophthalmopathy (TAO) is a complex pathology to treat and a considerable threat for Graves’ Disease (GD) patients. Thus, there is great interest to find tools able to predict the onset and prognosis of TAO. Chronic inflamed tissues are characterized by tissue damage and recruitment of cells from the bloodstream, events that can lead to self-antigen exposure and induce autoimmune phenomena. In this study, we determined whether the occurrence of antibody anti-extracellular matrix (ECM) molecules [Collagen I, III, IV, V, laminin (LM) and fibronectin, (FN)], anti-smooth muscle (ASM), anti-nuclear antigen (ANA), anti-ribonucleoprotein (RNP) and anti-thyroid-stimulating hormone (TSH) receptor (TRAbs) were associated with TAO in GD patients. We analyzed serum of 50 patients affected by GD, 24 of whom were affected by TAO, and 40 healthy donors (HD). The occurrence of TRAbs or ANA, anti-SM and anti-RNP antibodies did not allow to discriminate TAO+ from TAO- GD patients. Among the 24 TAO+ and 26 TAO- patients, 15/24 and 17/26 displayed TRAbs, respectively. None of the GD patients displayed anti-RNP antibodies, while 20/24 TAO+ and 17/26 TAO- patients were found to be positive for ANA and 3/24 TAO+ and 4/26 TAO- patients showed anti-SM antibodies. Conversely, when compared with HD control sera, GD sera showed antibodies to all individual ECM molecules. Remarkably, anti-CIII autoantibodies of the IgG isotype were significantly associated with GD TAO+ patients (p=0.045). Indeed, 6 out of 24 GD TAO+ patients scored positive for anti-CIII IgGs as compared to only 1 out of 26 TAO-. Our results suggest the potential involvement of anti-ECM antibodies in GD and a contribution of anti-CIII IgGs in TAO pathogenesis of GD patients.
Breast cancer is the most common malignant disease among women, with a lifetime risk of approximately 10%. Frequent and well-known locations of metastases are bone, liver, lung, skin and brain, but tumour repetition has been seen in almost any anatomic site. Orbital involvement is quite rare, or perhaps underestimated. Orbit metastases (OMs) represent 1-13% of all orbital cancers, and are difficult to discriminate with other differential diagnoses, such as a simple blepharitis, or orbital pseudotumor, up to more complex forms of cancer such as lymphoma. The prevalence of OMs is calculated to occur in 2-4.7% of primitive cancer patients. Typical manifestations of orbital metastases include overall regional inflammation, mass effect causing displacement or ocular globe proptosis, pain, bone infiltration, chemosis and eyelid swelling. Infiltration of soft tissue leads to ptosis, diplopia or enophthalmos. We report the case of a 70-year-old female patient who developed chronic inflammatory process of both orbital regions due to orbital metastases, without evidence of other systemic disease after 8 years from primary breast cancer diagnosis. The diagnostic pathway as well as the differential diagnosis are discussed.
LETTER TO THE EDITOR

EFFECT OF THERMOSETTING GEL WITH DOXYCYCLINE HYCLATE 3% ON POSTOPERATIVE DISCOMFORT AFTER THIRD MOLAR SURGERY: A PROSPECTIVE STUDY

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The study evaluated the effect of intra-alveolar administration of a thermosetting gel containing doxycycline hyclate 3% on patient discomfort after third molar surgery. Eighty-five consecutive patients requiring surgical removal of a single maxillary or mandibular impacted third molar were randomly selected and divided into 2 groups. After the onset of local anaesthesia, the experimental groups received 2 different antibiotic protocols: rifampicin for the first group and a thermosetting gel containing doxycycline hyclate 3% for the second group. Standardized surgical protocols were followed. The patients’ perception of the severity of symptoms (pain, swelling, reddening, bleeding and body temperature) was assessed with a follow-up questionnaire (PoSse scale). On the second postoperative day, pain, reddening and bleeding showed a statistically significant reduction in Group 2 compared with Group 1. There was no difference between the two groups when postoperative swelling was evaluated on the second day. From the third day, conversely, swelling decreased faster in Group 2 than in Group 1. Our data demonstrate that the use of the thermosetting gel containing doxycycline hyclate 3%, given as an intra-alveolar injection at the end of surgery, is effective in the prevention of postoperative symptoms after third molar extraction.
LETTER TO THE EDITOR

EXPRESSION OF PROCOLLAGEN Α1 TYPE I INDUCED BY TWO DIFFERENT DENTINE BONDING SYSTEMS IN HUMAN PULP FIBROBlastS

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This study aimed to evaluate the effects of two different dentine bonding systems (DBSs) on primary cultures of human pulp fibroblasts (HPFs). Cell viability and procollagen α1 type I expression were investigated. Polymerised resin disks of the bonding agent from a two-step self-etch system and of the primer/bonding agent from a two-step etch-and-rinse system were used to condition culture medium for 24 or 96 h. HPFs were incubated in control (untreated) or DBSs-conditioned medium for 24 h. HPF viability was determined using the 3-dimethylthiazol-2,5-diphenyltetrazolium bromide (MTT) assay. Western blot analysis was used to analyse procollagen α1 type I expression. Statistical analyses were performed using Student’s t-tests. The results showed that HPFs incubated with DBSs-conditioned medium for 24 h demonstrated a significant reduction in the percentage of viable cells versus cells incubated with control medium (45% for self-etch DBS and 30% for etch-and-rinse DBS; p < 0.05), whereas this percentage increased significantly after exposure to the 96h DBSs-conditioned medium (62% and 77%, respectively; p < 0.05). Procollagen α1 type I expression in HPFs was strong for control specimens, but decreased in 24 h-DBSs-conditioned medium, and was abolished with 96 h-DBSs-conditioned medium. In conclusion, HPF exposure to medium containing eluates of the different DBSs led to an early cytotoxic effect (24 h) that decreased after a conditioning time of 96 h, whereas procollagen α1 type I expression decreased at 24 h and was absent after 96 h. Procollagen α1 type I expression may be a useful parameter for evaluating DBSs biocompatibility.
LETTER TO THE EDITOR

OSTEORADIONECROSIS OF A MANDIBLE: A CASE REPORT OF IMPLANT-SUPPORTED REHABILITATION

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The head and neck are the sixth most common sites of cancer in the world; the survival rate at 5 years from diagnosis is 60%. Surviving patients, after the critical phase of the disease, require proper rehabilitation. The treatment of oral neoplasia, such as surgery and radiotherapy, may often determine significant disability, such as impaired speech, swallowing, mastication and facial deformity, with severe consequences on the quality of life of these patients. Dental implant-based prosthetic rehabilitation is a consolidated technique for improving the quality of life in patients who have overcome oral cancer. Implants provide stability and support for removable prostheses in oral cavities seriously deformed by surgical treatment. Moreover, mobile prostheses have the advantage of being removable, to check the health of oral tissues and intercept possible relapses of the neoplasia. On the other hand, a lack of residual bone following resection makes it difficult to place implants in an ideal position, and patients who have been submitted to radiotherapy of the head and neck are reported to have a reduced success rate. This paper presents the case of a 67-year-old woman rehabilitated with dental implant-based prosthesis after a hemimandibulectomy due to osteoradionecrosis, without bone reconstruction.