

THE IMMUNOLOGY OF GLUTEN SENSITIVITY BEYOND THE INTESTINAL TRACT

A. VOJDANI, T. O'BRYAN¹ and G.H. KELLERMANN²

*Immunosciences Lab., Inc., Beverly Hills, CA; 1Davis Parkway, Warrenville, IL;
2NeuroScience, Osceola, WI, U.S.A.*

Celiac disease and gluten-sensitive enteropathy are terms that have been used to refer to a disease process affecting the small bowel. However, evidence has been accumulated in literature demonstrating that gluten sensitivity or celiac disease can exist even in the absence of enteropathy, but affecting many organs. Based on overwhelming evidence, immunological pathogenesis has been demonstrated in the joint, the heart, thyroid, bone, and, in particular, the brain cerebellum and neuronal synapsin I. When blood samples of patients with celiac disease are tested against gliadin and different tissue antigens, in addition to gliadin antibody, a significant percentage of them exhibit elevation in antibodies against transglutaminase, heat shock protein, collagen, thyroid, myosin, endothelial cell, bone antigen (transglutaminase), myelin basic protein, cerebellar and synapsin. This elevation of autoantibodies in patients with celiac disease may result in neuroimmune disorders. In fact, in comparison to the general population, the incidence of various autoimmune disorders, including gluten ataxia, is increased up to 30-fold in patients with celiac disease. Therefore, immune evaluation of patients with gluten sensitivity or celiac disease, in addition to gliadin and transglutaminase, should include antibody measurement against thyroglobulin, thyroid peroxidase, heat shock protein, bone transglutaminase, myelin basic protein, cerebellar peptide and synapsin. This novel laboratory approach to gluten sensitivity and autoimmunity may enable clinicians to detect markers of autoimmune diseases. Early identification of gluten sensitive and celiac disease patients and implementation of a gluten-free diet may result in significant improvement and control of associated diseases.

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SUBSTANCE P: AN INFLAMMATORY PEPTIDE

G.S. KATSANOS, A. ANOGEIANAKI, C. ORSO¹, S. TETÈ², V. SALINI¹, P.L. ANTINOLFI³
and G. SABATINO⁴

Immunology Division, University of Chieti-Pescara, Chieti, Italy; 1Orthopaedic Division, University of Chieti-Pescara, Chieti; 2Dental School, University of Chieti-Pescara, Chieti; 3Orthopaedics Division, University of Perugia, Perugia; 4Paediatric Division, University of Chieti-Pescara, Chieti, Italy

Substance P (SP) is involved in neurogenic inflammation and in the pathogenesis of several inflammatory diseases, demonstrating that there is a narrow interrelationship between the nervous system and immunity. Macrophage functions are altered in stress, therefore, since SP is a macrophage activator, its biological effect has been intimately linked to stress. In fact, SP enhances LPS-induced macrophage TNF α production from stressed animals and stimulates the production of IL-8 CXC chemokine response in a mast cell line *in vitro*. The stress-induced cytokines from macrophage also alter and contribute to inflammation. Understanding the pathophysiology of inflammation and the role of the chemical mediator SP may improve inflammation management.

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PHYSICOCHEMICAL CHARACTERISTICS OF MOLECULES AND THEIR DIFFUSION ACROSS HUMAN VAGINAL MUCOSA

A.D. VAN EYK, P. VAN DER BIJL and L.M. MOLL

Division of Pharmacology, Department of Medicine, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa

The diffusion rate of permeant molecules through mucosal tissue depends on the physicochemical characteristics of the molecules themselves as well as the properties of the tissue. In this study the diffusion kinetics of various molecules was examined through intact as well as de-epithelialised human vaginal mucosa. The molecules studied included tritium-labelled water, 17β -estradiol, educedarecoline, vasopressin, oxytocin, bradykinin, tacrolimus, cyclosporin A, dihydro-alprenolol, cimetidine and benzylpenicillin. Freshly harvested human vaginal tissue was frozen in liquid nitrogen and stored at -85°C . A flow-through diffusion apparatus was used for the *in vitro* permeability studies (24 h, 20°C , 1.5 ml/h). The mean estimated – or mean steady-state flux values for all the molecules studied across intact human vaginal mucosa, were generally found to be lower than those of the corresponding deepithelialised tissue. Using an F-test and comparing whole curves, statistically significant differences in the diffusion rates of tacrolimus, reduced-arecoline, vasopressin, bradykinin, benzylpenicillin, water and cimetidine were found when comparing intact and de-epithelialised vaginal mucosa. Generally, smaller permeant molecules diffused at a higher rate than larger molecules. The epithelial layer retarded the diffusion rate of molecules carrying charges at physiological pH. Damage to the epithelial layer did not necessarily increase the diffusion rate of all molecules tested and small lipophilic molecules did not necessarily diffuse at higher rates than hydrophilic molecules.

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ELASTASE II GENE ENCODING AS INFLAMMATORY MOLECULES IN ACUTE MYELOBLASTIC LEUKEMIA

G. AHANGARI, N. SHAMSODIN, Z. CHAVOSHZADEH¹, K.A. MOGHADAM²,
A. GHAVAMZADEH² and S.H. NAZARIAN³

Department of Molecular Medicine and Immunology, National Institute for Genetic Engineering and Biotechnology, Tehran; 1Department of Clinical Immunology, Mofid Pediatric Hospital, Beheshti University of Medical Sciences, Tehran; 2Department of Hematology and Oncology, Center for Bone marrow Transplantation, Shariati Hospital, Tehran University of Medical Science, Tehran; 3Department of Hematology and Oncology, Mofid Pediatric Hospital, Beheshti University of Medical Sciences, Tehran, Iran

Acute myeloblastic leukemia (AML) is characterized by uncontrolled proliferation with the bone marrow (BM) of malignant myeloid progenitors arrested in their maturation process and the egress of these abnormal cells into the circulation. There is evidence that neutrophil production is a balance between the proliferative action of granulocyte-colony-stimulating factor (G-CSF) and a negative feedback from mature neutrophils. Recently, there have been reports on mutations in neutrophil

elastase (ELA2) gene in genomic DNA of cyclic neutropenia. These patients developed acute myeloblastic leukemia. Therefore, we hypothesized that elastase may play role in the abnormal AML. Peripheral blood was obtained from 42 patients with acute myeloblastic leukemia and 30 healthy individuals. Total RNA was isolated using RNA standard techniques from freshly separated cells by polymorphoprep. RNA was analyzed by employing PCR amplification of reverse transcribed using a total of ten specific primers. We amplified five exons of ELA2 gene separately and sequenced each exon. Mutational analysis was carried out by directed capillary sequencing method. We found no mutation in 42 Acute myeloblastic leukemia patients compared to healthy individuals. Interestingly, we found heterozygote 50% single nucleotide polymorphism (SNP) in exon II codon 44 of healthy individuals but not in AML patients. It was a silent mutation G to A substitution but no changes in amino acid sequences. The codon sequence was GCG that changed to GCA.

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ARTIFICIAL LIGHT-INDUCED CYTOKINE GENE EXPRESSION IN RABBIT CORNEA IN VIVO: EFFECT OF OCULAR DROPS CONTAINING FLURBIPROFEN

E. BASLI¹, A. GOULAS¹, V. KARAMPATAKIS², A. KAROUTIS², K. VARSAMIDIS³,
A. KOMNINO⁴, V. MIRTOSU-FIDANI¹ and B. KOKKAS¹

¹Department of Experimental Pharmacology, Medical School, Aristotle University of Thessaloniki;

²Department of Experimental Ophthalmology, Medical School, Aristotle University of Thessaloniki;

³Department of Physiotherapy, Technological Educational Institute of Thessaloniki; ⁴Department of Surgery, School of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

The purpose of this study is to examine the effect of artificial sunlight on the gene expression of TNF- α , IL-6 and IL-8 in rabbit cornea *in vivo*, as well as the potential of an ocular anti-inflammatory formulation containing sodium flurbiprofen to suppress this effect. New Zealand Albino rabbits were subjected to acute exposure of their eyes to irradiation emitted from a light bulb commonly used for artificial tanning purposes with and without topical application of a commercially available formulation containing sodium flurbiprofen. Semi-quantitative RT-PCR was used as a means of estimating gene expression. The gene expression of IL-6 and IL-8 was found statistically significantly increased at 24 hrs post-exposure time ($p = 0.003$ and 0.006 , respectively), as was that of TNF- α albeit in a non-statistically significant manner. A sodium flurbiprofen (0.03%) formulation was found to effectively reduce the lightinduced upregulation of all three cytokines in the rabbit cornea.

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PATIENTS WITH ALLERGIC RHINITIS SHOW AN ALLERGEN-SPECIFIC INTERFERON-GAMMA DEFECT

D. FENOGLIO, A. FERRERA, F. FERRERA, M.P. SORMANI¹, M. DI GIOACCHINO²
and G. CIPRANDI

DIMI-CEBR, University of Genoa and Azienda Ospedaliera Universitaria San Martino, Genoa;

1Unit of Biostatistics, Dept. of Health Sciences, University of Genoa; 2Allergy Related Disease Unit,

“G. d’Annunzio University” Foundation, Chieti, Italy

Allergic rhinitis (AR) is characterized by Th2 polarized immune response. Consequently, allergic patients have a defect in IFN- γ production. So far, however, all the experimental studies have investigated only the IFN- γ production induced by the causal allergen. The aim of this study is to investigate whether there is a difference in the *in vitro* IFN- γ production, using different allergens as stimuli, in patients presenting with rhinitis due to pollen allergy. Forty-one AR patients with pollen allergy were enrolled. IFN- γ -specific producing cells were stimulated with PHA, causal pollen, and House Dust Mite (HDM). IFN- γ production was assessed by cytokine ELISPOT. IFN- γ production of peripheral blood mononuclear cells (PBMC) stimulated by specific pollen was significantly lower than IFN- γ production of PBMC stimulated by HDM ($p < 0.001$). IFN- γ production of PBMC stimulated by specific pollen was significantly lower than IFN- γ production of PBMC stimulated by PHA ($p < 0.001$). Moreover, in the HDM-sensitized patients, there seems to be a trend for a different defect. The present study highlights that the defective IFN- γ production is allergen specific and that HDM sensitization may also affects this parameter.

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RHEUMATOID ARTHRITIS: TIME DISJOINTS

V. BRUZZESE

Department of Medicine ASL RM/A, UOC of Internal Medicine, Rheumatology Section, Nuovo Regina Margherita Hospital, Rome, Italy

“Time disjoints” is the best way to define how aggressive Rheumatoid Arthritis (RA) is concerning damage to the joints, and it also implies that the sooner the therapy is started, the better the prognosis that can be achieved in changing the natural outcome of the disease and in preventing disability.

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REVERSIBLE NORMOLIPEMIC XANTHELASMA PALPEBRARUM ASSOCIATED WITH INFLAMMATION IN CASTLEMAN’S DISEASE

C.S. FLOUDAS, X. YIAKOUMIS, M. TSIRONI and A. AESSOPOS

First Department of Internal Medicine, National and Kapodistrian University of Athens Medical School, Laiko General Hospital, Athens, Greece

Xanthelasma palpebrarum is a xanthomatous skin lesion sometimes associated with dyslipidemias. Little is known about the clinical significance of normolipemic xanthelasma lesions. We present a patient with localized Castleman’s disease of plasma cell type, accompanied by prominent bilateral *xanthelasma palpebrarum*, intense systemic inflammatory reaction, polyclonal hypergammaglobulinemia and reactive amyloidosis (AA type). Curative resection of the mass resulted in regression of the clinical and biochemical abnormalities and substantial improvement of the xanthelasma lesions. In this patient the skin lesion could be connected pathogenetically with the underlying disease and may represent an early marker of it. Furthermore, the regression of this lesion suggests that dissolution of lipid accumulation in atheromatous lesions may be possible.

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