EDITORIAL

GLIOBLASTOMA STEM CELLS: A NEW TARGET FOR METFORMIN AND ARSENIC TRIOXIDE

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The high malignancy of glioblastoma has been recently attributed to the presence, within the tumor, of glioblastoma stem cells (GSC) poorly responsive to chemo- and radiotherapy. Here, the potential employment of metformin and arsenic trioxide (ATO) in glioblastoma therapy is discussed focusing on their effects on GSC. Metformin exerts anticancer effects by primarily blocking the pivotal LKB1/AMPK/mTOR/S6K1 pathway-dependent cell growth, induces selective lethal effects on GSC by impairing the GSC-initiating spherogenesis and inhibits the proliferation of $CD133^+$ cells, while having a low or null effect on differentiated glioblastoma cells and normal human stem cells. Metformin and ATO induce autophagy and apoptosis in glioma cells by inhibiting and stimulating the PI3K/Akt and the mitogen-activated protein kinase pathways, respectively. Both drugs promote differentiation of GSC into non-tumorigenic cells. In this regard, metformin acts via activation of the AMPK-FOXO3 axis, whereas ATO blocks the interleukin 6-induced promotion of STAT3 phosphorylation. Blood-brain barrier, easily crossed by metformin but not by ATO, undergoes important glioblastoma-induced alterations that increase its permeability, thus allowing ATO to distribute more into the glioblastoma bulk than in the normal brain parenchyma. A prompt clinical assessment of metformin and ATO in glioblastoma patients would represent a valid attempt to improve their survival.

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INTERRELATIONSHIP BETWEEN IL-3 AND MAST CELLS

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It is well established that mast cells, which are found in the tissues in the proximity of small blood vessels and post-capillary venules, play a key role in the early phase of IgE-mediated allergic reactions. A greatly expanded understanding of the biology of IL-3 has emerged since the early 1980s. IL-3 is a specific factor that stimulates the growth of hematopoietic stem and progenitor cells of a variety of lineages and can promote the proliferation of certain classes of lymphocytes distinct from those that are dependent on IL-2. IL-3 has been identified among the most important cytokines for regulation of mast cell growth and differentiation, migration and effector function activities of many hematopoietic cells. IL-3 termed multi colony-stimulating-factor (multi-CSF) or mast cell growth factor (MCGF) is a haematopoietic growth factor which stimulates the formation of colonies for erythroid, megakaryocytic, granulocytic and monocytic lineages. It is predominantly produced by activated T cells, natural killer (NK) cells and mast cells and supports the growth-promoting effects of SCF on mast cell precursors. IL-3 causes severe hypersensivity reactions and plays a pivotal role in exacerbating the inflammatory *response in vivo.* Here we report the interrelationship between IL-3 and mast cells.

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CARBAMATE PESTICIDE-INDUCED APOPTOSIS AND NECROSIS IN HUMAN NATURAL KILLER CELLS

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We previously found that ziram, a carbamate fungicide, significantly induced apoptosis and necrosis in human NK-92MI, a natural killer cell line. To investigate whether other carbamate pesticides also induce apoptosis and necrosis in human natural killer cell, we conducted further experiments with NK-92CI, a human natural killer cell line using a more sensitive assay. NK-92CI cells were treated with ziram, thiram, maneb or carbaryl at 0.031-40 μM for 2-24 h in the present study. Apoptosis and necrosis were determined by FITC-Annexin-V/PI staining. To explore the mechanism of apoptosis, intracellular levels of active caspases 3 and mitochondrial cytochrome-c release were determined by flow cytometry. We found that ziram and thiram also induced apoptosis and necrosis in a time- and dose-dependent manner; however, maneb and carbaryl induced apoptosis and necrosis only at higher doses in NK-92CI cells. The strength of the apoptosis-inducing effect differed among the pesticides, and the order was as follows: thiram > ziram > maneb > carbaryl. NK-92CI was more sensitive to ziram than NK-92MI. Moreover, ziram and thiram significantly increased the intracellular level of active caspase 3 in NK-92CI and caspase inhibitor significantly inhibited the apoptosis. Ziram and thiram significantly caused mitochondrial cytochrome-c release in NK-92CI. These findings indicate that carbamate pesticides can induce apoptosis in natural killer cells, and the apoptosis is mediated by both the caspase-cascade and mitochondrial cytochrome-c pathways.

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THE INNATE IMMUNITY RECEPTOR TIR8/SIGIRR IS EXPRESSED IN THE EARLY DEVELOPMENTAL STAGES OF CHICKEN EMBRYOS

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The orphan receptor TIR8, also known as SIGIRR (Single Immunoglobulin IL-1R-Related molecule), belongs to the IL-1R/TLR (TIR) superfamily and plays an important role in the inflammatory responses. The signaling pathways of the receptors belonging to the TIR family are tightly regulated by both extracellular and intracellular mechanisms. TIR8 does not activate the transcription factors NFkB (nuclear factor kB) and IRF3 (interferon regulatory factor 3), although it negatively modulates the inflammatory responses. It acts as an antagonist for the IL-1 receptor family and triggers a negative pathway of the Toll-like/IL-1 receptor system, crucial for dampening inflammation stimuli in the gastrointestinal (GI) tract and in other organs (e.g. lung and kidney). The recent findings of TLRs expression in ovary and embryos of different species (mammals and chickens) are very important for an understanding of reproductive physiology and transovarian pathogen transmission. TIR8 was well characterized in mouse, humans and in other mammalian species, but it is still poorly characterized in the chicken. When *TIR8* expression was measured in selected organs of chicken embryos of both broiler and layer types at different time points a unique pattern of expression was observed. Interestingly, TIR8 was detected during the first stages of chicken development (day 1 of incubation), and reached a remarkable level of expression by day 10. We observed this receptor to be ubiquitously expressed in the kidney, GI tract, Bursa of Fabricius, with the highest expression levels in liver and kidney. This pattern was comparable to those observed in post-hatching chickens and in mammals examined to date. No expression differences were observed between the two different chicken breeds (layer- and broiler-type) in the first incubation period (8 days). Whereas in some organs starting from day 10, higher TIR8 expression was observed in broiler-type compared to layer-type. These are the first findings concerning *TIR8* expression in developmental stages and therefore they are of comparative value.

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TOLL-LIKE RECEPTOR 4 PROMOTES CONTROL OF *LEISHMANIA INFANTUM* INFECTION THROUGH INDUCEMENT OF LEISHMANICIDAL ACTIVITY IN HOST MACROPHAGES: ROLE OF MITOGEN-ACTIVATED KINASES

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Establishment of *Leishmania* infection inside macrophages requires deactivation of various signaling pathways that are dispensable for effective immune responses against the parasite. In the present study, we provide evidence that *Leishmania infantum* promastigotes attachment on the surface of peritoneal macrophages, internalization and transformation to amastigotes abrogated the activation of extracellular signal-regulated protein kinases (ERK) 1/2, p38 mitogen activated protein kinases (MAPK) and c-Jun NH_2-terminal kinases (JNK) and the production of pro-inflammatory cytokines IL-12 and TNFα. Subsequent macrophage stimulation with lipopolysaccharide (LPS) during the first hours of exposure to parasite or infection resulted in restoration of MAPK phosphorylation. However, LPS-mediated MAPK activation required parasite internalization (uptake) since cytochalasin-D pretreated macrophages did not responded to LPS stimulation. IL-12, TNFα, and NO production was positively regulated with MAPK phosphorylation in contrast to nuclear factor-kappaB (NF-κB) which was MAPK independent. Specifically, inhibition of MAPK activation with specific inhibitors revealed that IL-12 production required p38 MAPK activation, whereas TNFα and NO production required all three MAPK. The restoration of NO production resulted in decrease of infection rates. Hence, these results suggest that in contrast to phagocytosis of *L. infantum* promastigotes, establishment of infection does not desensitize macrophages to subsequent stimulation with LPS, resulting in parasite elimination through MAPK and NF-κB activation and partial restoration of IL-12, TNFα and NO synthesis.

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IRON SUPPLEMENTATION IN YOUNG IRON-DEFICIENT FEMALES CAUSES GASTROINTESTINAL REDOX IMBALANCE: PROTECTIVE EFFECT OF A FERMENTED NUTRACEUTICAL

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The aim of this study was to assess whether the concomitant supplementation of certified fermented papaya preparation (FPP, ORI, Gifu, Japan) together with iron supplementation could beneficially affect lipid peroxidation either systemically and at a intraluminal gut level in women with low iron stores. Treatment compliance and iron absorption was assessed as well. Fifty-two non-pregnant, fertile, non-smokers, healthy women with iron deficiency were recruited. The women were given iron supplements (100 mg Fe/d as ferrous sulfate) to be taken daily for 12 weeks (group A). Group B patients were also supplemented with 6g/day of a FPP. A detailed life style questionnaire was administered to all subjects. Iron, ferritin, transferrin receptors (Tf R) and malondialdehyde (MDA) in plasma were measured. The RBCs lysate was used for the estimation of superoxide dismutase (SOD) and glutathione peroxidase (GPx). The total and free iron concentration as well as analysis of oxidative stress in the feces was measured. FPP-supplemented subjects showed a significantly lower degree of gastrointestinal discomfort ($p<0.05$) and abolished the iron supplementation-induced increase of MDA ($p<0.001$) and the depletion of SOD and GPx ($p<0.01$). Moreover, the nutraceutical co-administration brought about a significant reduction of gut oxidative damage and lower fecal content of either total and free iron ($p<0.05$ *vs* group A). Overall, group B showed a better TfR/ferritin ratio response ($p<0.05$ *vs* group A). While iron supplementation maintains its clinical relevance considering the prevalence of iron deficiency among females, a careful clinical evaluation and a protective nutraceutical co-administration, as our data suggest with FPP, should be considered.

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THE USE OF ENGINEERED BIOMATERIAL BONE PLEXUR M® IN BENIGN EPIPHYSEAL TUMORS: OUR EXPERIENCE AT 20 MONTHS OF FOLLOW-UP

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The objective is to reconstruct the subchondral bone after curettage of benign tumors located in the epiphysis, a relevant topic in oncological orthopedics. Several bones substituted are commercially available, yet none of these are suitably moldable to repair or be placed in the bone defect; although autologous bone for little defects and homologous for bigger defects are still considered the standard in reconstruction, we verify the ability to adapt and support articular cartilage through the application of Plexur M®, a newly engineered biomaterial bone. In the present study, we enrolled the first ten consecutive cases referred to our department, where patients were affected by a benign epiphyseal tumor destroying the subchondral bone through to the articular cartilage. Every patient underwent curettage of the disease, apposition of a newly engineered biomaterial bone and filling with homologous morselized bone. The quality of reconstruction was evaluated by two surgeons and by a radiologist based on the achievement of surgical objectives and comparing pre and postoperative imaging. In seven out of eight cases of lesions located in the lower limbs the quality of reconstruction was considered good, restoring an adequate support to the articular cartilage. The quality of the remaining case was considered poor probably due to the extent of the spread of the disease, which destroyed the entire proximal tibial epiphysis. In the two cases where the disease was located in the upper limbs, the Plexur M® application restored support to the articular cartilage sufficiently well. However, in the case of a giant cell tumor of the distal radial epiphysis there was a slight reabsorption of the morselized homologous bone. Our series suggest that Plexur M® should be considered a valid option for orthopedic surgeons in restoring adequate mechanical support to the articular cartilage; nevertheless, considering its high cost, its use might be reserved to selected cases until further studies can verify the integration process, the effects on the survival of the articular cartilage and on the prevention of premature osteoarthritis.

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CATHELICIDIN LL-37 IN BRONCHOALVEOLAR LAVAGE AND EPITHELIAL LINING FLUIDS FROM HEALTHY INDIVIDUALS AND SARCOIDOSIS PATIENTS

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Sarcoidosis is a granulomatous disease of unknown etiology most often characterized by pulmonary manifestations. Changes in an innate immune system, involving antimicrobial peptides, have been noted during the course of pulmonary sarcoidosis. This study focuses on the level of LL-37 peptide, the only human cathelicidin, additionally characterized by a wide range of pleiotropic activities, in pulmonary sarcoidosis. A cross-sectional study was conducted in groups of 32 patients with sarcoidosis and 12 healthy individuals. Bronchoalveolar lavage fluid (BALF) sampling, followed by LL-37 measurements by mass spectrometry combined with previous immunoaffinity purification, was performed. Based on urea levels, concentrations of LL-37 in epithelial lining fluid (ELF) were calculated. The levels of LL-37 peptide in BALF samples derived from patients with pulmonary sarcoidosis (median: 17.45 pg/ml, 25th–75th percentile: 8.05-28.33 pg/ml) were significantly higher compared to the healthy group (median: 6.38 pg/ml, 25th–75th percentile: 4.90-11.55 pg/ml) (U Mann-Whitney test, p=0.04). Assessment of LL-37 in ELF confirmed the differences across the groups that were observed in BALF. The level of LL-37 in patients with sarcoidosis (median: 2.25 ng/ml, 25th–75th percentile: 1.03-5.06 ng/ml) was again higher compared to healthy individuals (median: 0.62 ng/ml, 25th-75th percentile: 0.43-2.17 ng/ml) (p=0.06, Mann-Whitney U test). The results of this study demonstrate that the level of LL-37 peptide is elevated in pulmonary compartment affected by sarcoidosis. This might have a meaning in the pathomechanism of the disease, especially taking into consideration versatile activity of human cathelicidin revealed in numerous experimental studies during the last years.

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EFFICACY AND SAFETY OF γδ T CELL-BASED TUMOR IMMUNOTHERAPY: A META-ANALYSIS

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P.L.D. and F.D. share last authorship for this work.

Vγ9Vδ2 T cells are important effector cells that may play a role in the anti-tumor immune response. Their capability to exert MHC-nonrestricted lytic activity against different tumor cells *in vitro* and their detection among tumor infiltrating lymphocytes in a variety of human cancers have supported the development of Vγ9Vδ2 T cell-based immunotherapy in the context of novel treatment against cancer. Accordingly, promising reports from recent clinical trials support the use of Vγ9Vδ2 T cells as immunotherapeutic agents, either via adoptive transfer of *ex-vivo* expanded Vγ9Vδ2 T cells or *in vivo* activation of Vγ9Vδ2 T cells with compounds such as phosphoantigens or aminobisphosphonates. In this study we have performed a meta-analysis to assess the objective efficacy and safety of Vγ9Vδ2 T cell-based immunotherapy. Database including Pubmed, Web of Science and SCOPUS were investigated to identify relevant studies. Thirteen clinical trials involving patients with advanced or metastatic cancer were selected. In order to estimate the strength of association between Vγ9Vδ2 T cell-based immunotherapy and favorable clinical effect or toxicity grade we used event rate (ER) with 95% confidence interval (CI). The total effective rate provided significant results (ER = 0.407; *P* <0.014) while no correlation was found between serious adverse effects and Vγ9Vδ2 T cell-based therapy. This meta-analysis demonstrates that Vγ9Vδ2 T cell-based immunotherapy improves overall survival and, in view of its low toxicity grade, provides a proof of principle for its utilization as adjuvant to conventional therapies for resistant/refractory patients care.

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BASOPHILS ARE RAPIDLY MOBILIZED FOLLOWING INITIAL AEROALLERGEN ENCOUNTER IN NAÏVE MICE AND PROVIDE A PRIMING SOURCE OF IL-4 IN ADAPTIVE IMMUNE RESPONSES

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Chronic aeroallergen inhalation elicits the expansion of IL-4-producing Th2 cells and the production of IgE antibodies. In sensitized subjects, who have established IgE and Th2 responses, re-exposure to allergen leads to rapid recruitment of basophils, which are thought to be important effectors of late phase allergic reactions. Several investigations of responses to parasites and injected antigens have identified an additional role for basophils as innate immune effectors during initial antigen encounter in immunologically naïve hosts. These cells constitutively express IL-4 and promote Th2 polarized adaptive responses to such antigens. Their early recruitment and modulation of cellular immune responses to natural inhaled allergens in the airways has been scarcely investigated. In this study, basophils were enumerated in lung tissue, blood and spleen from BALB/c mice in the first days after inhalation of an aqueous extract of the allergen, *Aspergillus fumigatus* (*Af*). *Af* inhalation induced rapid increases in basophil numbers in the lung, blood and spleen. This was Rag-1-, MyD88- and IL-3-independent. The basophils expressed abundant IL-4. Their depletion during *Af* sensitization resulted in an attenuated induction of both IL-4 producing Th lymphocytes and specific IgE and IgG1 responses to an inhaled protein antigen, ovalbumin, which was co-administered. Our results suggest that basophils are rapidly recruited to the airways of naïve mice following initial fungal allergen exposure, produce IL-4 and influence the development of the adaptive immune response.

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OLEA EUROPEA-DERIVED PHENOLIC PRODUCTS ATTENUATE ANTINOCICEPTIVE MORPHINE TOLERANCE: AN INNOVATIVE STRATEGIC APPROACH TO TREAT CANCER PAIN

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Morphine and related opioid drugs are currently the major drugs for severe pain. Their clinical utility is limited in the management of severe cancer pain due to the rapid development of tolerance. Restoring opioid efficacy is therefore of great clinical importance. A great body of evidence suggests the key role of free radicals and posttranslational modulation in the development of tolerance to the analgesic activity of morphine. Epidemiological studies have shown a relationship between the Mediterranean diet and a reduced incidence of pathologies such as coronary heart disease and cancer. A central hallmark of this diet is the high consumption of virgin olive oil as the main source of fat which contains antioxidant components in the non-saponifiable fraction, including phenolic compounds absent in seed oils. Here, we show that in a rodent model of opiate tolerance, removal of the free radicals with phenolic compounds of olive oil such as hydroxytyrosol and oleuropein re-instates the analgesic action of morphine. Chronic injection of morphine in mice led to the development of tolerance and this was associated with increased nitrotyrosin and malondialdehyde (MDA) formation together with nitration and deactivation of MnSOD in the spinal cord. Removal of free radicals by hydroxytyrosol and oleuropein blocked morphine tolerance by inhibiting nitration and MDA formation and replacing the MnSOD activity. The phenolic fraction of virgin olive oil exerts antioxidant activities *in vivo* and free radicals generation occurring during chronic morphine administration play a crucial role in the development of opioid tolerance. Our data suggest novel therapeutic approach in the management of chronic cancer pain, in particular for those patients who require long-term opioid treatment for pain relief without development of tolerance.

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LETTER TO THE EDITOR

EVALUATION OF THE EFFECTS OF A PROBIOTIC SUPPLEMENTATION WITH RESPECT TO PLACEBO ON INTESTINAL MICROFLORA AND SECRETORY IgA PRODUCTION, DURING ANTIBIOTIC THERAPY, IN CHILDREN AFFECTED BY RECURRENT AIRWAY INFECTIONS AND SKIN SYMPTOMS

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Antibiotic therapy, especially in pediatric patients, is often associated with significant modifications of the gut microflora, which can lead to intestinal dysbiosis and influence intestinal physiology and immune system functionality. Herein we report the results from a double blind controlled clinical trial in 77 pediatric patients affected by recurrent airway infections, receiving antibiotic therapy with amoxicillin and clavulanic acid. A group was treated with an oral probiotic preparation composed of *Lactobacillus paracasei* ssp.*paracasei* CRL-431, *Bifidobacterium* BB-12, *Streptococcus thermophilus* TH-4 and a fructooligosaccharide (FOS) during and after antibiotic therapy for seven days, while the other group received placebo. The study revealed a reduction in the Clostridia population, with a contemporary increase in Bifidobacteria and Lactobacilli in fecal samples in the probiotic group and an increase in the Enterobacteria population in the placebo group. Moreover, there was a decreasing trend in secretory IgA production in the probiotic group. Some relevant, but not statistically significant probiotic supplementation effects were identified.

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THE EFFECT OF HYDROXYAPATITE-COATED SCREW IN THE LATERAL FRAGILITY FRACTURES OF THE FEMUR. A PROSPECTIVE RANDOMIZED CLINICAL STUDY

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Due to a growing numbers of lateral fragility fractures of the femur and their high social costs the need to work out an effective strategy in order to find a better solution for these patients is warranted. From January 2010 to July 2011, we carried out a prospective randomized clinical study comparing the results of patients with femoral lateral fractures treated by nail and cephalic hydroxyapatite coated screws (study group including 27 patients) compared to the patients with the same fractures treated with nail and head standard screws (control group including 27 patients). We defined the two parts of the femoral neck as ROI 1 (under the head screw) and ROI 2 (above the femoral screw) on the AP view. The bone density of the two areas was calculated using DEXA at T0 (1st day post-surgery), at T1 (40th day post-surgery), at T2 (3 months later), at T3 (1 year later). The clinical-radiography evaluations were based on the Harris Hip Score (HHS), ADL test and x-ray views of the hip. As far as the bone mineral density average of ROI 1 and ROI 2 is concerned, we found a significant statistical increase at T1 and T3 in the study group, while it was not significant in the control group. We could account for this data through the higher mechanical stability of hydroxyapatite coated screws than standard screws. In fact, this material was responsible for improved implant osteointegration. Thanks to a 1 year follow-up we were able to demonstrate the implant utility associated with augmentation and the importance of densitometry exams such as easily repeatable and low cost diagnostics to prevent the onset of complications linked to screw loosening.

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IMMUNOMODULATING TREATMENT WITH LOW DOSE INTERLEUKIN-4, INTERLEUKIN-10 AND INTERLEUKIN-11 IN PSORIASIS VULGARIS

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Psoriasis is a chronic inflammatory skin disease affecting approximately 2-3% of the world population; it is characterised by hyperproliferation and hyperplasia of the superficial layers of the epidermis. Inappropriate signals released by the immune system determine an altered keratinocyte differentiation, resulting in the formation of desquamating, thickened, inflamed and erythematous plaques. The aim of this investigation was to study the pharmacological activity and safety of three low dose cytokines, Guna-Interleukin 4, Guna-Interleukin 10 and Guna-Interleukin 11 at the concentration of 10 fg/ml in patients affected by moderate to slight psoriasis vulgaris. The multicenter, double-blind, randomized, placebo-controlled clinical trial involved 48 patients who were enrolled and followed up according to a 8-month experimental project. All patients received, according to a cross-over model, either the experimental treatment or placebo, alternatively. Globally, in the 41 evaluated patients it was observed a PASI significant reduction (Friedman test: p=0.00960). The DLQI too decreased significantly in all subjects compared to baseline (Friedman test: p=0.00007). The safety of the treatment with three low dose cytokines administered simultaneously was proved; no adverse event was reported during the whole trial.

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LETTER TO THE EDITOR

WHITE MULBERRY SUPPLEMENTATION AS ADJUVANT TREATMENT OF OBESITY

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Body weight is controlled by our genes and managed by a neuro-hormonal system, in particular by insulin and glucagon. The meristematic extract of Japanese white mulberry blocks the alpha-glucosidase and then the intestinal hydrolysis of polysaccharides, thereby reducing the glycaemic index of carbohydrates. The target of our research was to evaluate the adjuvant slimming effect of the extract of white Japanese mulberry in the dietetic treatment of some patients who are obese or overweight. 46 overweight people were enrolled and divided into two subgroups: the subjects of both subgroups were given an identical balanced diet of 1300 kcal: subjects of the subgroup α received 2400 mg of white Japanese mulberry extract, the subgroup b subjects receive placebo. Each subgroup was followed-up every 30 days at 30, 60 and 90 days of treatment. Both in the periodic inspections and in the final inspection measurements of body weight and waist circumference in all the subjects and thigh circumference in women only were repeated. All subjects repeated blood tests. In the subgroup α,weight loss was about 9 kg in 3 months, equal to approximately 10% of the initial weight, significantly higher than subgroup β (P<0.0001); moreover, the plasma insulin and glucose curves of the volunteers in this subgroup at the end of the trial were lower than those performed at the time of enrolment. In the 20 women of the β subgroup treated with only low-calorie diet and with placebo, weight reduction was globally of 3.2 kg, approximately equal to 3% of the initial weight; moreover, the blood glucose curves and the insulin curves showed a slight decline compared to baseline, but not so significantly as was the case for group α. Waist circumference and thigh circumference (in women) decreased in all participants, obviously more evidently in subjects who lost more kg. The extract of white Japanese mulberry may represent a reliable adjuvant therapy in the dietetic treatment of some patients who are obese or overweight.

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LETTER TO THE EDITOR

DIURNAL TRAJECTORIES OF SALIVARY CORTISOL, SALIVARY α-AMYLASE, AND PSYCHOLOGICAL PROFILES IN ORAL LICHEN PLANUS PATIENTS

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Although many reports have been published on the link between oral lichen planus (OLP) and the stress-related neuro-psycho-endocrine clinical features of the disease over the last 20 years, the data still remain controversial. Therefore, the aim of this study was to explore the personality traits of OLP subjects and assess the subjects' capability of coping with stress challenges. Cortisol and α-amylase were measured as reliable markers of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) activities in salivary samples collected by the participants at their home during the sampling day (07:30, 12:00, and 19:30). Compared with the healthy controls, the OLP patients demonstrated a less effective coping ability, had higher scores in stress perception and loneliness, and had no significant variation in their anxiety and depressive symptoms. The OLP patients also showed dysregulation of the HPA axis activity with a significant reduction of diurnal salivary cortisol production, which was particularly significant in the morning hours. No significant variation was found in the OLP salivary α-amylase diurnal fluctuation and production, which was measured at the same time point as that for cortisol. In conclusion, we report that OLP subjects had a reduced capability of coping with stress events and presented a dysregulation of HPA axis activity with hypocortisolism detected in the morning hours.

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LETTER TO THE EDITOR

SAFETY PROFILE AND PROTOCOL PREVENTION OF ADVERSE REACTIONS TO UROANGIOGRAPHIC CONTRAST MEDIA IN DIAGNOSTIC IMAGING

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The purpose of the study is to examine the incidence of adverse reactions caused by non-ionic contrast media in selected patients after desensitization treatment and to evaluate the safety profile of organ iodine contrast media (i.c.m.) in a multistep prevention protocol. In a population of 2000 patients that had received a CT scan, 100 patients with moderate/high risk for adverse reactions against iodinated contrast agents followed a premedication protocol and all adverse reactions are reported and classified as mild, moderate or severe. 1.7% of the pre-treated patients reported a mild, immediate type reaction to iodine contrast; of these five patients with allergy 0.71% had received iomeprol, 0.35% received ioversol and 0.71% received iopromide. The incidence of adverse reactions was reported to be higher (4 out of 5 patients) among those that referred a history of hypersensitivity against iodinated i.c.m. Although intravenous contrast materials have greatly improved, especially in terms of their safety profile, they shoud not be administered if there is not a clear or justified indication. In conclusion, even if we know that the majority of these reactions are idiosyncratic and unpredictable we propose, with the aim of improving our knowledge on this subject, a multicenter study, based on skin allergy tests (prick test, patch test, intradermal reaction) in selected patients that have had previous experiences of hypersensitivity against parenteral organ iodine contrast media.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.