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W14.04

ASTROCYTE-DERIVED TGF β IS SECRETED DURING PERSISTENT CORONAVIRUS INFECTION.

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Transforming growth factor beta (TGF-β) belongs to a family of highly pleiotropic polypeptides which are potent immunomodulators and play an important role in cell growth and development. Our laboratory has been studying the influence of persistent infection by the neurotropic murine coronavirus JHMV on primary murine astrocytes. Primary astrocyte cultures were isolated from the brain of newborn C57BL/6 mice, and persistent infection was established with JHMV (moi=1) in the presence of JHMV-specific polyclonal antiserum begining on day 7 post-infection. TGF-β was detected in the supernatants in either active or latent forms with a biological assay using mink lung epithelial cells as a target. The data show that uninfected astrocytes constitutively secrete both active and latent forms of TGF-β. During persistent, but not acute infection, secretion of both forms increased 3-6 fold. TGF-β production was not induced by U.V.-inactivated virus, indicating that TGF-β secretion requires infectious virus. However, U.V. treated supernatants from persistently infected astrocytes dramatically increased TGF-β secretion, suggesting involvement of an astrocyte-derived soluble factor. These data suggest an important role for TGF-β in the pathobiology of persistent JHMV infection.

P06.04

ANTIGEN PRESENTATION BY HUMAN AUTOREACTIVE PLP SPECIFIC T-CELL CLONES.

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Because activated human T cells express MHC Class II molecules it has been suggested that human T cells may be capable of acting as antigen presenting cells (APCs) to soluble antigens (Ags) for the activation of resting T cells. This hypothesis was tested using T-cell clones (TCCs) specific for PLP peptide 104-117. Eleven TCRαβ$^+$ CD4$^+$ TCCs were isolated by limiting dilution. All were capable of proliferation and lymphokine production (IL-4, IL-6, IL-10, TNF and IFNγ) in response to PLP 104-117 and in the presence and absence of professional APCs (adherent autologous irradiated PBMNC). Furthermore, TCCs were able to stimulate alloresponses by resting T cells, in the absence of other accesory cells. However, they did not respoad to total PLP protein, thus indicating an inability to process antigen. Peptide presentation by TCCs was HLA-DR restricted, but did not correlate with the levels of MHC Class II molecules expressed. Furthermore, Ag presentation was antigen nonspecific and was not influenced by the TCC TCR Vβ usage or by the secretion of specific cytokines or cytokine patterns. Finally, the expression of the co-stimulatory molecule B7, correlated with the ability to present soluble Ags by TCCs, and Ag presentation was specifically inhibited by anti-B7 monoclonal antibody. Thus, B7$^+$ PLP TCCs are competent APCs and may perpetuate or amplify an immune response previously initiated by professional APCs.

P01.01

CTLA4-Ig Treatment Prevents Murine Experimental Autoimmune Encephalomyelitis by A.H. Cross[1], T.J. Girard[2], K.S.Giacoletto[2], R.J. Evans[2],R.W.Karr[2] Departments of [1]Neurology, Washington University School of Medicine and [2]Immunology, G.D. Searle and Co., St. Louis, Missouri USA

Introduction: T cell activation involves not only recognition of antigen presented by MHC but also nonspecific receptor-ligand interactions termed "co-stimulation". The co-stimulatory molecules B7-1 and B7-2 are ligands for CD28 and CTLA-4 receptors on T cells. A fusion protein consisting of human CTLA4 linked to mouse IgG2 Fc (CTLA4-Ig) has been shown to bind B7-1 and B7-2 with high avidity and prevent specific T cell activation. In the present studies, we investigated the effects of recombinant CTLA4-Ig in experimental autoimmune encephalomyelitis (EAE), a T-cell-mediated disease which serves as a prime model for multiple sclerosis (MS). **Methods:** A soluble fusion protein consisting of the extracellular domain of human CTLA-4 linked to mouse IgG2a Fc, or a control mouse IgG2a, was administered to SJL mice that had been immunized with myelin to induce EAE. Clinical disease was scored blindly from 0-5. CNS sections were scored blindly for inflammation, demyelination and axonal necrosis. **Results:** CTLA4-Ig treatment completely prevented EAE in all 10 CTLA4-Ig-treated mice (mean maximum score 0+/-0). All 9 control mice developed EAE (mean max score = 2.9). Less inflammation and no axon loss occurred in CTLA4-Ig-treated mice. Lymphocytes from treated and control mice proliferated equally to myelin antigens and activated splenocytes from treated mice were able to transfer EAE; neither experiment supporting T cell anergy as the underlying therapeutic mechanism. **Conclusions:** The B7/CD28 system appears crucial to the development of actively-induced murine EAE, suggesting an area of investigation with therapeutic potential for MS. [Supported by the National Multiple Sclerosis Society and Monsanto Company]

P07.03

MICROGLIA REACTION ON THE NEUROTOXIC EFFECT OF MPTP (1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE) IN THE NIGROSTRIATAL PATHWAY IN MICE

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Introduction: The precise function of the microglia cells is not yet fully understood, but they are considered to play an active role in the variety of neurological diseases. An increased expression of class II antigens on microglia cells has been found in Parkinson's disease (P.D.). MPTP treated mice showed behavioral, biochemical and neuropathological changes similar to those observed in human P.D.

Methods: MPTP 10 mg/kg was given intraperitoneally to 8 months old C 57 BL mice in four injections administered at 1 hr. intervals. Survival times were 1, 2, 3, 4, 7 and 14 days. Microglia cells were stained with lectin GSA-I-B4 derived from *Griffonia simplicifolia* coupled with peroxidase. Dopaminergic neurons were marked by tyrosine hydroxylase antibodies.

Results: Pronouced microglia reaction (increase in number of cells and hypertrophy) was already seen one day after intoxication and at the begining it was more evident in striatum than in substantia nigra. 7 and 14 days after MPTP injection the microglia reaction was not longer observed. Most evident depletion of dopaminergic neurons was observed on day 7.

Conclusion: Microglia reaction preceeded morphological damage of dopaminergic neurons. Microglia cells could play a crucial role in the sequence of pathological changes that lead to the selective neuronal necrosis.

P13.04

T-lymphocyte subset abnormalities in the Guillain-Barré Syndrome

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Blood samples from 12 patients with Guillain-Barré syndrome (GBS) were studied with flowcytometry during their disease course to define circulating T-cell populations. The proportion of T-helper cells (CD4+) was decreased mean value (41±15%, p=0.01) and the proportion of cytotoxic/suppressor cells (CD8+) was increased (35±18%, p=0.0006) as compared to the control group of healthy blood donors (47±8% and 26±7% respectively). The CD4+ population is divided into the helper|inducer (CD4+CD29+) and suppressor/inducer (CD4+CD45RA+) subsets, which normally are equally distributed (mean values in our control group were 45±15% and 44±15% respectively). In patients with GBS, the helper|inducer (CD4+CD29+) subset was increased (54±10%, p=0.05) and the suppressor/inducer (CD4+CD45RA+) subset was decreased (31±9, p=0.005) compared to the controls. The proportion of activated HLA-DR expressing T-cells was increased (7±6%, p=0.005) as compared to controls (3±3%). The total proportions of T-cells (CD2+), B-cells (CD19+) and natural killer (NK) cells (CD56+) were similar in patients and controls.The deviations within the CD4+ population also tended to normalize, but even at follow up after 6-33 (mean 23) months, some abnormalities remained. In conclusion, we confirm previous reports of T-cell activation in peripheral blood from patients with GBS. A new finding is the deviation of T helper subpopulations with an increased helper/inducer (CD4+CD29+) subset and a decreased suppressor/inducer (CD4+CD45RA+) subset, which indicates a possible autoimmune character of GBS.

W02.03

A FUNCTIONAL INTERLEUKIN-1 TYPE I RECEPTOR ON RAT BRAIN ENDOTHELIAL CELLS

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An inflammatory response include physiological changes such as fever, neuroendocrine changes, modifications in behaviour, increased sleepiness, depression, anorexia and are called non-specific sickness symptoms. Interleukin-1 appears to play a pivotal role in the orchestration of sickness symptoms. We have demonstrated immunoreactive IL-1 in the brain after peripheral injection of endotoxin. So far, receptors for IL-1 in rat brain parenchyma are difficult to detect. In mouse and rat brain however, mRNA for IL-1 receptor type I has been found in brain endothelial cells. This celltype may be important in the communication between the periphery and the brain during inflammatory processes as it can be reached from both sides. In this study we demonstrate by IL-1 competition studies and polymerase chain reaction that an IL-1 receptor type I can be found on rat brain endothelial cells in vitro. Furthermore, IL-1 induces the production of other pro-inflammatory factors: interleukin-6 (IL-6) and prostaglandins (PG) by these brain endothelial cells. Receptors for IL-6 and PG have been detected in the rat central nervous system and IL-6 as well as PG can induce non-specific symptoms of sickness. Therefore, these results have led to the hypothesis that after injection of endotoxin, IL-1 produced in the brain and periphery can act on its brain endothelial receptor to induce the production of IL-6 and PGE2 which by themselves can induce non-specific symptoms of sickness.