

INTERLEUKIN-19 (IL-19) NETWORK REVISITED

D. KEMPURAJ, S. FRYDAS, K. KANDERE, B. MADHAPPAN, R. LETOURNEAU, S. CHRISTODOULOU, W. BOUCHER, G. RICCIONI, P. CONTI AND T. C. THEOHARIDES

The objective of this study is to review the biological role of IL-19 in immunity and inflammation. *Int. J. Immunopathol. Pharmacol.* 16:95.

EFFECT OF THE COMPOUND L-MIMOSINE IN AN IN VIVO MODEL OF CHRONIC GRANULOMA FORMATION INDUCED BY POTASSIUM PERMANGANATE (KMNO₄)

S. FRYDAS, M. PAPAZHARIADOU, N. PAPAIOANNOU, M. HATZISTILIANOU, M. TRAKATELLIS, D. MERLITTI, M. DI GIOACCHINO, A. GRILLI, M.A. DELUTIIIS, G. RICCIONI, P. CONTI AND I. VLEMMAS.

The plant amino acid L-mimosine has recently been suggested to inhibit cells at a regulatory step in late G₁ phase before establishment of active DNA replication forks. In addition, L-mimosine is an extremely effective inhibitor of DNA replication in chromosomes of mammalian nuclei. In this work, the effect of L-mimosine on chronic inflammation induced by dorsal injections of 0.2 ml of a 1:40 saturated crystal solution of potassium permanganate in mice, was studied. Seven days afterwards, all mice developed a subcutaneous granulomatous tissue indicative of chronic inflammatory response at the site of infection. The intraperitoneal administration of L-mimosine (200 µg/dose) to the potassium permanganate treated mice for 5 consecutive days (the first at the same time of inoculation of the KMnO₄), produced a significant decrease in size and weight of the granuloma when compared to mice not treated with L-mimosine (controls). In addition, in all mice treated with L-mimosine, there was a strong inhibition of tumor necrosis factor alpha that was revealed in the serum (P<0.05) and in the minced granulomas. Interleukin-6 was not detected in the serum of treated and untreated mice. These findings show for the first time, that L-mimosine may have an anti-inflammatory effect on chronic inflammation and an inhibitory effect on tumor necrosis factor alpha and interleukin-6 generation in supernatant fluids of minced granulomas. *Int. J. Immunopathol. Pharmacol.* 16:99

PREVALENCE OF *BORRELIA BURGDORFERI* SENSU LATO GENOMOSPECIES AND OF THE HUMAN GRANULOCYTIC EHRLICHIOSIS (HGE) AGENT IN *IXODES RICINUS* TICKS COLLECTED IN THE AREA OF MONTI LEPINI, ITALY

I. SANTINO, A. IORI, M. NICOLETTI, S. VALLETTA, C. CIMMINO, G.L. SCOARUGHI, D. SANTAPAOLA, R. SESSA, and M. DEL PIANO.

Ticks are obligate hematophagous arthropods that are parasites in every class of vertebrates in most regions of the world. They are also considered to be important vectors for the transmission of

human infectious diseases. In the present study we used polymer chain reaction (PCR) amplification analysis to determine the prevalence of *Borrelia burgdorferi* and *Ehrlichia phagocytophila*, the agents of, respectively, Lyme borreliosis and human granulocytic ehrlichiosis, among ticks inhabiting the area of Monti Lepini, a wild area located in the Latium Region of Italy. A total of 141 *I. ricinus* ticks (125 nymphs and 16 adults) were collected in the studied area. Total DNAs were extracted from *I. ricinus* nymphs (pooled in groups of five) and from individual adults. The DNA samples were examined for the presence of *B. burgdorferi* sensu lato and *E. phagocytophila* by PCR using two specific pairs of oligonucleotides that specifically amplify distinct DNA regions of the 16S rRNA genes of the two species. The prevalence of vectors infected with *B. burgdorferi* s. l. was 16% in pooled nymphs samples, and 12.5% in adult ticks, while *E. phagocytophila* was found only in pooled nymphs samples (8%). Three genomospecies were identified, namely *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia valaisiana*, in samples found positive for *B. burgdorferi* s. l. No sample was found positive for *Borrelia burgdorferi* sensu stricto. *Int. J. Immunopathol. Pharmacol.* 16:105

DETECTION OF TT VIRUS IN LYMPH NODE BIOPSIES OF B-CELL LYMPHOMA AND HODGKIN'S DISEASE, AND ITS ASSOCIATION WITH EBV INFECTION

A.R. GARBUGLIA, T. IEZZI, M.R. CAPOBIANCHI, P. PIGNOLONI, A. PULSONI, J. SOURDIS, E. PESCARMONA, D. VITOLO and F. MANDELLI

Human TT virus (TTV) recently isolated from the serum of a patient with post-transfusion hepatitis does seem to have only hepatopathic effect. The virus can also infect the serum, peripheral blood mononuclear cells (PBMC) and bone marrow cells (BMC). Additional evidence has indicated that TTV is also present in the serum of people with hematopoietic malignancies. A significant increase in the incidence of lymphoma has recently been observed worldwide. We have investigated the presence of TTV DNA in lymph node biopsies of Italian patients affected with the most common lymphoma types in Western Countries: follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and nodular sclerosis Hodgkin's disease (NS-HD). The possible role of a co-infection with Epstein-Barr virus (EBV) has also been investigated. DNA was extracted from 73 paraffin-embedded and 38 snap-frozen tissue specimens. From these, only 67 samples (29 paraffin-embedded and 38 snap-frozen tissues) from a total of 56 patients, were suitable for PCR analysis. TTV and EBV were detected by PCR using primers from two different conserved region in TTV and EBV genomes respectively. TTV DNA was detected in 30.0-50.0% of FL, 30.8% of DLBCL and 30.0-50.0% of NS-HD cases, depending on the primers used. All cases of non-specific reactive lymphoid hyperplasia (RLH), used as a putative control, were negative. The two major TTV genotypes circulating in Italy (G1 and G2) were detected in the analysed lymphoid neoplasms. EBV DNA was detected in 40.0% of FL, in 72.7% of DLBCL, in 80.0% of SN-HD and in 40.0% of RLH cases. EBV co-infection was found in 90% of TTV positive cases. The in situ hybridization assay was performed in TTV positive frozen samples.

The significant prevalence of TTV DNA in lymphocytes circulating in the lymph nodes of both B-cell lymphomas and HD reported herewith suggests an implication of TTV infection in the development of these lymphoproliferative disorders. *Int. J. Immunopathol. Pharmacol.* 16:109

HETEROGENEITY OF VIRULENCE-RELATED PROPERTIES IN *LISTERIA MONOCYTOGENES* STRAINS ISOLATED FROM PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

C. LONGHI, M. PENTA, M. P. CONTE, C. GIRMENIA and L. SEGANTI

Listeria monocytogenes is an intracellular foodborne pathogen of humans and animals for which there are indications of virulence differences among strains. Various virulence properties related to different phases of infection process were investigated in *L. monocytogenes* strains isolated from patients affected by haematological malignancies. In these isolates, besides to the clinical history, we analysed the haemolysin production, the survival to acidic pH, the ability to enter and proliferate in human intestinal-like and human macrophagic-like cells, as well as the allelic polymorphism of the *actA* gene involved intracellular movement. A general heterogeneity in the virulence properties was detected which did not appear correlated with the clinical outcome of listeriosis but more probably was influenced by the status of the immune defence of the host. *Int. J. Immunopathol. Pharmacol.* 16:119

NO SPECIFIC REACTIVITY TO *E. COLI* GLUTAMIC ACID DECARBOXYLASE FROM SERA OF NEWLY-DIAGNOSED INSULIN DEPENDENT DIABETIC PATIENTS

C. KONIDARIS, P.G. MITLIANGA AND G. K. PAPADOPOULOS

The 65 kD isoform of Glutamic Acid Decarboxylase (GAD), is one of the major autoantigens in human type 1 diabetes mellitus. This enzyme shares aminoacid identity, in select regions already determined as antigenic with its counterpart from *E. coli*. We tested the reactivity of diabetic and normal sera and an *E. coli* GAD-specific monoclonal antibody (2D9) to *E. coli* GAD by solid phase and competition ELISA, as well as immunoblotting to check for cross-reactivity of autoantibodies to the two antigens. Specific antibodies for *E. coli* GAD are present in diabetics and normal subjects without any differences in frequency and titer. The reactivity of such antibodies in ELISA could be blocked in a dose-dependent manner by the addition of excess antigen in the liquid phase. Furthermore, the monoclonal antibody against *E. coli* GAD does not recognise human recombinant GAD65 in an ELISA. We conclude that there is no basis for cross-reactivity between the two antigens, and antibody reactivity to GAD65 in man cannot arise from cross-reactivity to the *E. coli* enzyme. *Int. J. Immunopathol. Pharmacol.* 16:128

NEUROBEHAVIORAL, AUTONOMIC NERVOUS FUNCTION AND LYMPHOCYTE SUBSETS AMONG ALUMINUM ELECTROLYTIC WORKERS

S. C. HE, N. QIAO and W. SHENG

The purpose of our study is to determine the alteration of neurobehavioral parameters, autonomic nervous function and lymphocyte subsets in aluminum electrolytic workers of long-term aluminum

exposure. 33 men who were 35.16 ± 2.95 (mean \pm S.D) years old occupationally exposed to aluminum for 14.91 ± 6.31 (mean \pm S.D) years. Air Al level and urinary aluminum concentration was measured by means of graphite furnace atomic absorption spectrophotometer. Normal reference group were selected from a flour plant. Neurobehavioral core test battery (NCTB) recommended by WHO was utilized. Autonomic nervous function test battery recommended by Ewing DJ was conducted on subjects. FAC SCAN was used to measure the lymphocyte subsets of peripheral blood. The mean air aluminum level in the workshop was 6.36 mg/m^3 , ranged from 2.90 to 11.38 mg/m^3 . Urinary aluminum of the Al electrolytic workers (40.08 ± 9.36 microgram/ $\mu\text{g.cre}$) was obviously higher than that of control group ($26.84 \pm 8.93\mu\text{mg.cre}$). Neurobehavioral results showed that the scores of DSY, PAC and PA in Al electrolytic workers were significantly lower than those of control group, The score of POMSC, POMSF and SRT among Al exposed workers were significantly augmented in relation to those of control group. Autonomic nervous function test results showed that R-R interval variability of maximum ratio of immediately standing up in Al electrolytic workers were decreased compare with the control group, while the BP-IS, HR-V, HR-DB, $R_{30:15}$ had no significant change. Peripheral blood lymphocyte subsets test showed that $\text{CD4}^+ \text{CD8}^+$ T lymphocyte in Al electrolytic workers increased. This study suggests that Al exposure exerts adverse effects on neurobehavioral performance, especially movement coordination and negative mood, and parasympathetic nervous function; moreover it increase $\text{CD4}^+ \text{CD8}^+$ T lymphocyte subsets. *Int. J. Immunopathol. Pharmacol. 16:139*

POLYAROMATIC HYDROCARBONS ADMINISTERED IN HUMANS BY DERMAL ROUTE INCREASE TOTAL IGE

G. MASTRANGELO, C. VELLER FORNASA, S. PAVANELLO, G. MARCER, M. LAZZARO, G. MILAN, E. FADDA, U. FEDELI, and E. CLONFERO

Inhalation of polyaromatic hydrocarbons (PAHs) extracted from diesel exhaust particles (DEP) enhances local (nasal) production of IgE in humans. The aim of the present research is to investigate whether in humans dermal exposure to PAHs which are not extracted from DEPs increases serum IgE, and whether host factors modify the immunologic effect. In thirty-two patients with acute psoriatic lesions, a cream containing 3% of coal tar (which holds a variety of PAHs) was applied to the skin for 24 hours. Serum IgE were measured before (IgE0) and four (IgE4) and eight (IgE8) days after application. Replicated means were compared by analysis of variance for repeated measures and by the Newman-Keuls' test. IgE0, IgE4 and IgE8 were 151.19, 159.69 (a 6% excess) and 170.90 kU/L (a 13% excess) respectively; pairwise comparison showed IgE8 was significantly higher than IgE0 ($p < 0.05$). At multiple linear regression analysis, the percentage increase in serum IgE across observation days was the dependent variable against age, sex, cigarettes/day, urinary 1-pyrenol, atopy, skin area treated, and grams of cream. Of the independent variables, only age had a significant ($p < 0.028$) influence: the younger the age, the higher the IgE response to PAHs. We conclude that whatever the source and the route of entry (skin or respiratory tract), PAHs increase total serum IgE, mainly in younger age groups. *Int. J. Immunopathol. Pharmacol. 16:145*

COMPARTMENTALISATION BETWEEN GUT AND LUNG MUCOSAE IN A MODEL OF SECONDARY IMMUNODEFICIENCY. EFFECT OF THYMOMODULIN.

M.E. ROUX, M.G. MARQUEZ, S. OLMOS, C.A. FRECHA and A. FLORIN-CHRISTENSEN

Compartmentalisation of mucosal immune response seems to be the result mainly of the preferential migration of activated cells back to their inductive sites. The aim of this report was to demonstrate, in a model of secondary immunodeficiency in Wistar rats (severely protein deprived at weaning and refed with casein 20 %; group R21), that the oral administration of Thymomodulin (group:R21TmB) has different effects on gut and BALT (Bronchus-associated lymphoid tissue). Tissue sections (5 μ) were studied by immunohistochemistry 1) .The oral administration of Thymomodulin restores only in gut Lamina propria (LP) the IgA B and CD4 T cell populations to control levels. The CD8 α and CD25 subpopulations do not vary in gut as they return to control levels when refed with 20% casein diet. All the populations mentioned above remained decreased even after receiving Thymomodulin by the oral route. However, the same behaviour was observed for the TCR $\gamma\delta$ T cells that were decreased and return to normal levels in both mucosae by the effect of the immunomodulator; 2) when studying the iIEL (intestinal intraepithelial lymphocytes) CD8 α , CD25 and TCR $\gamma\delta$ T cells, that were increased in R21, return to control levels in R21TmB. In BALT intraepithelium CD8 α and CD25 T cells remained decreased, while only TCR $\gamma\delta$ T cells (increased in R21) return to control values. Conclusions: 1) there exists a compartmentalisation between both mucosae, as T CD4+ and IgA B+ cells are restored by TmB only in gut; 2) only those iIEL involved in inflammation (CD8 α + /CD25+ and TCR $\gamma\delta$ + /CD25+) are normalised by means of the Thymomodulin 3) however, in BALT ,only TCR $\gamma\delta$ + T cells are restored 4) the oral administration of the present immunomodulator may be useful as a therapeutic agent, although the preferential survival in the tissue of initial stimulation is the major factor in the preferential distribution of activated cells. *Int. J. Immunopathol. Pharmacol.* 16:151

INTERLEUKIN-4 AND INTERFERON-GAMMA PRODUCTION DURING HIV-1 INFECTION AND CHANGES INDUCED BY ANTIRETROVIRAL THERAPY

J. VECCHIET, M. DALESSANDRO, F. TRAVASI, K. FALASCA, A. DI IORIO, C. SCHIAVONE, P. ZINGARIELLO, E. DI ILIO, E. PIZZIGALLO and R. PAGANELLI

Several lines of evidence indicate that a switch of the cytokine pattern from a predominant type 1 (antiviral and cell mediated response) to type 2 (polyclonal humoral immune response) occurs during the course of Human Immunodeficiency Virus-1 (HIV-1) infection, and represents a key event in the progression of immunodeficiency and dysregulated immune activation. We proposed to further investigate this immunological aspect of HIV-1 disease, in naive and in patients treated with Highly Active Antiretroviral Therapy (HAART). The prototypic cytokines chosen were Interleukin (IL)-4 and Interferon-gamma (IFN- γ), whose in vitro production was determined in mononuclear cell cultures stimulated with different T lymphocyte mitogenic agents (anti-CD3, Phytohaemoagglutinin-P -PHA-, E. coli B04/035 Lipopolysaccharide -LPS-).

We classified all the patients on the basis of the number of CD4⁺ lymphocytes and we found a progressive, even if not significant decrease in the baseline production of IFN- γ with the progression of the immunodeficiency. The mean value of baseline IFN- γ in the group of patients with CD4⁺>500 cells/ μ L was 7.79 \pm 3.1 pg/mL while in the group with CD4⁺<200 cells/ μ L it was 4.66 \pm 2.22. We didn't find significant differences in the baseline production of IL-4 in these groups and in IFN- γ and IL-4 production in LPS-stimulated cultures.

We also re-assessed 12 patients after one year's follow-up. They presented a significant increase in IFN- γ production compared to the first assessment in the LPS-stimulated cultures (baseline IFN- γ 2.87 \pm 1.17 pg/mL, after 12 months 19.15 \pm 5.19 pg/mL; p= 0.03). In the 12 patients in follow-up IL-4 production showed a decreased in PHA-stimulated cultures with mean values of 16.65 \pm 14.32 pg/mL at baseline and 6.54 \pm 6.54 pg/mL after follow-up. These results highlight the immunorestoring effects of HAART.

IL-4 production was lower in the treated subjects compared to the naive ones in PHA-stimulated cultures (mean values: IL-4=13.42 \pm 11.08 pg/mL in the naive patients and 9.75 \pm 6.5 pg/mL in the treated patients). The IFN- γ values in anti-CD3 stimulated cultures were also higher in the treated patients, but this increase was not significant. *Int. J. Immunopathol. Pharmacol. 16:157*

IMMUNE SYSTEM ALTERATIONS IN LUNG CANCER PATIENTS

G. MAZZOCOLI, M. GRILLI, S. CARUGHI, F. PUZZOLANTE, A. DE CATA, M. LA VIOLA, A. GIULIANI, N. URBANO, R. TARQUINI and F. PERFETTO

The immune system plays an important role in the defense against neoplastic disease and immune responses show temporal changes related to circadian variations of antibodies, total lymphocytes in the peripheral blood and cell mediated immune responses. In this study we evaluate lymphocyte subpopulations and interleukin-2 (IL-2) serum levels in peripheral blood samples collected at four-hour intervals for 24-hours starting at 06.00h from ten healthy subjects aged 65-79 years (mean age \pm s.e. 67.28 \pm 3.11) and from ten subjects suffering from untreated non small cell lung cancer aged 65-78 years (mean age \pm s.e. 68.57 \pm 1.81). Areas under the curve, mean diurnal levels (mean of 06.00-10.00-14.00h) and mean nocturnal levels (mean of 18.00-22.00-02.00h) were calculated, and the presence of circadian rhythmicity was evaluate. When we compared AUC values there was a decrease in CD8^{bright} (T suppressor subset) and an increase in CD16 (natural killer cells) and of IL-2 serum levels in cancer patients. When we compared mean diurnal levels, CD8 (T suppressor/cytotoxic subset) and CD8^{bright} levels were lower, and CD16 levels were higher in cancer patients. When we compared mean nocturnal levels, CD16 and CD25 (T and B activated lymphocytes with expression of the α chain of IL-2 receptor) levels were higher, while CD8, CD8^{bright}, CD20 (total B-cells), TcR δ 1 (epitope of the constant domain of δ chain of T-cell receptor 1) and δ TcS1 (epitope of the variable domain of δ chain of T-cell receptor1) levels were lower in cancer patients. A clear circadian rhythm was validated for the time-qualified changes in CD4, CD20, HLA-DR with acrophase at night, and CD8, CD8^{bright}, CD8^{dim}, CD16, TcR δ 1 and δ TcS1 with acrophase in the morning in the control group. A clear circadian rhythm was validated for the time-qualified changes in CD4 with acrophase at night, in the group of cancer patients. Results obtained in our study show that lung cancer is associated with anomalies of proportion and circadian variations of lymphocyte subsets that must be considered when adoptive immunotherapy has to be planned. *Int. J. Immunopathol. Pharmacol. 16:167*

SIMPLE RENAL CYSTS IN HYPERTENSIVE PATIENTS: RELATION BETWEEN CYST GROWING AND ANTI-HYPERTENSIVE THERAPY

C. SCHIAVONE, L. SALVATORE, A. PRIMAVERA, F. CUCCURULLO, N. VERNA, F. DI STEFANO, E. THOMSON, R. TENAGLIA and M. DI GIOACCHINO

The study investigates relationship between simple renal cyst enlargement studied by ultrasonography and anti-hypertensive treatment. To this purpose we enrolled 42 patients with newly diagnosed hypertension affected by simple renal cysts. Fourteen were randomly assigned to treatment with ACE-Inhibitors (group 1), twelve to diuretics (group 2) and sixteen to Ca-Antagonists (group 3). Patient performed a basal ultrasonography to evaluate basal cyst dimension before starting anti-hypertensive treatment. Following 12 months of the anti-hypertensive regimen, a new echograph was performed to evaluate changes in cyst size. A control group consisting of 15 patients with normal blood pressure and simple renal cysts was enrolled (group 0). An enlargement of cysts was detected in all patients. However, the enlargement observed in patients treated by Ca-Antagonists was significantly greater than that observed in the other groups ($p < 0,05$). Our study supports the hypothesis that Ca-Antagonists may favor cyst enlargement by enhancing cyclic AMP production. In fact, cAMP and cAMP agonists stimulate fluid secretion by lining cells of the cyst wall, inducing cyst enlargement. *Int. J. Immunopathol. Pharmacol.* 16:175

ANTIEPILEPTIC DRUGS LOWER CONTRACEPTIVE SEX HORMONE AND INCREASE THE RISK OF UNPLANNED PREGNANCIES IN WOMEN WITH EPILEPSY: REVISITED STUDY

S.H. HUANG, F. GAMBI, F. CONTI, G. CARRATELLI, C.M.V. CONTI, I. MASTROMAURO, G. RICCIONI, A. GRILLI, U. BELLATI and R. L. DOYLE

No abstract. Int. J. Immunopathol. Pharmacol. 16:181