

EDITORIAL

MIND-BODY RESPONSE AND NEUROPHYSIOLOGICAL CHANGES DURING STRESS AND MEDITATION: CENTRAL ROLE OF HOMEOSTASISR. JERATH¹, V.A. BARNES² and M.W. CRAWFORD¹*¹Augusta Women's Center, Augusta, GA, USA; ²Georgia Prevention Institute, Georgia Regents University, Augusta, GA, USA**Received December 17, 2013 – Accepted July 31, 2014*

Stress profoundly impacts quality of life and may lead to various diseases and conditions. Understanding the underlying physiological and neurological processes that take place during stress and meditation techniques may be critical for effectively treating stress-related diseases. The article examines a hypothetical physiological homeostatic response that compares and contrasts changes in central and peripheral oscillations during stress and meditation, and relates these to changes in the autonomic system and neurological activity. The authors discuss how cardiorespiratory synchronization, which occurs during the parasympathetic response and meditation, influences and modulates activity and oscillations of the brain and autonomic nervous system. Evidence is presented on how synchronization of cardiac and respiratory rates during meditation may lead to a homeostatic increase in cellular membrane potentials in neurons and other cells throughout the body. These potential membrane changes may underlie the reduced activity in the amygdala, and other cortical areas during meditation, and research examining these changes may foster better understanding of the restorative properties and health benefits of meditation.

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

TARGETING PROSTATE-SPECIFIC MEMBRANE ANTIGEN FOR PERSONALIZED THERAPIES IN PROSTATE CANCER: MORPHOLOGIC AND MOLECULAR BACKGROUNDS AND FUTURE PROMISES

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Prostate-specific membrane antigen (PSMA) is an integral, non-shed membrane glycoprotein that is highly expressed on prostate epithelial cells and strongly upregulated in prostate cancer (PCa). Prostatic neoplastic transformation results in the transfer of PSMA from the apical membrane to the luminal surface of the ducts. However, the role of PSMA in tumor angiogenesis and carcinogenesis is poorly understood. PSMA is characterized by folate hydrolase and carboxypeptidase activity and internalization function, and its levels are directly correlated to androgen independence, metastasis and PCa progression. As largely substantiated by preclinical and clinical findings, PSMA could represent a promising target for Positron Emission Tomography (PET) radiopharmaceuticals for PCa imaging. Furthermore, PSMA could prove an important target for the development of new therapeutic approaches, including PSMA-based aptamers, peptides, antibody-drug conjugated therapy, as well as radiotherapy and immunotherapy. This review will summarize the role of PSMA in PCa development and progression and its potential role in the diagnosis and treatment of patients with initial and advanced PCa.

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EDITORIAL

CAN PROBIOTIC ADMINISTRATION DURING PREGNANCY AND THE FIRST YEAR OF LIFE EFFECTIVELY REDUCE THE RISK OF INFECTIONS AND ALLERGIC DISEASES IN CHILDHOOD?

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Infections and allergic disorders are common pediatric diseases. It has been reported that probiotics, which are live microorganisms, confer health benefits to hosts when administered in appropriate amounts. Probiotics have been widely used in the treatment of pediatric infections and allergic disorders through modulating the microbial environment of host. However, it is still not clear whether probiotic administration during pregnancy and/or the first year of life is an efficient approach for the prevention of infections and allergic diseases in childhood. The present study aims to address this question through reviewing previous publications on this topic. Analysis of previous studies suggests that probiotic administration during pregnancy and/or the first year of life could reduce the prevalence of infectious diseases in infancy. The effects of probiotic administration during pregnancy and/or the first year of life on the prevention of allergic disorders are still not clear. In addition, the available studies differ in probiotic species, number of probiotics, dosage of probiotics, inclusion and exclusion criteria, outcomes, and diagnostic and follow-up methods. These differences highlight further studies for better understanding the effects of probiotic administration on the prevention of infections and allergic diseases in childhood.

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INTERLEUKIN-33 PROMOTES THE PROLIFERATION OF MOUSE MAST CELLS THROUGH ST2/MyD88 AND p38 MAPK-DEPENDENT AND Kit-INDEPENDENT PATHWAYS

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Interleukin-33 (IL-33), a member of the IL-1 cytokine family, is emerging as a new modulator of immune and inflammatory responses. Although IL-33 and its associated receptor ST2 are reportedly expressed in mast cells (MCs), the precise role of IL-33 in modulating MC function has not been determined. In the present studies, we explored IL-33 effects on MCs *in vivo* and *in vitro*. IL-33 increased the number of peritoneal and skin MCs *in vivo*. IL-33 also resulted in increased proliferation of MCs *in vitro*, as explored by WST assay. Cell cycle analysis further confirmed this result by showing increased G2 cell populations in MCs stimulated with IL-33. We found that IL-33-mediated MC proliferation requires ST2 and MyD88, is independent of Kit, and is mediated through a p38 MAPK-dependent pathway. IL-33 did not induce degranulation and was not cytotoxic for MCs. This novel mechanism for increasing MC proliferation and numbers further defines the role of IL-33 in MC-dependent diseases including allergies and may help to develop novel approaches for the treatment of these disorders.

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EDITORIAL

NOVEL MECHANISM OF PLASMA PREKALLIKREIN (PK) ACTIVATION BY VASCULAR SMOOTH MUSCLE CELLS: EVIDENCE OF THE PRESENCE OF PK ACTIVATORJ.S. KEUM¹, M.A. JAFFA², L.M. LUTTRELL¹ and A.A. JAFFA^{1,2,3}

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The contribution of plasma prekallikrein (PK) to vascular remodeling is becoming increasingly recognized. Plasma PK is activated when the zymogen PK is digested to an active enzyme by activated factor XII (FXII). Here, we present our findings that vascular smooth muscle cells (VSMC) activate plasma PK in the absence of FXII. Extracted plasma membrane and cytosolic fractions of VSMCs activate PK, but the rate of PK activation was greater by the membrane fraction. FXII neutralizing antibody did not affect PK activation by extracted proteins of VSMCs. VSMC PKA was inhibited by the serine protease inhibitors such as aprotinin, phenylmethylsulfonyl fluoride, leupeptin and CTI with CI_{50} of 0.78 μ M, 1 mM, 3.13 μ M and 40 nM on the cultured cells, respectively. No inhibition of PK activation by cysteine, aspartic acid, and metalloprotease inhibitors was observed. This is the first report of the presence of an intrinsic PKA in VSMC. Considering that VSMCs are normally separated from the circulating blood by endothelial cells, direct PK activation by VSMCs may play a role in disease states like diabetes, hyperlipidemia or hypertension where the endothelial layer is damaged.

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MISSENSE VARIANTS OF THE ALANINE: GLYOXYLATE AMINOTRANSFERASE 2 GENE CORRELATED WITH CAROTID ATHEROSCLEROSIS IN THE JAPANESE POPULATION

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Alanine:glyoxylate aminotransferase 2 (AGXT2; EC 2.6.1.44) degrades asymmetric dimethylarginine (ADMA), a competitive inhibitor of nitric oxide (NO) synthase. Increased ADMA, reduced NO, and hypertension are shown in Agxt2 knockout mice. There are four single nucleotide polymorphisms (rs37370, rs37369, rs180749, and rs16899974) with which AGXT2 activity changes in humans and may be related to vulnerability of vascular sclerosis. To examine the relationship between them, we studied the functional haplotypes of the AGXT2 gene and decided their relationship with arteriosclerotic changes via carotid intima-media thickness (carotid IMT) in Japanese subjects. Genotyping of those polymorphisms and the carotid IMT in 1,426 Japanese subjects were then evaluated. Subjects with C-A-A-A haplotype (rs37370, rs37369, rs180749, rs16899974) showed low AGXT2 activity ($P < 0.0001$; Pearson's correlation coefficients: 0.497). The C-A-A-A haplotype was significantly associated with mean carotid IMT ($P = 0.049$) and max carotid IMT ($P = 0.004$). Subjects with two C-A-A-A haplotypes exhibited thicker mean carotid IMT ($P = 0.022$) and maximum carotid IMT ($P = 0.001$). In multiple regression analysis, subjects with two C-A-A-A haplotypes were independently and positively associated with mean carotid IMT ($P = 0.02$) and maximum IMT ($P = 0.005$) after correction. There was a significant correlation between the functional variants in the AGXT2 gene and carotid IMT in Japanese. The AGXT2 genotype may be an important factor underlying atherosclerosis.

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MicroRNA-133a FUNCTIONS AS A TUMOR SUPPRESSOR IN GASTRIC CANCERX-C. XU¹, Y-H. ZHANG², W-B. ZHANG¹, T. LI¹, H. GAO¹ and Y-H. WANG¹

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The first two authors contributed equally to this article

MicroRNAs (miRNAs) are small and highly conserved non-coding RNAs that regulate gene expression of target mRNAs through posttranscriptional inhibition involved in the tumorigenesis and progression of multiple malignancies. Although miR-133a has been shown to function as a tumor suppressor in some cancers, the clinical significance and function of miR-133a in gastric cancer remain unclear. Hence, we were focused on the expression and mechanisms of miR-133a in the development of gastric cancer in this study. It was found that the expression of miR-133a was downregulated ($P<0.001$), while transgelin-2 (TAGLN2) was upregulated ($P<0.05$) in primary gastric cancer tissues, compared to the adjacent non-cancerous tissues (ANCT). Furthermore, decreased expression of miR-133a and increased expression of TAGLN2 were both associated with lymph node metastases in patients with gastric cancer ($P<0.001$; $P=0.011$). Functional analysis studies revealed that ectopic expression of miR-133a reduced cell proliferation and invasion, and induced cell apoptosis and cycle arrest via suppressing the level of TAGLN2 from transcriptional and translational levels and downregulated the expression of proliferating cell nuclear antigen (PCNA) and matrix metalloproteinase-2 (MMP-2) in gastric cancer cells. In conclusion, these results demonstrate that decreased expression of miR-133a is associated with the lymph node metastases of patients with gastric cancer. Overexpression of miR-133a inhibits cell growth and invasion and induces cell apoptosis and cycle arrest through repressing TAGLN2 gene, suggesting that miR-133a might be used as a biomarker or therapeutic target for the treatment of gastric cancer.

STUDY ON CONNEXIN GENE AND PROTEIN EXPRESSION AND CELLULAR DISTRIBUTION IN RELATION TO REAL-TIME PROLIFERATION OF PORCINE GRANULOSA CELLS

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Granulosa cells (GCs) play an important role during follicle growth and development in preovulatory stage. Moreover, the proteins such as connexins are responsible for formation of protein channel between follicular-cumulus cells and oocyte. This study was aimed to investigate the role of connexin expression in porcine GCs in relation to their cellular distribution and real-time cell proliferation. In the present study, porcine GCs were isolated from the follicles of puberal gilts and then cultured in a real-time cellular analyzer (RTCA) system for 168 h. The expression levels of connexins (Cxs) Cx36, Cx37, Cx40 and Cx43 mRNA were measured by RQ-PCR analysis, and differences in the expression and distribution of Cx30, Cx31, Cx37, Cx43 and Cx45 proteins were analyzed by confocal microscopic visualization. We found higher level of Cx36, Cx37, and Cx43 mRNA expression in GCs at recovery (at 0 h of *in vitro* culture, IVC) compared to all analyzed time periods of IVC (24, 48, 72, 96, 120, 144 and 168 h; $P < 0.001$). On the other hand, the expression level of Cx40 transcripts was higher after 24 h of IVC compared to 0 h and the other times of IVC ($P < 0.001$). Similarly to mRNAs, the expression levels of Cx31, Cx37 and Cx45 proteins were higher before (0 h) compared to after 168 h of IVC. The expression of Cx30 and Cx43, however, did not vary between the groups. In all, the proteins were distributed throughout the cell membrane rather than in the cytoplasm both before and after IVC. After 24 h of IVC, we observed a significant increase in the proliferation of GCs (log phase). We found differences in the proliferation index between 72-96 and 96-140 h within the same population of GCs. In conclusion, the decrease in the expression of Cx mRNAs and proteins following IVC could be associated with a breakdown in gap-junction connections (GJCs), and leads to the decreased of their activity, which may be a reason of non-functional existence of connexon in follicular granulosa cells. These data indicated that the differentiation and proliferation of GCs and lutein cells are regulated by distinct mechanisms in pigs.

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MICROARRAY ANALYSIS OF INFLAMMATORY RESPONSE-RELATED GENE EXPRESSION IN THE UTERI OF DOGS WITH PYOMETRA

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Pyometra, which is accompanied by bacterial contamination of the uterus, is defined as a complex disease associated with the activation of several systems, including the immune system. The objective of the study was to evaluate the gene expression profile in dogs with pyometra compared with those that were clinically normal. The study included uteri from 43 mongrel bitches (23 with pyometra, 20 clinically healthy). RNA used for the microarray study was pooled to four separated vials for control and pyometra. A total of 17,138 different transcripts were analyzed on the uteri of female dogs with pyometra and of healthy controls. From 264 inflammatory response-related transcripts, we found 23 transcripts that revealed a 10- to 77-fold increased expression. Thereby, the expression of interleukin 8 (IL8), interleukin-1-beta (IL1B), interleukin 18 receptor (IL18RAP), interleukin 1-alpha (IL1A), interleukin receptor antagonist (IL1RN) and interleukin 6 (IL6) increased 77-, 20-, 17-, 13-, 13- and 11-fold, respectively. Furthermore, the expression of the calcium binding proteins S100A8 was 44-fold higher, and that of S100A12 and S100A9 37-fold, respectively, in the uteri of canines with pyometra compared with that of the controls. Moreover, the expression of the transcripts of toll-like receptors (TLR8 and TLR2), integrin beta 2 (ITGB2), chemokine ligand 3 (CCL3), semaphorin 7A (SEMA7A), CD14 and prostaglandin-endoperoxide synthase 2 (PTGS2) was increased between 10- and 18-fold. Furthermore, after using RT-qPCR we found an increased expression of AOA, IL1A, IL8, CCL3, IL1RN and SERPINE 1 mRNAs which can be served also as markers of the occurrence of pyometra in domestic bitches. In summary, it is concluded that up-regulation of interleukins may be used as a marker of the inflammatory response in dogs with pyometra. Moreover, all of the 23 up-regulated transcripts may be novel molecular markers of the pathogenesis of canine pyometra. Several proteins – products of these genes - may be recognized as potential biomarkers of this disease or as therapeutic targets in other mammalian species, including humans.

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KNOCKDOWN OF THE INFLAMMATORY FACTOR PENTRAXIN-3 SUPPRESSES GROWTH AND INVASION OF LUNG ADENOCARCINOMA THROUGH THE AKT AND NF-KAPPA B PATHWAYS

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The first two authors contributed equally to this article

Pentraxin-3 (PTX3), a modulator of tumor-associated inflammation, is known to be positively correlated with tumor grade and severity of malignancies, but the function and molecular underlying mechanisms of PTX3 remain unclear. In the present study, the expression of PTX3 in human lung adenocarcinoma (LAC) was examined by immunohistochemical assay using a tissue microarray procedure. A loss-of-function experiment was performed to explore the effects of lentiviral vector-mediated PTX3 shRNA (Lv-shPTX3) on cell growth and invasive potential in LAC cell lines (A549 and LETP α -2), assessed by MTT and Transwell assays, respectively. We found that the expression of PTX3 protein was significantly increased in LAC tissues compared with that in adjacent non-cancerous tissues (ANCT) (60.42% vs. 29.17%, $P=0.004$), and positively correlated with lymphatic invasion of the tumor ($P=0.006$). Furthermore, knockdown of PTX3 suppressed tumor proliferation and invasion of LAC cells, followed by decreased expression of p-AKT, p-NF-kappa B, PCNA, and MMP-9. Taken together, our findings demonstrate that upregulation of PTX3 expression is correlated with tumor metastasis of LAC patients, and knockdown of PTX3 blocks the development of LAC through inhibition of the AKT and NF-kappa B pathways, suggesting that PTX3 may serve as a potential therapeutic target for the treatment of cancer.

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GENE EXPRESSION PROFILES IN THREE HISTOLOGIC TYPES, CLEAR-CELL, ENDOMETRIOID AND SEROUS OVARIAN CARCINOMAS

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Ovarian carcinoma is the most lethal type of gynecologic malignancy in the Western world. Majority of early stage ovarian cancers are asymptomatic and this is the main reason that more than two-thirds of patients are diagnosed with advanced disease. Ovarian tumors are heterogeneous and the different histologic subtypes are further classified as benign, borderline (low-grade) and malignant (high-grade) to reflect their behavior. The aim of the study was to analyze gene expression profiles in three histologic types of ovarian carcinoma in an attempt to find the molecular differences among serous, endometrioid and clear cell subtypes. The analysis of gene expression was performed on 57 samples of ovarian carcinoma. RNA was isolated from the ovarian cancer tissues. The gene expression changes were determined by microarray analysis and quantitative real time polymerase chain reaction (qRT-PCR). Measurement of relative gene expression levels was used to identify molecular differences among three histologic types of ovarian carcinoma (clear-cell, endometrioid and serous). Unsupervised statistical analysis revealed four biological subtypes among three histotypes under study. The endometrioid ovarian carcinoma was divided into two molecular subtypes. The biggest molecular differences were observed between clear-cell and serous carcinomas (1070 genes, FDR 0.05), the smallest between endometrioid and serous carcinomas (81 genes, FDR 0.05). The biggest group of differentially expressed genes was involved in transport and metabolism. This finding can explain the differences in the response to chemotherapy observed among different histologic types of ovarian carcinomas. In conclusion, we found TCF2 (HNF1B) gene as a suitable marker for ovarian clear cell carcinoma. Gene expression profiling also shed light on the molecular mechanisms of different chemoresistance among the analyzed histotypes.

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COMPARATIVE STUDY ON CT PERFUSION PARAMETERS OF DIFFERENT TYPES OF LUNG CANCER BEFORE AND AFTER CHEMORADIOTHERAPY

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The aim of this paper was to observe the changes in computed tomography (CT) perfusion parameters of patients with lung cancer in early stage before and after chemoradiotherapy. Twenty-five previously treated lung cancer patients underwent a first CT perfusion scan and then a following one before the second course of chemotherapy. CT images of the fourth course of treatment were compared with the initial images. The cases were divided into a remission group and a non-remission group according to Response Evaluation Criteria In Solid Tumors (RECIST). Blood flow (BF), blood volume (BV), Patlak permeability Surface (PS) and Pallak blood volume (PBV) in the different groups were respectively compared before and after treatment. In addition, SPSS17.0 was applied for statistical analysis. $P < 0.05$ signified that the difference had statistical meaning. CT perfusion parameters were all found to be changed compared to before the treatment. BV and PBV parameters decreased twice. BV and PBV parameters in the non-remission group showed an increasing trend. The difference before and after the treatment of these parameters had the highest statistical significance, as well as the difference of remission rate of PBV increasing group and decreasing group. Through the contrasting χ^2 test of remission rate of BV and PBV, it was found that the remission rate of the BV increasing group and the decreasing group had no statistical difference; the remission rate in the PBV decreasing group was higher than the increasing group. All the findings suggest that the change in size of the damaged tissue had no statistical meaning in the early stage of CT perfusion parameter change; CT perfusion parameter of the remission group in the early stage after chemotherapy decreased while the non-remission group increased; the change of BV and PBV was significant.

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THE MECHANISM AND SIGNIFICANCE OF E-CADHERIN, ANTI-APOPTOSIS B-CELL LYMPHOMA-2 PROTEIN AND SE-CADHERIN ROLES IN CANCER

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Women are most likely to suffer from breast cancer of all the malignant tumors. Its incidence is growing rapidly, which severely threatens the health of females. E-cadherin (E-cad), as the mediator of tumor tissue cells, when adhesion between the cells decreases, can improve the wettability and migration ability of cells, and help cell growth and proliferation in the new area. E-cad serves not only as a cancer inhibitor but also as a cancer promoter. sE-cadherin (sE-cad) is formed as a result of the degradation and exfoliation of N-end extracellular domain of E-cad and its level is closely related to the invasion and metastasis of tumor cells. B-cell lymphoma-2 protein (Bcl-2 protein) is the key regulatory factor for the mitochondria apoptosis pathway during the apoptosis of cells, and it plays an important role in the signal transduction pathway of cell apoptosis. Its abnormal expression may induce disorder of the mechanism. This paper, through the study of the expression and relationship of E-cad, Bcl-2 protein and sE-cad, attempts to explain their expression changes during the development of breast cancer, providing clues clinically useful for further recognition of occurrence and development, early diagnosis, interference and early treatment of breast cancer.

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PROFILE OF SELECT HEPATIC INSULIN SIGNALING PATHWAY GENES IN RESPONSE TO 2-AMINOANTHRACENE DIETARY INGESTION

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Some genes that regulate various processes such as insulin signaling, glucose metabolism, fatty acid, and lipid biosynthesis were profiled. The objective of the current investigation is to examine the mRNA expression of some genes that mediate insulin signaling due to 2AA toxicity. 2AA is a polycyclic aromatic hydrocarbon (PAH) that has been detected in broiled food and tobacco smoke. Twenty-four post-weaning 3-4-week-old F344 male rats were exposed to 0mg/kg-diet, 50mg/kg-diet, 75mg/kg-diet, and 100mg/kg-diet 2AA for 2 weeks and 4 weeks. The mRNA expression of AKT1, G6PC, GCK, GLUT4, INSR, IRS1, PP1R3C, PAMPK, SOCS2, and SREBF1 was determined by qRT-PCR followed by the quantification of G6PC and AMPK via ELISA. The results suggest that 2AA modulates these genes depending on the length of exposure. Up-regulation of AMPK and SOCS2 genes in animals treated with 100mg/kg-diet and 50mg/kg-diet, respectively, during 14 days of feeding was noted. G6PC expression was inhibited in the 2-week group while being dose-dependently increased in the 4-week group. Hepatic activity of G6PC was enhanced significantly in the livers of rats that ingested 2AA. It appears that 2AA intoxication leads to the activation of *irs1* and *akt1* genes in the liver. Quantified AMPK amounts increased significantly in the short-term treatment group. Dose-dependent rise of AMPK in animals treated to 2AA showed an increased production of hepatic AMPK in response to the toxicity of 2AA in order to maintain cellular homeostasis. In contrast, the reduction in AMPK concentration in treated animals within the 4-week set indicated an adaptive recovery.

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

NEURAL CORRELATES OF OBSERVATION OF DISGUSTING IMAGES IN SUBJECTS WITH FIRST EPISODE PSYCHOSIS AND POST-TRAUMATIC STRESS DISORDER

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The aim of this study was to analyze neural responses to disgusting images in individuals with first episode psychosis and post-traumatic stress disorder (PTSD). Although anhedonia is a common symptom in both disorders we expected that they would be associated with different neurophysiological abnormalities and patterns of activation. We recruited three groups of participants: 13 individuals with first episode psychosis, 10 individuals with PTSD who had survived the April 2009 L'Aquila earthquake and 25 healthy controls matched for age and education. All individuals participated in a functional imaging experiment in which they watched six alternating blocks of disgusting and scrambled images whilst undergoing scanning with a General Electric 1.5T whole-body scanner. We estimated individuals' beta-weights, extracting 22 clusters corresponding to 22 significant areas. Findings were consistent with other neuroimaging studies; the active areas (i.e. amygdala, insula, inferior and medial frontal gyrus) have consistently been associated with emotional experiences. Statistical analysis revealed important group differences in intensity and direction (positive or negative) of signal from baseline during disgusting condition. Although these results are preliminary they show that functional neuroimaging techniques may make a valuable contribution to differential diagnosis of first episode psychosis and PTSD.

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IN VITRO EXPANSION OF TUMOUR CELLS DERIVED FROM BLOOD AND TUMOUR TISSUE IS USEFUL TO REDEFINE PERSONALIZED TREATMENT IN NON-SMALL CELL LUNG CANCER PATIENTS

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The clinical development of locally and advanced non-small cell lung cancer (NSCLC) suffers from a lack of biomarkers as a guide in the selection of optimal prognostic prediction. Circulating Tumour Cells (CTCs) are correlated to prognosis and show efficacy in cancer monitoring in patients. However, their enumeration alone might be inadequate; it might also be critical to understand the viability, the apoptotic state and the kinetics of these cells. Here, we report what we believe to be a new and selective approach to visually detect tumour specific CTCs. Firstly, using labelled human lung cancer cells, we detected a specific density interval in which NSCL-CTCs were concentrated. Secondly, to better characterize CTCs in respect to their heterogeneous composition and tumour reference, blood and tumour biopsy were performed on specimens taken from the same patient. The approach consisted in comparing phenotype profile of CTCs, and their progenitor Tumour Stem Cells, (TSCs). Moreover, NSCL-CTCs were cultivated in short-time human cultures to provide response to drug sensitivity. Our bimodal approach allowed to reveal two items. Firstly, that one part of a tumour, proximal to the bronchial structure, displays a predominance of CD133+. Secondly, specific NSCL-CTCs Epithelial Cell Adhesion Molecule (EpCAM)+CD29+ can be used as a negative prognostic factor as well the high expression of CTCs EpCAM+. These data were confirmed by drug-sensitivity tests, *in vitro*, and by the survival curves, *in vivo*.

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INCREASED RISK OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN WITH TYPE 2 DIABETES MELLITUS: A THREE-YEAR LONGITUDINAL STUDY WITH PHALANGEAL QUS MEASUREMENTS

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Type 2 diabetes mellitus (T2DM) is associated with a higher risk of fractures even in presence of normal or increased bone mineral density. The purpose of this three-year longitudinal study was to evaluate the risk of osteoporotic fractures by assessing the changes of Quantitative Ultrasound (QUS) parameters in a group of postmenopausal women with type 2 diabetes mellitus (T2DM) compared with non-diabetic controls. The measurements were taken on a group of 18 postmenopausal women affected by T2DM and 18 healthy age-matched controls, aged 55-70 years, referring to the Osteolab laboratory at the ISBEM Research Institute (Brindisi, Italy) between 2009 and 2013. Subjects had baseline and 3-year follow-up measurements with phalangeal QUS carried out by a DBM Sonic Bone Profiler 1200 (Igea®); medical history, current drug therapies and risk factors for fractures were recorded for each patient. The analyzed phalangeal QUS parameters were Amplitude-Dependent Speed of Sound (AD-SoS), Bone Transmission Time (BTT), Fast Wave Amplitude (FWA) and Signal Dynamic (SDy). At the baseline visit we found no statistically significant difference between T2DM and non-diabetic patients when looking at phalangeal QUS parameters. At the three-year follow-up visit, a significantly higher decrease of both BTT ($P<0.001$) and AD-SoS ($P<0.001$) parameters was found in the T2DM group. On the contrary, the decrease of FWA was significantly higher in non-diabetic controls ($P<0.001$). Our data confirm the ability of phalangeal QUS to detect differences in the risk of osteoporotic fractures in T2DM postmenopausal women compared to non-diabetic controls. The study suggests that T2DM women present a higher cortical porosity and increased trabecular bone density compared to non-diabetic controls, respectively shown by the higher decrease of both AD-SoS and BTT and the lower decrease of FWA.

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INHIBITORY EFFECTS OF DIFFERENT LACTOBACILLI ON *CANDIDA ALBICANS* HYPHAL FORMATION AND BIOFILM DEVELOPMENT

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The aim of this study was to investigate the effects of different species of Lactobacilli on hyphal formation and biofilm development by the opportunistic fungal pathogen *Candida albicans*. We employed 4 different Lactobacillus species, namely *L. rhamnosus*, *L. acidophilus*, *L. plantarum* and *L. reuteri*, and 2 *C. albicans* strains, the reference DAY286 and its isogenic *hwp1/hwp1* mutant, the FJS24 strain. As assessed by morphological analysis and quantitative colorimetric assays, Lactobacillus crude filtrate supernatant fluids (CFSF) affected *Candida*, impairing both hyphal formation and biofilm production. The CFSF-mediated phenomenon occurred in a dilution- and time-dependent manner and was consistently observed, irrespective of the *C. albicans* *HWPI* genotype.

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

THE IMMUNOMODULATORY MOLECULE PIDOTIMOD INDUCES THE EXPRESSION OF THE NOD-LIKE RECEPTOR NLRP12 AND ATTENUATES TLR-INDUCED INFLAMMATION

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Pidotimod (3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid) (PDT) is a synthetic dipeptide with *in vitro* and *in vivo* immunomodulatory properties that is largely used for treatment and prevention of infections in paediatric and disease-prone patients. However, the effects of PDT on cellular immune responses are still poorly characterized and there is little information on the mechanism of action of this compound. It has been speculated that PDT action may be exerted through the interaction with a Pattern Recognition Receptor (PRR). Therefore, to gain a further understanding of the immune pathways involved by PDT, we first decided to investigate whether PDT could modify the immune response triggered by TLR ligands. Monocytic cells were exposed to PDT then stimulated with a panel of TLR agonists. Under these experimental conditions, we observed a significant decrease in the synthesis of key proinflammatory mediators in comparison to the production observed in TLR-stimulated cells that were not treated with PDT. Using RT² Profiler PCR Array we have observed that PDT specifically up-regulates the expression of the NOD-like receptor NLRP12 mRNA in the absence of any further co-stimulation. Increase of NLRP12 in cells treated with PDT was confirmed using specifically designed real-time quantitative PCR and western blotting assays where a clear increase in the amount of NLRP12 protein was detected. Furthermore, in myeloid/monocytic cells we demonstrated that PDT treatment counteracts the NLRP12 reduction induced by TLR agonists. Finally, the results obtained using NLRP12 silenced cells showed that down-regulation of the proinflammatory function occurring in PDT-treated cells upon interaction with TLRs is associated with the increased levels of NLRP12 induced by PDT. To our knowledge this is the first evidence of an immunomodulatory peptide that upregulates NLRP12 and, through this molecule, antagonizes the TLR-induced inflammatory response. These results pave the way for the development of innovative therapeutic approaches aimed at controlling different pathological settings such as tumorigenesis, systemic inflammatory processes and autoimmunity, where NLRP12 plays a crucial role.

NITRIC OXIDE SYNTHASE EVALUATION IN ORAL PRECANCEROUS AND CANCEROUS LESIONS

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Nitric Oxide (NO) has been linked to several cardiovascular, neurological and immunological physiological and pathological functions. Several studies have shown that the eNOS, nNOS and iNOS effects on cancer cell growth and proliferation are related to the upregulation of the Wnt pathway and have a central role during metastasis development. Recent studies suggest that cancer cells undergo metabolic reprogramming, which drives cancer cell growth and progression. The aim of this study was to observe the NOS activity in the pathogenesis of oral precancerous and cancerous lesions. The results showed changes in eNOS activity levels, which increased from healthy oral mucosa to oral squamous cell carcinoma SCC, through different dysplasia levels. The iNOS activity levels increased in precancerous lesions compared to healthy mucosa, where iNOS was absent, while it decreased in SCC lesions. Moreover, a gradual increase of nNOS activity together with the progression of the lesions was also found. These results may suggest how NO could play a critical role during pathogenesis, growth and development of precancerous lesions to cancer degeneration.

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

**A NATURAL FORMULATION (IMOVIRAL™) INCREASES MACROPHAGE
RESISTANCE TO LPS-INDUCED OXIDATIVE AND INFLAMMATORY STRESS
*IN VITRO***

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Imoviral™ is a natural product formulation containing a mixture of uncaria, shiitake and ribes extracts. All ingredients are recognized as antioxidant, anti-inflammatory agent and immunomodulant. In order to evaluate the rational basis of extract mixture as immunomodulatory agent, we tested the effect of Imoviral™ formulation on macrophage response to lipopolysaccharide (LPS)-induced stress. The effect was evaluated as variation of reactive oxygen species (ROS) and prostaglandin E₂ (PGE₂) production and as cytokine gene expression. The extract did not affect cell viability up to 250µg/ml. Treatment with extract (10-150µg/ml) reduced ROS and PGE₂ production as well as IL-8 and TNF-α gene expression. A pre-treatment with extract blunted LPS-induced production of ROS and PGE₂, markers of oxidative and inflammatory stress, as well as the gene expression of all cytokines tested, indicators, *in vitro*, of immune response activation. In conclusion, we demonstrated that Imoviral™ formulation could be a useful tool to modulate the immune function, reducing the oxidative and inflammatory markers related to bacterial attack. Experimental data suggest that Imoviral™ extract mixture could also represent a preventive pharmacological strategy to enhance cell resistance to bacterial infections.

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LETTER TO THE EDITOR

SARCOID-LIKE PATTERN IN A PATIENT WITH TUBERCULOSIS

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The first three authors equally contributed to this work

For several decades the “mystery” of sarcoidosis has continued to evade revelation. Nowadays, due to medical progress and the opportunity of performing highly specialized tests which assist the identification of this condition as a separate disease, the understanding of the eternal mystery appears closer. Nevertheless, many contemporary studies focus on the putative link between sarcoidosis and infectious antigens isolated from skin lesions. On the other hand, a golden rule to differentiate sarcoidosis from other conditions such as tuberculosis and sarcoid-like reactions is the sterility of granulomas. However, there are hypotheses which state that sarcoidosis could be related to tuberculosis and, in particular, to the Mycobacterium species. The similarities that many authors identify between the genetic signatures of the two conditions definitely raise concerns regarding: i) the inability to categorize every single case in a clear-cut way, namely in inflammatory/autoimmune or infectious; ii) the need of new criteria to clearly differentiate sarcoid-type reactions in the context of infectious diseases from sarcoidosis as an autonomous disease. We report the case of a 35-year-old male patient with histopathological evidence of sarcoid-like granulomas in cutaneous lesions on the face and imaging studies consistent with a systemic form of sarcoidosis. However, a positive QuantiFERON-TB Gold test and Ziehl-Neelsen staining was found, leading to the diagnosis of a rare case of TBC with histopathological evidence of sarcoid-like lesions. The following are also discussed: i) the potential role of tuberculosis antigens in the context of occult tuberculosis as generators of sarcoid-type of reaction; and ii) the necessity of additional diagnostic panels as a standard procedure in patients with suspected sarcoid granulomas of unknown origin.

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LETTER TO THE EDITOR

MACROPHAGES AND DENDRITIC CELLS IN THE DEVELOPMENT OF LIVER INJURY LEADING TO LIVER FAILURE

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Liver failure (LF) continues to be a serious problem due to different underlying disorders. Not only hepatocytes but Kupffer cells (KCs) and dendritic cells (DCs) are of importance in this instance. We wanted to investigate the possible role of KCs and liver DCs in the development of liver injury in patients with liver failure. Liver specimens from 23 patients who died after liver failure were examined for the presence and distribution of CD68-positive KCs and CD83-positive DCs by immunohistochemistry. The distribution of the CD83-positive DC in the sinusoidal and the periportal spaces was not even. While 39.1% of patients had a high sinusoidal density of CD83-positive cells, 60.9% demonstrated a high density of CD83-positive cells in the periportal tract. The number of CD83-positive DCs in periportal tracts in patients with advanced liver fibrosis (n = 5) were high, while those with mild liver fibrosis (n = 18) had low numbers of mature dendritic cells ($\chi^2=4.107$; $p=0.043$). In addition, all patients with intensive fibrosis had low counts of CD68-positive KC's in portal tracts vs patients with mild fibrosis of which 67% had high counts ($\chi^2=6.97$; $p=0.008$). In seven of the patients with moderate steatosis (87.5%) low numbers of CD68-positive KCs were found in sinusoids, in contrast to those with severe steatosis, where 12 patients (80%) had high KC counts ($\chi^2=13.4$; $p<0.001$). The distribution and number of CD68-positive KC and CD83-positive DC reflect the progression of liver fibrosis leading to liver failure.

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LETTER TO THE EDITOR

ALEXITHYMIA AND ITS RELATIONSHIPS WITH ACUTE PHASE PROTEINS AND CYTOKINE RELEASE: AN UPDATED REVIEW

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LETTER TO THE EDITOR

EXPRESSION OF POLY(ADP-RIBOSE) POLYMERASE IN BONE REGENERATION

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Poly(ADP-ribose) polymerase (PARP) is a 116kDa enzyme catalysing the synthesis of ADP-ribose polymers from NAD⁺. PARP is activated in response to DNA strand breaks and plays a critical role in the maintenance of genomic integrity. However, considering its role also in transcription, proliferation as well as apoptosis in biological process, in the present study the role of PARP in bone regeneration was evaluated, in particular in bone cell proliferation and differentiation processes. Thus, formalin fixed paraffin embedded specimens of 10 human bone samples after sinus lift were collected and investigated by immunohistochemistry using a mouse monoclonal anti-human PARP antibody. PARP was expressed in cells with morphological features of osteoblasts in the areas of new bone formation at the junction between mineralized and unmineralized tissue, between osteoid tissue and bone. Few osteoclasts were observed and showed only focal nuclear expression of PARP, while osteocytes showed no positivity for PARP. Our data showed an overall involvement of PARP enzyme in human bone tissues, in particular during bone regeneration process.

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