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P15.03

Prevention of EAE in Non-human Primates by a Type IV Phosphodiesterase Inhibitor that Suppresses Tumor Necrosis Factor. C. P. Genain, M.H. Nguyen, D. Faulds, A. Uccelli, R. L. Davis, J. Hedgpeth, and S. L. Hauser. University of California, San Francisco, CA.

Objective. To evaluate the efficacy of a type IV phosphodiesterase (PDE-IV) inhibitor with a novel, specific profile of tumor necrosis factor (TNF-α) inhibition in preventing EAE in the common marmoset *C. jacchus*. This model of EAE was selected because of its characteristics of chronic, relapsing remitting course and early and prominent demyelination closely reminiscent of human MS.
Methods. Marmosets were treated for 7 weeks with either the PDE-IV inhibitor Rolipram (10mg/kg every 48 hrs subcutaneously) or placebo (controls), starting at day 7 after EAE induction with human whole white matter. Assessment of EAE was done by examination of clinical status, cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI).
Results. Clinical signs of EAE (grade 2 to 3), CSF pleocytosis (150-190 WBC/mm3), and cerebral white matter foci of Gadolinium enhancement developed within 17 days after EAE induction in 2 controls and in none of 3 Rolipram-treated animals. The drug protected against EAE as long as treatment was continued, but failed to suppress antibody and T-cell responses to Myelin Basic Protein in peripheral blood. In contrast to controls, pathologic examination of the brain and cord in the treatment group revealed only subtle inflammation and no demyelination.
Conclusion. Specific inhibition of TNF-α protects EAE-primed *C. jacchus* from blood-brain barrier breakdown and substantially suppresses CNS white matter inflammation and demyelination. Similar strategies may be considered for therapy of human MS.

W13.05

T CELL RECEPTOR Vβ SEQUENCE ANALYSIS IN TARGET TISSUE SUGGESTS CONTRIBUTION OF MYELIN BASIC PROTEIN AUTOREACTIVITY TO EXPERIMENTAL ALLERGIC NEURITIS

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Introduction: Experimental autoimmune neuritis (EAN), an animal model of Guillain-Barre Syndrome and chronic inflammatory demyelinating polyneuropathy, is induced in Lewis rats by T cells reactive against peripheral nerve myelin (PNM) proteins. Both P2 and P0 protein have been identified as target autoantigens in EAN. To identify the T cell receptor (TCR) β usage of T cells infiltrating peripheral nervous tissue in EAN, we amplified cDNA derived from sciatic nerves of rats immunized with PNM.
Materials and Methods: We studied sciatic nerves of Lewis rats immunized with PNM using RNA extraction, cDNA synthesis and PCR with primers established for the variant (V) and constant (C) part of the β chain of TCR. The PCR products were purified, cloned and sequenced. All Vβ and Jβ sequences were compared with previously established sequences of MBP and P2 specific rat T cell clones.
Results: Surprisingly we detected TCR Vβ 8.2 chain expression in the sciatic nerves of 2 animals immunized in different experiments. The VDJ junctional regions showed a high degree of homology to previously published TCR β sequences of MBP specific T cell clones. We did not detect TCR sequences resembling those used by P2 specific T cell lines.
Conclusion: Our results suggest that T cells specific for MBP, a minor constituent in PNS, might contribute to the pathogenesis of inflammatory demyelinating neuropathies, in addition to P2 and P0 autoreactive T cells.

W09.05

MYASTHENIA GRAVIS; ANTIGEN PRESENTATION BY THYMOMA EPITHELIAL CELLS

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Cultured thymoma epithelial cells from 2 patients with myasthenia gravis (MG) were able to present synthetic acetylcholine receptor (AChR) peptides to HLA-sharing responder T cell lines. Similar thymoma epithelial cells from non-HLA sharing MG patients did not present. Anti-HLA-class II antibodies inhibited the responses. T cell responses depended on AChR peptide dose and number of thymoma epithelial cells. The thymoma cells presented the peptides nearly as efficiently as did blood mononuclear cells. However, the processing of longer recombinant AChR polypeptides was clearly less efficient. There was no sign of presentation of any endogenous AChR epitopes. One of the epithelial cell cultures expressed the presenting HLA-DQ allele spontanously but the others required preculture with IFN-γ. The T cell responses depended on the presence of LFA-3 on the thymoma cells. ICAM-1 was also present on the thymoma cells, but anti-ICAM-1 antibodies did not inhibit. Chloroquine pretreatment of the thymoma cells prevented the AChR polypeptide processing, whereas this processing could be increased by IL1α+β plus IL6.
Thymoma epithelial cells have the capacity to stimulate T cells in vivo and could well be responsible for sensitizing the AChR-specific T cells in MG patients with thymoma.

P11.04

TRANSPLANTATION OF MURINE OLIGODENDROCYTES AND JHMV-INFECTED ASTROCYTES INTO DEMYELINATING LESIONS IN THE RAT SPINAL CORD. W. Gilmore, J. Correale, M. Cullen*, N. Ko and L.P. Weiner. Departments of Neurology and *Anatomy and Cell Biology, University of Southern California, Los Angeles, CA. 90033.

Neurotropic strains of mouse hepatitis virus, such as JHMV, cause both acute and chronic encephalomyelitis and demyelination in susceptible strains of mice and rats. During chronic infection, virus tends to be restricted to astrocytes in a non-lytic infection, suggesting that the astrocyte may play a central role in JHMV neuropathogenesis. It has been reported that oligodendrocyte remyelination of discrete ethidium bromide-induced lesions in the spinal cord of the rat requires the presence presence of astrocytes (Blakemore, W.F. and A.J. Crang, J. Neurocytol. 18:519, 1989). In these studies, we have examined the ability of JHMV-infected primary murine astrocytes to support remyelination by primary murine oligodendrocytes using the EB model of demyelination in Wistar rats. Primary astrocyte and oligodendrocyte cultures were prepared from the brains of neonatal C57BL/6 mice. Persistent, non-productive JHMV infection (moi = 1) was established in the astrocytes following the addition of JHMV-specific polyclonal antiserum to the culture medium at day 7 post-infection (p.i.). Lack of release of infectious virus from the cells was confirmed prior to and following transplantation. However, astrocytes retained viral RNA and protein. Preliminary data suggest that oligodendrocyte remyelination does not proceed normally in the presence of the infected astrocytes, further suggesting that their support functions are impaired.

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P14.06

MHV-JHM INFECTION IN IMMORTALIZED MURINE OLIGODENDROCYTES. W. Gilmore, N.A. Jensen*, J. Correale, S. Li, T. Le and L.P. Weiner. Department of Neurology, University of Southern California, Los Angeles, CA. USA 90033, and *Institute of Human Genetics, Aarhus University, Aarhus, Denmark

The murine coronavirus JHMV is a neurotropic strain of mouse hepatitis virus (MHV) that causes encephalitis and paralytic-demyelinating disease in susceptible strains of mice and rats. Our laboratory has been studying the effect of JHMV infection on oligodendrocyte activities *in vitro* using 6E12 cells, which are immortalized oligodendrocytes isolated from the spinal cord of a C57BL/6 x DBA F1 mouse carrying an MBP-SV40 large T transgene (Jensen *et al.* J. Neurosci. Res. 34:257, 1993). One goal of our studies is to determine whether JHMV-induced demyelinatiing disease involves a specific influence on oligodendrocyte activities during non-lethal infection. Thus, JHMV infection was established in 6E12 cells at an moi = 1, followed by monitoring of the infection and 6E12 functions at various post-infection (p.i.) intervals. The data indicate that JHMV replicates at low efficiency in 6E12 cells, but readily establishes a chronic, productive infection for 20-30 passages. Chronic infection was associated with a decrease in cell growth, a decrease in cell size and an increase in process formation. In addition, an increase in CNPase mRNA was detected during chronic infection. Finally, MBP mRNA was either reduced or increased in a fashion dependent on the status of virus replication in the cells. Overall, the data indicate that JHMV alters myelin gene expression in chronic infection.

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P02.04

INTERLEUKIN-1 (TYPE II) RECEPTOR EXPRESSION IN NORMAL AND PATHOLOGICAL HUMAN BRAIN

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Interleukin-1 induces important inflammatory effects on the CNS. Morphological analysis of IL-1 receptor (IL-1R) distribution in the human brain may help to identify the target cells in this tissue and may give insight on the IL-1 actions at cellular level in human CNS. In this study, different clinical conditions ranging from normal brain to inflammatory (MS), degenerative (AD) and tumor (Gliomas) changes were analysed in order to characterize the cells expressing IL-1R. An affinity purified mab anti-IL-1R type II was applied to acetone fixed sections and a peroxidase method with avidin-biotin amplification was used to visualize the reactions. In all the cases studied, a reactivity with the mab was detected in perivascular elements. In MS a wide reactivity was also found on the membrane of infiltrating macrophages and in parenchymal microglial cells; moreover, in some area, endothelial cells expressed IL-1R. In AD and in MS IL-1R were detected also in reactive hypertrophic astrocytes.In gliomas, IL-1R were expressed by infiltrating macrophages and in some anaplastic tumor by neoplastic elements. The finding of IL-1R detection on the membrane of reactive or anaplastic astrocytes supports the hypothesis that, besides the inflammatory effects, IL-1 may mediate gliosis or be involved in neoplastic astrocyte proliferation.