

## EDITORIAL

## ALZHEIMER'S DISEASE: FROM GENES TO NUTRITION

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Alzheimer's disease (AD) is widely identified as the most common cause of sporadic dementia. Its aetiology is still debated, as despite several hypotheses, different factors seem to play a role in its establishment and development. Recent studies have proposed a possible preventing role of nutrition. The weight loss typical of earlier phase of disease and the finding of malnutrition as a common trait between patients leads to hypothesize that a supplementation of specific nutrients seems to be useful and effective in terms of improvement of cognitive functions. Malnourished patients show also altered parameters when investigating inflammation markers: for example, hyperhomocysteinemia is a typical finding in elderly affected by dementia, and it can be prevented and corrected by using a proper nutrients supplementation. Pro-inflammatory state can be reduced with supplementation of polyunsaturated fatty acids, vitamins of the group B and phosphatidylserine, that can act reducing IL-1 $\beta$  (pro-inflammatory cytokine) and improving IL-10 (anti-inflammatory cytokine) synthesis. While investigating the role of nutrition, it seems to be deeply linked with genetic; a genetic onset AD-related could be latent and can be influenced by nutritional attitude. AD can be considered a sort of latent clinical condition that would disclose or not, depending also on micro-environment and nutritional parameters. The genetic expression can be influenced by assumptions or not of specific nutrients, with the promotion of different pro- or anti-inflammatory settings. The specific role of each micronutrient (in particular vitamins) and trace elements still needs to be punctuated, as they are involved in a pool of different reactions. Also genes acts not independently but in an interconnected pattern, in which the role of a single gene needs to be cleared, depending on others. This complex system of predisposing conditions and a possible role of nutrition as modulator of the inflammatory state is the object of this review.

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

**OBESITY, INFLAMMATION AND NEUROLOGICAL ALTERATIONS**

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**Inflammation, neurodegeneration, imbalance of neurotransmitter systems, oxidative stress and depression are all risk factors for obesity. There is evidence regarding the cross-talk between adipose tissue and the immune system and obese patients may show an alteration of immune functions with major depression, including immune suppression with reduced T-cell and macrophage activity. Obesity is mediated by inflammatory cells such as lymphocytes, macrophages and mast cells which release pro-inflammatory cytokines and chemokines. Obesity-induced leukocyte infiltrations in adipose tissue cause cytokine/chemokine release and inflammation. Here, we report the relationship between obesity, neurological alterations and inflammation.**

## IMMUNOHISTOCHEMICAL ANALYSIS OF MATRIX METALLOPROTEINASES-1, -9 AND TENASCIN IN ODONTOGENIC LESIONS

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**Ameloblastoma (ABL) and keratocystic odontogenic tumor (KOT) are benign odontogenic tumors with local aggressive behaviors. The purpose of our study was to compare MMP-1, MMP-9 and tenascin staining patterns between “aggressive” ameloblastoma / keratocystic odontogenic tumors and “non-aggressive” radicular cysts (RC)/ dentigerous cysts (DC). Ameloblastoma, keratocystic odontogenic tumor, radicular cyst (RC) and dentigerous cyst (DC) specimens were chosen from the archives of Gazi University Faculty of Dentistry, Department of Oral Pathology, and immunohistochemically stained with MMP-1, -9 and tenascin antibodies. The immunohistochemical expressions were noted and statistically analyzed. The ABLs and KOTs showed significantly higher MMP-1 and -9 positivity than the RCs and DCs ( $p < 0.05$ ). The ABL and KOT basement membranes showed more continuous tenascin expression. Tenascin intensity was significantly higher in the ABLs and KOTs compared to the RCs and DCs ( $p < 0.05$ ). The results suggest that higher expression of MMP-1 and -9 may play an essential role in the growth and progression of these tumors. Continuous tenascin positivity may reflect strong connective tissue reaction against the invasive epithelial parts of ABLs and KOTs.**

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## THE RELATIONSHIP BETWEEN SOLUBLE TUMOR NECROSIS FACTOR-LIKE WEAK INDUCER OF APOPTOSIS LEVELS AND CARDIAC FUNCTIONS IN PERITONEAL DIALYSIS PATIENTS

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Tumor necrosis factor (TNF)-like weak inducer of apoptosis (sTWEAK) levels has been reported to be decreased in patients on hemodialysis (HD) and patients with heart failure. We aimed to study the relationship between sTWEAK levels and cardiac functions in peritoneal dialysis (PD) patients. This cross-sectional study was carried out on patients on chronic PD programs for more than three months. Patients aged under 18 or over 80 years, patients with overt cardiac disease, overt hypervolemia, active systemic infection, malignancy, peritonitis within the last month were excluded. The patient group was compared with the control group including healthy adults aged 24-61 years. Fifty-two PD patients were included in the study (mean age: 52.7±15.4 years; female/male ratio: 30/22). The corresponding data of the control group were 41.3±10.7 years and 17/14. There was no statistically significant difference between demographic parameters of the groups except age. The mean sTWEAK level of the patient and the control groups were similar (564±17 pcg/ml vs 535±126 pcg/ml, p=0.419). No correlation was detected between any of the demographic variables and sTWEAK levels. Among the echocardiographic parameters, only ejection fraction was found to be correlated negatively with sTWEAK levels. Patients with ischemic heart disease (IHD) and heart failure had significantly higher sTWEAK levels compared with the patients without these diseases. With linear regression analysis, only age and the presence of heart failure were found to be the independent determinants of sTWEAK levels. Level of sTWEAK is significantly high in PD patients with heart failure and IHD. sTWEAK may be a marker of cardiac functions in PD patients.

## THE RELATIONSHIP BETWEEN PLASMA SOLUBLE TNF-LIKE WEAK INDUCER OF APOPTOSIS LEVEL AND INFLAMMATORY MARKERS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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**Soluble TNF-like weak inducer of apoptosis (sTWEAK) is a member of the TNF super family with many biological activities. There is a limited number of studies on the role of sTWEAK in chronic kidney disease. We aimed in this study to examine the relation of sTWEAK with albuminuria and inflammatory markers in patients with type 2 diabetes mellitus (DM). One hundred and eighteen diabetic patients with varying levels of albuminuria were included. Group 1 comprised patients with albuminuria less than 30 mg/day, while Group 2 and Group 3 were composed of patients with albuminuria between 30-300 mg/day or more than 300 mg/day, respectively. Groups were compared for sTWEAK levels besides demographic, clinical and biochemical data. There was no difference between groups regarding sTWEAK and TNF- $\alpha$  levels. IL-1 levels in Group 1 were higher than in Group 3. hsCRP levels were significantly higher in Group 3 compared to other groups. Use of a renin angiotensin system blocker did not have any effect on sTWEAK, TNF- $\alpha$  and hsCRP levels, while IL-1 level was significantly lower in patients using a renin angiotensin blocker. A statistically significant positive correlation was detected between sTWEAK and IL-1 levels ( $r=0.245$ ;  $p=0.008$ ). The groups were found to be similar regarding sTWEAK and TNF- $\alpha$  level. This finding may be interpreted as there being no effect of proteinuria on sTWEAK levels. But the close correlation between proteinuria and IL-1, and between IL-1 and sTWEAK may be a clue for an indirect relationship. Lack of difference between groups regarding sTWEAK levels may be due to involvement of patients with GFR more than 60 ml/minute only.**

## INHIBITION OF CXCR 1 AND 2 DELAYS PRETERM DELIVERY AND REDUCES NEONATAL MORTALITY IN A MOUSE MODEL OF CHORIOAMNIONITIS

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Intrauterine infection is one of the main etiologies associated with preterm delivery. Cytokines involved in chorioamnionitis, including IL-1, TNF- $\alpha$ , IL-6, IL-8, and MCP1, activate different pathways that lead to preterm delivery. Antileukinate (AL) is a potent selective IL-8 inhibitor that binds to CXC receptors 1&2 on neutrophils, thereby inhibiting IL-8-induced neutrophil chemotaxis and degranulation. Since CXC receptors 1&2 are critically involved in the pathology of chorioamnionitis, their inhibition with AL may have therapeutic potential. Four timed-pregnant C57BL6 mice groups were studied. LPS group received LPS intraperitoneally on gestational day (GD) 15. The AL group received LPS on GD15 followed immediately by intraperitoneal AL injection and repeated on GD16, and 17. Control groups received either saline, or no injections. In the LPS group, 90% delivered within 24 hours after LPS administration compared to 20% in the AL group. The LPS group had 85% stillborn compared to 15% in the AL group. Uterine histopathology AL group showed evidence of less inflammatory reaction compared to the LPS group. Uterine tissue and serum from the AL group had a significant reduction of inflammatory cytokines compared with the LPS group. Cytokine levels in brain and lung tissues from surviving pups were not significantly different between the AL and control groups. Our data show that antileukinate significantly delays preterm delivery in a mouse model of chorioamnionitis, and reduces neonatal mortality and morbidity.

## EFFICACY AND TOLERABILITY OF A NEW PHARMACEUTICAL FORM OF BETAMETHASONE VALERATE IN THE PREVENTION OF HYPERTROPHIC SCARS FOLLOWING ANTERIOR TRUNK PLASTIC SURGERY: A PRELIMINARY EXPLORATORY STUDY

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Hypertrophic scars are fibroproliferative diseases of the skin. Many treatment options are now available, but none is completely effective. The primary objective of this study was to compare the efficacy of a betamethasone valerate (BMV) 2.25 mg plaster *versus* no treatment in the prevention of hypertrophic scars after anterior trunk plastic surgery. An exploratory, open, prospective, controlled study was carried out on 16 consecutive patients with postoperative wounds. A 12-week daily treatment was initiated after wounds cicatrization. The effect of a daily application of the plaster was compared to no treatment by dividing the wound into 2-4 parts. The wound evaluation was performed during the treatment period at 2, 4, 8 and 12 weeks, and 6 months after the end of the treatment. A total of 60 wounds was evaluated. Pain and itching improved in both groups after 12 weeks. However, only the wounds treated with BMV plaster showed a significantly greater and more rapid improvement as compared with the non-treated wounds after 4 and 8 weeks of treatment in all the evaluated parameters ( $p < 0.0001$ ). The efficacy and tolerability of BMV plaster in the prevention of hypertrophic scar development is promising.

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## FEASIBILITY AND SAFETY OF INTRAOPERATIVE ELECTROCHEMOTHERAPY IN LOCALLY ADVANCED PANCREATIC TUMOR: A PRELIMINARY EXPERIENCE

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Electrochemotherapy is an effective treatment for various cutaneous tumors and could be translated into treatment of deep-seated tumors. With this aim, a prospective clinical phase I/II study was conducted to evaluate the feasibility and safety of intraoperative Electrochemotherapy (ECT) in locally advanced pancreatic adenocarcinoma: the preliminary results are reported in this study. The secondary endpoint was to assess treatment response in terms of morphological and functional criteria based on Magnetic Resonance Imaging. Eleven consecutive patients were enrolled in a clinical phase I/II study approved by the Ethics Committee of the National Cancer Institute G. Pascale Foundation - IRCCS of Naples. Electrochemotherapy with bleomycin was performed during open surgery. All patients underwent MR and CT scan, before and after ECT treatment, using morphological and functional imaging. RECIST criteria were used to evaluate ECT response on CT and MR images. Functional parameters were also used to evaluate ECT response on MR images. No acute (intraoperative) and/or postoperative serious adverse events related to electrochemotherapy were observed; no clinically significant electrocardiographic, hemodynamic, or serum biologic changes were noted. No clinically relevant elevation of amylase or lipase levels was observed and no bleeding or damage to surrounding viscera occurred. Electrochemotherapy of locally advanced pancreatic adenocarcinoma proved to be a feasible and safe treatment modality. Dynamic and diffusion MR imaging is more suitable to assess ECT treatment response than CT imaging and morphological MR alone, after one month of treatment.

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## DIABETES AND OBESITY AS INDEPENDENT RISK FACTORS FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN: A POPULATION STUDY

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We aimed to analyze bone mineralization and the effect of different risk factors for osteoporosis in postmenopausal women. We studied 2,756 postmenopausal subjects out of  $\geq 10,000$  records from the ROIS registry in the frame of the PROF Project, a population study carried out in Salento (Taranto, Brindisi, Lecce) from 2009 to 2012. All subjects were assessed by phalangeal Quantitative Ultrasound (QUS) to evaluate their bone mineralization (assessed by Amplitude Dependent Speed of Sound, AD-SoS) and the association between demineralization and the presence of other conditions or risk factors. Mean age was  $64 \pm 9.5$  years and mean BMI was  $28.7 \pm 3.5$  Kg/m<sup>2</sup>. Pearson correlation analyses revealed a negative association between bone mineralization (AD-SoS) and BMI ( $P < 0.001$ ). By using multivariate logistic regression analysis, we observed significant values of Odds Ratios of osteoporosis (adjusted for age, physical activity and the use of drugs known to increase the risk of fractures) in subjects with diabetes and obesity: 1.39 (CI: 1.05-1.83) and 1.46 (CI: 1.20-1.78), respectively. A statistically significant linear trend of higher Odds Ratios of osteoporosis was found for increasing values of BMI. The percent change in the odds of vertebral fractures per single SD decrease of AD-SoS was 47% ( $P < 0.001$ ). Diabetes and obesity in postmenopausal women are likely to represent independent risk factors for osteoporosis. Phalangeal QUS showed a good power of predictivity in identifying subjects with vertebral fractures.

**EVALUATING THE MURINE ANTI-HUMAN ANTIBODY RESPONSE AND  
ASSESSMENT OF GENERAL ACTIVITY AND COGNITION AFTER TREATMENT  
WITH HUMAN INTRAVENOUS IMMUNOGLOBULINS  
IN HEALTHY ADULT C57/B6J MICE**

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**Human intravenous immunoglobulin (IVIG) is a fractionated blood product that is used for the treatment of several autoimmune and immunodeficiency disorders. Recently, IVIG has been suggested for the treatment of Alzheimer's disease (AD). However, the molecular mode of action is still largely unknown. Therefore, preclinical assessment of the therapeutic efficacy of IVIG in animals may provide valuable information of the function of IVIG *in vivo*. However, it is recommended to determine the murine-anti-human antibody (MAHA) response in those animals before starting immunotherapy and subsequent assessment of the therapeutic efficacy in animal models for AD. After weekly administration of 400 µg IVIG in C57/B6J mice for the duration of twelve weeks, we found a significant increase of MAHA response against human IgG. Even after increased MAHA levels starting from week nine after treatment, there was no significant change in basic exploratory behavior, anxiety, and cognition. Therefore, it is suitable to study pharmacological and immunological activity, therapeutic efficacy, as well as mode of action of IVIG in animal models only for a short duration to avoid interference with IVIG treatment and neutralize possible therapeutic effects.**

## MICROARRAY ANALYSIS OF ANTIGEN-DEPENDENT B-CELL ACTIVATION GENE EXPRESSION IN BITCHES WITH PYOMETRA

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Canine pyometra is defined as a complex disease associated with activation and proliferation of immune specific cells, B and T cells, as well as synthesis and activation of immune and pro-inflammatory molecules. Although all of these mechanisms are well recognized in several human immune diseases and cancers, the possible role or dysfunction of these molecules in dogs with pyometra still requires investigation. This study was aimed to examine antigen-dependent B-cell activation gene expression (CD4, CD28, CD40, CD80, Fas, HLA-DRB1 and IL10) in a total of 24 mixed-breed bitch uteri with pyometra and 20 healthy controls. Using canine RNA microarray assays (Affymetrix) altogether 17,138 different transcripts were analyzed. A significant increase was found of CD28, CD40, HLA-DRB1 ( $P<0.001$ ), and CD4, CD80, Fas and IL10 ( $P<0.01$ ) in the group of bitches with pyometra, as compared to controls. In the affected group an increased share of CD4, CD28, CD40, CD80, Fas, HLA-DRB1 and IL10, (13.6-, 2.8-, 2.9-, 5.6-, 3.3-, 4.4-, and 6.5-fold increase, respectively) was also detected. It is suggested that an increased expression of B cell-specific immune response molecules may be associated with recruitment of immunologically specific cells in bitches with pyometra as well as with activation of pro-inflammatory proteins as a consequence of exposure to foreign antigens due to bacterial infection.

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## SILENCING OF YAP GENE INHIBITS METASTASIS IN A SEVERE COMBINED IMMUNE DEFICIENCY MICE ORTHOTOPIC IMPLANTATION GASTRIC CANCER MODEL

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**YAP signaling has been proved to be involved in cell growth, invasion and metastasis in multiple malignancies. But little has been reported about the effects of YAP transduction on gastric cancer metastases. The present study was aimed to explore the effects of shRNA-mediated targeting of YAP gene on human gastric cancer metastases in severe combined immune deficiency (SCID) mice. Human gastric carcinoma cell line SGC7901 was implanted into the stomach of SCID mice, which were randomly divided into 3 groups (n=10). Via intraperitoneal injection, mice received YAP-shRNA, negative control, or normal saline respectively. The results of TUNEL and FQ-PCR showed an obvious induction of apoptosis in the YAP-shRNA group. Intratumoral vascular density and lymphatic density were suppressed in the YAP-shRNA group. In conclusion, silencing of YAP gene effectively induces the cell apoptosis and inhibits microvascular angiogenesis and lymphangiogenesis of gastric cancer cells *in vivo*, suggesting that YAP may serve as a promising therapeutic target for treatment of cancer.**

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## LETTER TO THE EDITOR

**HONEYCOMB-LIKE STRUCTURED FILM REGULATES MEDIATOR RELEASE FROM NON-TUMOR MAST CELLS**K. SUGIMOTO<sup>1</sup>, H. CHOI<sup>1,2</sup> and M. TANAKA<sup>2</sup>

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**We previously reported a honeycomb-like structured film (HCF) stimulates mast cell proliferation and multinucleated formation. In this study, we examined the role of HCF in regulating the release of mediators from cultured mast cells. We measured the release of histamine, substance P, tumor necrosis factor (TNF)- $\alpha$ , and leukotriene B4 (LTB-4) from NCL-2 cells (proliferative mouse non-tumor mast cells). After 7 days of culture, HCF selectively down-regulated the release of TNF- $\alpha$ , LTB-4, and (to a lesser extent) substance P, but not histamine. Mast cell attachment to HCF may have a greater effect on release of *de novo* synthesized molecules.**

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## LETTER TO THE EDITOR

**TLR4 AND TLR9 POLYMORPHISMS EFFECT ON INFLAMMATORY RESPONSE IN END-STAGE RENAL DISEASE PATIENTS**

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Toll-like receptors (TLRs) play a key role in the response of innate and adaptive immune system to microbial and endogenous ligands. Inflammation is a common feature in end-stage renal disease (ESRD) patients; however, the mechanisms/factors triggering the inflammatory process are still poorly clarified. Our aim was to analyze the impact of the c.-1486T>C and c.896A>G polymorphisms in TLR9 and TLR4 genes, respectively, on the inflammatory response of ESRD patients. Clinical and laboratory evaluation was carried out on 184 ESRD patients. Polymerase chain reaction followed by restriction fragments length polymorphisms (PCR-RFLP) was employed for genotyping of TLR-4 c.896A>G and TLR-9 c.-1486T>C polymorphisms. The prevalence of AA and AG of TLR4 c.896A>G polymorphism in ESRD patients was 97.8% and 2.2%, respectively. None of the individuals showed a homozygous TLR4 polymorphism. Concerning the TLR9 c.-1486T>C polymorphism, we found that ESRD patients showed a prevalence of TC and CC genotypes of 57.1% and 20.6%, respectively. We found that the heterozygous patients for the TLR4 c.896A>G polymorphism presented an increased level in lymphocyte count, a decrease in neutrophil/lymphocyte ratio and in serum levels of hepcidin. Regarding the TLR9 c.-1486T>C polymorphism, we found that it is associated with decreased white blood cell and neutrophil counts, ferritin and CRP serum levels, and with an increase in serum levels of creatinine. Our data suggest that the presence of the studied polymorphisms is associated with a decreased inflammatory response in ESRD patients under hemodialysis, and, thus its presence might have beneficial effects in ESRD patients. Moreover, our data provide new insights in the role of TLR polymorphisms in renal disease, which might have impact in the near future for the development of innovative therapies.

LETTER TO THE EDITOR

**IN VITRO STUDY OF BCG GRANULOMA MACROPHAGE MORPHOFUNCTIONAL STATUS**V.A. SHKURUPY<sup>1,2</sup>, S.A. ARKHIPOV<sup>1,2</sup>, E.S. AKHRAMENKO<sup>1</sup>,  
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We studied the morphofunctional and cytophysiological status of macrophages emigrating from BCG granulomas forming in spleen and free splenic macrophages that are not associated with granulomas. The experimental BCG granulomatosis was induced by intravenous injection of male BALB/c mice with BCG vaccine mycobacteria. The number of granulomas in spleen, their diameter, the proportion of granuloma macrophages with mycobacteria, the number of mycobacteria in granuloma macrophages, the proportion of live bacteria in granuloma macrophages and the number of granulomas macrophages capable of expressing IL-1 $\alpha$ , TNF- $\alpha$ , GM-CSF were evaluated. BCG granulomas were explanted in cultures *in vitro*. Fractions, containing free splenic macrophages from BCG-infected animals, were explanted in separate cultures *in vitro*. The phagocytic activity of macrophages that migrated from BCG granulomas explanted in cultures one month after mycobacterial infection of mice, was much higher than those of splenic macrophages of intact mice. The phagocytic activity of free macrophages and macrophages from granulomas decreased with time after infection. By contrast, the antimycobacterial activity of free splenic macrophages and macrophages from BCG granulomas increased with time after infection. The correlational analysis showed that there are different correlational relationships between the number of granuloma macrophages expressing IL-1 $\alpha$ , TNF- $\alpha$ , GM-CSF and phagocytic activity of macrophages from BCG granulomas. The results of the study are important for understanding the molecular and cellular mechanisms of development of chronic granulomatous inflammation induced by mycobacterial infection.

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