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Journal of Neuroimmunology (78)

Bauer, J., U. Ganter, et al. (1993). "Effects of interleukin-1 and interleukin-6 on metallothionein and amyloid precursor protein expression in human neuroblastoma cells: Evidence that interleukin-6 possibly acts via a receptor different from the 80-kDa interleukin-6 receptor." Journal of Neuroimmunology **45**(1-2): 163.

<http://www.sciencedirect.com/science/article/B6T03-476WCFH-WM/2/9f385781b125e3e5aeebd6441f7ef5bf>

Since immunohistochemical studies indicated the presence of interleukin-6 in the cortices of patients with Alzheimer's disease, we were interested in the eventual biological effects of this cytokine on neuronal cells. We found that interleukin-6 and interleukin-1 induced metallothionein expression in a human neuronal (SH-SY5Y neuroblastoma) cell line. In contrast to metallothionein, amyloid precursor protein expression was unaffected by both cytokines. When searching in the same cell line for the expression of the classical 80-kDa interleukin-6 binding protein, which is part of the dimeric interleukin-6 receptor, we were unable to detect the respective mRNA. Our findings either indicate that the interleukin-6 receptor in these cells is expressed in extremely low levels or that interleukin-6 may act upon neuronal cells via a different, yet unknown neuronal receptor.

Bencsik, A., C. Malcus, et al. (1996). "Selective induction of cytokines in mouse brain infected with canine distemper virus: structural, cellular and temporal expression." Journal of Neuroimmunology **65**(1): 1.

<http://www.sciencedirect.com/science/article/B6T03-3VXN38M-1/2/58491b94d58ac7369728972e5406dad0>

We have previously shown that, in experimentally inoculated mice, canine distemper virus (CDV), a neurotropic virus, selectively infects certain brain structures (hypothalamus, hippocampus, monoaminergic nuclei, etc). Here we demonstrate that tumor necrosis factor (TNF)-[alpha], interleukin (IL)-1 [beta] and IL-6 transcripts are selectively expressed in these CDV-targeted structures, except in the dentate gyrus, where cytokines are induced without prior CDV replication. The time-course of TNF-[alpha] expression vs. viral replication in the hypothalamus was different from that in hippocampus. In addition, we show that a substantial number of neurons express TNF-[alpha] and IL-6. These findings provide new insights into the possible participation of cytokines in the neurological disorders triggered by CDV infection.

Blanco-Jerez, C., J. F. Plaza, et al. (2002). "Increased levels of IL-15 mRNA in relapsing-remitting multiple sclerosis attacks." Journal of Neuroimmunology **128**(1-2): 90.

<http://www.sciencedirect.com/science/article/B6T03-45Y6MNW-1/2/09a8a6a5fc44d41e36826545f77b7584>

IL-15 is a proinflammatory cytokine which has recently been implicated in multiple sclerosis (MS) pathogenesis, where it may play a role in the initiation and/or progression of the disease. We have used reverse transcriptase-polymerase chain reaction (RT-PCR) to study IL-15 mRNA levels in peripheral blood mononuclear cells (PBMC) from healthy controls and relapsing-remitting MS (RRMS) patients in a stable phase of the disease and during a bout, both before and after corticosteroid treatment (CST). IL-15 mRNA expression was found to be similar in controls and stable patients. We have detected an increased level of IL-15 mRNA in PBMC of patients with a relapse, which was maintained after CST. We have also found an inverse correlation between PBMC IL-15 mRNA levels at the onset of the relapse and the time elapsed since the previous attack, as well as an absence of correlation between IL-15 mRNA levels and the patient demographic and clinical characteristics. Results in the present work further suggest a role for IL-15 in MS pathophysiology.

Braun, A., P. Wiebe, et al. (1999). "Differential modulation of human immunoglobulin isotype production by the neuropeptides substance P, NKA and NKB." *Journal of Neuroimmunology* **97**(1-2): 43.

<http://www.sciencedirect.com/science/article/B6T03-3WS61MX-7/2/10ed0fa9c335c765b28aef507c095727>

The modifying effects of tachykinins substance P, neurokinin A and neurokinin B on immunoglobulin production were analyzed in an in vitro culture system. Purified human T- and B-cells were stimulated with TGF[β]₂ and IL-5 to induce preferential IgA production. Neuropeptides had the following effects. (1) The levels of IgA and IgG₄ production were enhanced by IL-5 and TGF[β]₂; IgA levels remained constant or were slightly augmented by neuropeptides, whereas IgG₄ was further augmented. (2) IL-5 and TGF[β]₂ did not alter IgG₃ production, but neuropeptides stimulated secretion of this subclass. (3) IgG₁ and IgM production were inhibited by IL-5 and TGF[β]₂. This effect was prevented by neuropeptides. (4) Other isotypes including IgG₂ and IgE remained unaffected. Except for IgM, these effects were blocked by specific receptor antagonists indicating specificity. The tachykinin receptor NK-1 mRNA was detected in B- and T-cells, whereas NK-3 mRNA was only present in T- and B-cell coculture following activation. Furthermore, neuropeptide effects depended on cytokine co-stimulation and the presence of T-cells. These results suggest that neuropeptides are potent modifiers of preferential IgA synthesis.

Breijl, E. C. W., W. L. van der Pol, et al. (2003). "No association of Fc[γ]RIIa, Fc[γ]RIIIa and Fc[γ]RIIIb polymorphisms with MS." *Journal of Neuroimmunology* **140**(1-2): 210.

<http://www.sciencedirect.com/science/article/B6T03-491GS5M-8/2/eafc30d47bdc4254bfdc5c5b86ba2cf7>

Anti-myelin IgGs occur in the cerebrospinal fluid (CSF) and serum of multiple sclerosis (MS) patients, and can induce inflammatory effector functions in leukocytes by crosslinking IgG receptors (Fc[γ]R). The efficiency of Fc[γ]R-mediated inflammatory processes is affected by functional polymorphisms of three Fc[γ] receptors (Fc[γ]RIIa, Fc[γ]RIIIa, Fc[γ]RIIIb). The relevance of Fc[γ]R polymorphisms in MS was evaluated by studying the distribution of Fc[γ]RIIa, Fc[γ]RIIIa and Fc[γ]RIIIb genotypes in 432 MS patients and 515 healthy controls. No significant differences were found between MS patients and controls, or between subgroups of patients. We conclude that

Fc[gamma] receptor polymorphisms influence neither susceptibility nor clinical disease course of MS.

Carlson, K. A., J. Limoges, et al. (2004). "OTK18 expression in brain mononuclear phagocytes parallels the severity of HIV-1 encephalitis." Journal of Neuroimmunology **150**(1-2): 186.

<http://www.sciencedirect.com/science/article/B6T03-4C09KS6-1/2/79a3e718c365989b2d693ad4b037a167>

OTK18 was isolated by mRNA differential display of human monocyte-derived macrophages (MDM) infected with human immunodeficiency virus type one (HIV-1). Northern blot and real-time reverse transcription polymerase chain reaction showed low levels of OTK18 expression in human tissue, which markedly increased during advanced HIV-1 encephalitis (HIVE). Immunocytochemistry, using rabbit polyclonal antisera, showed OTK18 localized to brain mononuclear phagocytes (MP) in moderate to severe HIV-1 encephalitis. OTK18 expression was selective and not found in HIV-1-infected brain tissue with limited neuropathological abnormalities, nor in cytomegalovirus encephalitis, multiple sclerosis, Alzheimer's disease, or uninfected control brains. Thus, OTK18 expression in brain mononuclear phagocytes is a signature for advanced HIV-1 encephalitis.

Charles, P. C., K. S. Weber, et al. (1999). "Cytokine, chemokine and chemokine receptor mRNA expression in different strains of normal mice: implications for establishment of a Th1/Th2 bias." Journal of Neuroimmunology **100**(1-2): 64.

<http://www.sciencedirect.com/science/article/B6T03-3YC05J7-9/2/6dda8cfd3b491dfc1490c8ab514194e9>

The resistance or susceptibility of inbred strains of mice to various pathogens and autoimmune diseases such as EAE has been linked to differences in the balance between cytokines associated with Th1- and Th2-type immune responses. Previous work from this laboratory on the mouse strain specific resistance to mouse adenovirus type I (MAV-1)-induced encephalopathy revealed subtle differences in the transcription rates of several immunologically important molecules that was evident prior to infection. In this study, we show striking differences in cytokine, chemokine and chemokine receptor mRNA expression in the spleens of normal, immunologically naive C57BL/6J, BALB/cJ and SJL/J mice. Messenger RNAs for interferon (IFN)-[gamma] and the chemokine IFN [gamma] inducible protein (IP)-10 were preferentially expressed in C57BL/6J spleens, whereas in BALB/cJ spleens mRNAs for lymphotoxin-[beta], interferon-[beta], transforming growth factor-[beta], and the chemokine receptors CCR3 and CXCR4 predominated. A unique profile of chemokine receptors was found in spleens from normal SJL/J mice that correlated with the presence of polymorphisms within the CCR-3 gene. The patterns of gene expression fit well into the Th1/Th2 paradigm for C57BL/6J and BALB/cJ strains and suggest an important role for chemokines, as well as cytokines, in contributing to the genetic basis of the immune response.

Chataway, J., S. Sawcer, et al. (1999). "A screen of candidates from peaks of linkage: evidence for the involvement of myeloperoxidase in multiple sclerosis." Journal of Neuroimmunology **98**(2): 208.

<http://www.sciencedirect.com/science/article/B6T03-3WXNYG7-H/2/a11f7977dd34eebeb084cd06f0ba4f00>

We tested 11 microsatellite markers for evidence of transmission distortion in 744 trio families with multiple sclerosis. Ten of the markers lie within or near to candidate genes selected on the basis that they map within the regions of potential linkage identified in our previously reported linkage genome screen, while the eleventh is an anonymous marker which had previously shown modest evidence for transmission distortion in our sibling pair families. Only the marker related to the myeloperoxidase (MPO) gene revealed tentative evidence for linkage disequilibrium and further work on this gene is clearly needed in order to resolve the status of this region in conferring susceptibility to multiple sclerosis.

Chataway, J., S. Sawcer, et al. (1999). "No evidence for association of multiple sclerosis with the complement factors C6 and C7." Journal of Neuroimmunology **99**(1): 150.

<http://www.sciencedirect.com/science/article/B6T03-3Y9H4FG-M/2/006eb49aaead687e5912560850d8ed38>

Four genome screens in multiple sclerosis have been completed and each has identified evidence for linkage in the pericentromeric region of chromosome 5. This region encodes a number of candidate genes including those for the complement components C6, C7 and C9. We have used a multiplexed oligoligation assay (OLA) to test single nucleotide polymorphisms (SNPs) from the C6 and C7 genes for evidence of association with multiple sclerosis in our sibling pair families. There was no statistically significant difference in the allele frequencies of these polymorphisms in the index cases from our families when compared with locally derived controls. No evidence for transmission distortion was seen with any of the polymorphisms, or with the haplotype built from the three SNPs from the C7 gene. Despite offering themselves as potential candidates these complement genes appear not to confer susceptibility to multiple sclerosis.

Cross, A. H., R. M. Keeling, et al. (1996). "Inducible nitric oxide synthase gene expression and enzyme activity correlate with disease activity in murine experimental autoimmune encephalomyelitis." Journal of Neuroimmunology **71**(1-2): 145.

<http://www.sciencedirect.com/science/article/B6T03-3R867H0-N/2/398eccff619d17193412e3b089c7f4d>

Messenger RNA encoding inducible NO synthase (iNOS) was measured by competitive reverse transcriptase polymerase chain reaction (cRT-PCR) and ribonuclease protection assays in spinal cords from mice at varying stages of experimental allergic encephalomyelitis (EAE) and from control mice. iNOS mRNA was increased in spinal cords from mice with acute EAE. cRT-PCR assays revealed a 10-20-fold increase in iNOS mRNA in spinal cords during acute EAE compared with the level observed in normal mouse spinal cords. Functional iNOS activity, as assessed by assay of calcium-independent citrulline production, was also significantly increased in spinal cords from mice with acute EAE in comparison to normal controls. The correlation of functional iNOS expression with active disease in EAE is consistent with a pathogenic role for excess NO in this model of cell-mediated central nervous system autoimmunity.

DeVry, C. G., M. Valdez, et al. (2004). "RDP58, a novel immunomodulatory peptide, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalomyelitis." Journal of Neuroimmunology **152**(1-2): 33.

<http://www.sciencedirect.com/science/article/B6T03-4CPP63V->

4/2/48b93709658bd511b2083b1e6b810abe

The therapeutic value of a novel immunomodulatory peptide, RDP58, was investigated in the acute experimental autoimmune encephalomyelitis (EAE) model of Multiple Sclerosis (MS). RDP58 is a 10-amino acid peptide with two major activities: (i) inhibition of inflammatory TH1 cytokines such as TNF[alpha], IFN[gamma], and IL12 and (ii) up-regulation of heme oxygenase-1 (HO-1) expression. Experiments in which EAE-induced Lewis rats exhibit an acute monophasic episode of disease demonstrated that a single intracerebroventricular injection of RDP58 is effective in preventing clinical signs of disease. The therapeutic effect on disease activity was observed at all pre-onset administration times and at all doses tested. Consistent with disease activity in vivo, RDP58-treated animals had reduced cellular infiltration within the spinal cord along with decreased TNF[alpha] expression levels. The data in this proof of concept study support the premise that RDP58, as a platform molecule, may be a promising new therapeutic intervention in autoimmune and inflammatory diseases.

Elovaara, I., U. Utz, et al. (1995). "Limited T cell receptor usage by HTLV-I tax-specific, HLA class I restricted cytotoxic T lymphocytes from patients with HTLV-I associated neurological disease." Journal of Neuroimmunology **63**(1): 47.

<http://www.sciencedirect.com/science/article/B6T03-4002J2F-M/2/26443ea37a654ce0141374195444a3b5>

T cell receptor (TCR) V[alpha] and V[beta] chain usage of HTLV-I tax-specific, HLA class I restricted CD8+ cytotoxic T cells (CTL) was determined from lymphocytes obtained from peripheral blood of patients with HTLV-I associated neurological disease. To characterize TCR repertoire, CD8+ lymphocytes from peripheral blood were cloned in limiting dilution, and the resulting wells were screened for HTLV-I-specific precursor CTL activity. RNA was isolated from HLA-A2 restricted HTLV-I tax peptide-specific (tax 11-19; LLFGYPVYV) CD8+ CTL lines and cDNA was analyzed by PCR amplification using V[alpha] and V[beta] chain family-specific oligonucleotide primers. The results indicate that CD8+ cytotoxic T cell lines from HLA-A2 HAM/TSP patients express a limited repertoire of T cell receptor chains which may correlate with duration and severity of disease. The restricted use of TCR genes expressed by antigen-specific CTL may play a critical role in the pathogenesis of HAM/TSP and may be of value in developing immunotherapeutic strategies that focus on eliminating these cells or inhibiting their activity.

Floris, S., S. R. Ruuls, et al. (2002). "Interferon-[beta] directly influences monocyte infiltration into the central nervous system." Journal of Neuroimmunology **127**(1-2): 69.

<http://www.sciencedirect.com/science/article/B6T03-45NGR1M-1/2/4f80169144df9e63ab2767cdcf88c273>

Interferon-[beta] (IFN-[beta]) has beneficial effects on the clinical symptoms of multiple sclerosis (MS) patients, but its exact mechanism of action is yet unknown. We here suggest that IFN-[beta] directly modulates inflammatory events at the level of cerebral endothelium. IFN-[beta] treatment resulted in a marked reduction of perivascular infiltrates in acute experimental allergic encephalomyelitis (EAE), the rat model for MS, which was coupled to a major decrease in the expression of the adhesion molecules ICAM-1 and VCAM-1 on brain capillaries. In vitro, IFN-[beta] reduced the mRNA levels and protein expression of adhesion molecules of brain endothelial cell cultures and diminished monocyte transendothelial migration. Monocyte adhesion and subsequent migration was found to be predominantly regulated by VCAM-1. These data indicate that IFN-[beta] exerts direct antiinflammatory effects on brain endothelial cells thereby

contributing to reduced lesion formation as observed in MS patients.

Fujii, T., N. Ushiyama, et al. (2002). "Effects of human antithymocyte globulin on acetylcholine synthesis, its release and choline acetyltransferase transcription in a human leukemic T-cell line." Journal of Neuroimmunology **128**(1-2): 1.

<http://www.sciencedirect.com/science/article/B6T03-45V716F-1/2/e7bf261425e7842c25a4ec782ac473ce>

Lymphocytes possess an independent, nonneuronal cholinergic system. In the present study, we investigated the short- and long-term effects of antithymocyte globulin (ATG)-Fresenius (ATG-F), a human antithymocyte globulin that binds to CD2, CD7 and CD11a, on acetylcholine (ACh) synthesis and transcription of choline acetyltransferase (ChAT) in CCRF-CEM cells, a human leukemic T-cell line. In the short-term (6 h), ATG-F enhanced ACh release, likely through transient increases in intracellular Ca²⁺ ([Ca²⁺]_i) mediated by CD7, which led to declines in intracellular ACh content. By 48 h, however, the ACh content had increased as compared to control due to up-regulation of ChAT expression mediated by CD11a.

Fujii, T., S. Yamada, et al. (1998). "Induction of choline acetyltransferase mRNA in human mononuclear leukocytes stimulated by phytohemagglutinin, a T-cell activator." Journal of Neuroimmunology **82**(1): 101.

<http://www.sciencedirect.com/science/article/B6T03-3SR9W9C-G/2/5fb9e082b826e109d86bc5dd93d250a8>

The induction of mRNA for choline acetyltransferase (ChAT), which catalyzes acetylcholine (ACh) synthesis was investigated in human mononuclear leukocytes (MNL) stimulated by phytohemagglutinin (PHA), a T-cell activator, using the reverse transcription-polymerase chain reaction. Stimulation of MNL by PHA induced the expression of ChAT mRNA, and potentiated ACh synthesis. ChAT mRNA induction required more time than the induction of interleukin-2 mRNA. Expression of the gene encoding the vesicular ACh transporter, which mediates ACh transport in cholinergic neurons, was not observed in PHA-stimulated MNL, suggesting that the mechanisms controlling ACh release from T-lymphocytes differ from those in cholinergic neurons. These findings demonstrate that activation of T-lymphocytes up-regulates ACh synthesis in the blood, and suggest that ACh plays an important role as a neuroimmunomodulator besides its role as a neurotransmitter.

Fyhr, I.-M., A.-R. Moslemi, et al. (1998). "T cell receptor [beta]-chain repertoire in inclusion body myositis." Journal of Neuroimmunology **91**(1-2): 129.

<http://www.sciencedirect.com/science/article/B6T03-3V5VDX7-K/2/5022ebb62f3b601e7ec172e1bb382457>

Inclusion body myositis (IBM) is the most common muscle disease affecting individuals over 50 years of age. The inflammatory reaction is characterized by cell infiltrates predominated by CD8+ cytotoxic T cells. To analyze clonality of muscle infiltrating lymphocytes, we studied the complementarity determining region 3 (CDR3) length distribution of the T cell receptor (TCR). Muscle infiltrating lymphocytes were studied in three IBM patients and compared with peripheral blood lymphocytes (PBL) in two of these patients. The study was performed by reverse

transcription polymerase chain reaction (RT-PCR) of RNA extracted from muscle tissue and PBL followed by analysis of fragment length distribution of the CDR3 region in each of 24 different V[beta] families. There was a restricted usage of TCR V[beta] gene families in muscle infiltrating T cells in all three patients. Some of the TCR V[beta] gene families showed oligoclonal expansions but polyclonal patterns were dominating. The CDR3 distribution of most V[beta] families differed between muscle infiltrating lymphocytes and PBL indicating that T cells have expanded locally or selectively accumulated in muscle.

Goldmuntz, E. A., R. L. Wilder, et al. (1993). "The origin of the autoimmune disease-resistant LER rat: An outcross between the Buffalo and autoimmune disease-prone Lewis inbred rat strains." Journal of Neuroimmunology **44**(2): 215.

<http://www.sciencedirect.com/science/article/B6T03-476W9PJ-7C/2/e5c0f182c0482ff214cd8266eeedd8d5>

The Lewis (LEW) rat strain is highly susceptible to a large number of experimentally induced inflammatory and autoimmune diseases. The Lewis resistant (LER) rat strain, which reportedly arose as a spontaneous mutation in a closed colony of LEW rats, is resistant to many of these disorders. The mechanism of resistance is not yet clear. We report the analysis of 19 simple dinucleotide repeat polymorphisms in 13 rat strains including the LEW/N and LER/N rat strains. The LEW/N and LER/N alleles were the same in only 42% of cases. For all of the other polymorphisms, the LER/N and Buffalo (BUF/N) rat strain alleles were identical. These data provide evidence that the LER strain did not arise as a spontaneous mutation in the LEW strain but is the result of an outcross between the LEW and BUF rat strains. The LER rat strain is now a recombinant inbred rat strain. This information should facilitate the genetic analysis of the loci responsible for resistance to experimental autoimmune disease in the LER rat.

Guo, C.-J., J.-P. Lai, et al. (2002). "Substance P up-regulates macrophage inflammatory protein-1[beta] expression in human T lymphocytes." Journal of Neuroimmunology **131**(1-2): 160.

<http://www.sciencedirect.com/science/article/B6T03-46WV6NX-6/2/4406c82190b5431c55606624ffa4d78b>

Substance P (SP) is an important modulator of neuroimmunoregulation. We have demonstrated that human T lymphocytes express SP and neurokinin-1 receptor (NK-1R), a primary SP receptor. In the present study, we investigated whether SP stimulates synthesis of macrophage inflammatory protein-1[beta] (MIP-1[beta]) in human T lymphocytes. SP significantly enhanced MIP-1[beta] expression at both the mRNA and protein level in a human T cell line (Jurkat) containing the SP receptor gene (J-SPR) as determined by real-time PCR and ELISA assays. SP-induced MIP-1[beta] expression is abrogated by the specific NK-1R antagonist (CP-96,345). The supernatants from SP-stimulated J-SPR T cell cultures enhanced T lymphocyte chemotaxis in vitro, indicating functional activity of SP-induced MIP-1[beta]. In addition, SP augmented secretion of MIP-1[beta] from primary cultures of peripheral blood lymphocytes (PBL) isolated from some of the donors. This donor variability was due to differential expression of the primary SP receptor (NK-1R) on PBL from different donors. PBL from two of seven donors that did not respond to SP stimulation had undetectable NK-1R expression. Our mechanistic studies showed that SP activated NF-[kappa]B promoter-directed luciferase activity, which may be responsible for its effect on MIP-1[beta] expression in human T cells. Our data provide a potential mechanism by which SP selectively influences cellular immune responses such as [beta]-chemokine expression in human T lymphocytes through NK-1R, which may have an important in vivo implication in inflammatory diseases.

Hackstein, H., A. Bitsch, et al. (2001). "Analysis of interleukin-4 receptor [alpha] chain variants in multiple sclerosis." Journal of Neuroimmunology **113**(2): 240.

<http://www.sciencedirect.com/science/article/B6T03-427JWJW-9/2/128f9e707281c5647e0ffc1b474a8027>

A recent candidate gene study employing microsatellite markers suggested a possible linkage of multiple sclerosis (MS) with the interleukin-4 receptor (IL4R) gene. Consequently, we investigated the association of different IL4R variants with MS in 341 German MS patients and 305 healthy controls. Analysis of the first 100 MS patients for six IL4R variants showed an increased frequency of the R551 variant in MS patients versus healthy controls and carriage of the same IL4R variant was weakly associated with myelin oligodendrocyte glycoprotein (MOG) autoantibody production. However, further analysis of all 341 MS patients did not confirm the finding that this IL4R variant represents a general genetic risk factor for MS but revealed an increased frequency of the R551 variant in MS patients with primary progressive MS (PPMS, n=48) as compared to patients with relapsing remitting MS or secondary progressive MS (RR/SPMS n=284; P=0.005 for genotype differences) and to 305 healthy controls (P=0.001 for genotype differences). This association was statistically independent of the presence of the well-known MS susceptibility allele HLA-DRB1*15. After correction for multiple comparisons only the genotype differences between PPMS patients and healthy controls remained statistically significant. These results indicate, that the IL4R variant R551 may influence the genetic predisposition for PPMS but does not represent a general genetic risk factor for MS.

Hardin-Pouzet, H., P. Giraudon, et al. (1996). "Cytokines are increased in the rat hippocampus after serotonergic neuron degeneration and upregulate the expression of GDH, an enzyme involved in glutamate detoxification." Journal of Neuroimmunology **69**(1-2): 117.

<http://www.sciencedirect.com/science/article/B6T03-49GTP2H-19/2/6932d464541a8f40161aff277bcc5a8a>

The degeneration of serotonergic neurons increases the expression of glutamate dehydrogenase (GDH) in hippocampal astrocytes. This process was demonstrated to be independent of the serotonin level. At the same time, upregulation of tumor necrosis factor (TNF) α and interleukin (IL)-1[α] mRNA were observed, whereas levels of transforming growth factor (TGF) [β]1 mRNA remained unchanged. The level of GDH mRNA was increased in primary cultures of hippocampal astrocytes treated with TNF[α] and IL-1[α] suggesting that these cytokines act on the GDH metabolism. TNF α and IL-1[α] induced an increase in GDH promoter activity in C8S (an astrocytic cell line) transfected with constructs containing 5' flanking genomic sequences of GDH driving the expression of a reporter gene. These observations suggest that cytokines may be signals that upregulate the astrocytic GDH expression in response to the degeneration of serotonergic terminals in the hippocampus.

He, B., V. Navikas, et al. (1995). "Tumor necrosis factor [alpha]-308 alleles in multiple sclerosis and optic neuritis." Journal of Neuroimmunology **63**(2): 143.

<http://www.sciencedirect.com/science/article/B6T03-4002J1P-5/2/2c722b17a858484652efeaefd753399>

Tumor necrosis factor-[α] (TNF-[α]), a proinflammatory cytokine, is believed to play an

important role in multiple sclerosis (MS) pathogenesis. A bi-allelic polymorphism in the TNF-[alpha] promoter region (TNF[alpha]-308), has been reported to influence levels of TNF-[alpha] production. In the present study, we investigated the TNF[alpha]-308 polymorphism in 93 patients with MS, 17 patients with optic neuritis (ON) and 95 healthy individuals using an allele-specific PCR technique. Allelic genotype was compared with TNF-[alpha] mRNA expression levels and HLA class II phenotypes. No significant difference regarding the TNF[alpha]-308 polymorphism was observed between MS patients and controls. Specifically, the less common allele, TNF2, which is associated with higher expression levels of TNF-[alpha], was somewhat less frequent among MS patients. In fact, analysis of 19 patients homozygous for the MS associated HLA-DR-DQ haplotype HLA-Dw2 showed that this haplotype does not carry the TNF2 allele. In addition, in 47 patients, the TNF-[alpha] alleles did not correlate with expression levels measured as numbers of TNF-[alpha] expressing cells. Thus, we found no evidence for an important role of TNF[alpha]-308 polymorphism for genetic susceptibility to MS.

Hewett, S. J., T. P. Misko, et al. (1996). "Murine encephalitogenic lymphoid cells induce nitric oxide synthase in primary astrocytes." Journal of Neuroimmunology **64**(2): 201.

<http://www.sciencedirect.com/science/article/B6T03-3VXHJX1-D/2/eeb3c53904ce561b0cb253ab169fe335>

A cytokine-inducible form of nitric oxide synthase (iNOS), capable of producing large quantities of nitric oxide (NO), can be induced in many cell types. We demonstrate that conditioned medium from encephalitogenic myelin basic protein-sensitized lymphoid cells (MBP-CM) induces the expression of iNOS in primary cultures of murine astrocytes in a time- and concentration-dependent manner. iNOS mRNA was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) as early as 3 h post-exposure. Accumulation of nitrite into the astrocyte culture medium, an indirect measure of NO, was measurable 3 h post-exposure, plateaued at 24 h, and was prevented by the simultaneous administration of the NOS inhibitors, -NG-nitroarginine methyl ester, NG-nitro--arginine or aminoguanidine. Astrocyte expression of iNOS protein, detected by immunohistochemistry and immunoprecipitation/Western blot, was prevented by inhibitors of RNA or protein metabolism, consistent with its dependence on de novo protein synthesis.

Horiuchi, Y., T. Fujii, et al. (2003). "The endogenous, immunologically active peptide apelin inhibits lymphocytic cholinergic activity during immunological responses." Journal of Neuroimmunology **144**(1-2): 46.

<http://www.sciencedirect.com/science/article/B6T03-49W2KP6-4/2/b9052cc9ad50e308cefb0615d3f156b6>

We investigated the effects of apelin, an immunologically active peptide ligand for orphan receptor APJ, on acetylcholine (ACh) synthesis in MOLT-3 human leukemic T cells. We initially confirmed expression of APJ mRNA in several human T- and B-cell lines by reverse transcription-polymerase chain reaction (RT-PCR). We also found that in phytohemagglutinin (PHA)-stimulated MOLT-3 cells, an active apelin fragment, apelin-13, down-regulates expression of choline acetyltransferase (ChAT) mRNA and significantly reduces ChAT activity and cellular ACh content and release. It thus appears that apelin inhibits lymphocytic cholinergic activity via APJ during immunological responses.

House, S. D., X. Mao, et al. (2001). "Chronic morphine potentiates the inflammatory response by disrupting interleukin-1[beta] modulation of the hypothalamic-pituitary-adrenal axis." Journal of Neuroimmunology **118**(2): 277.

<http://www.sciencedirect.com/science/article/B6T03-43N673R-B/2/69b056794a9c791b29b84ae0c65a8b1e>

Interleukin-1-beta (IL-1[beta]) can promote inflammation by up-regulating vascular adhesion molecules and inhibit inflammation by activating the hypothalamic-pituitary-adrenal (HPA) axis to produce anti-inflammatory glucocorticoids. In this study, chronic morphine was shown to suppress IL-1[beta]-induction of corticotropin releasing factor (CRF) mRNA and plasma corticosterone levels. Leukocyte-endothelial adhesion (LEA) in rat mesenteric venules increased during IL-1[beta]- and FMLP-induced inflammation. Chronic morphine potentiated the LEA response to either IL-1[beta] or FMLP alone, and greatly enhanced LEA in response to combined IL-1[beta] and FMLP. Thus, it appears that chronic morphine exposure may promote a potentially damaging inflammatory reaction by disrupting the balance between IL-1[beta]-mediated local inflammation and the anti-inflammatory effects of the HPA axis.

Hvas, J., J. R. Oksenberg, et al. (1993). "[gamma][delta] T cell receptor repertoire in brain lesions of patients with multiple sclerosis." Journal of Neuroimmunology **46**(1-2): 225.

<http://www.sciencedirect.com/science/article/B6T03-47DKVNK-62/2/8821bee32de713ea71f69b1ea6917720>

The identification of activated T cells in the brains of patients with multiple sclerosis (MS) suggests that these cells are critical in the pathogenesis of this disease. Recently we have used the PCR method to analyse rearrangements of V[alpha] and V[beta] genes of the T cell receptor (TCR) in samples of MS and control brains. The results of these studies showed that TCR V gene usage in MS brains may be restricted and in particular that V[beta] genes may be preferentially rearranged in certain HLA haplotypes associated with susceptibility to MS. In view of the recent evidence that T lymphocytes bearing the [gamma][delta] chains may have autoreactive potential, we have assessed whether or not such TCR-bearing lymphocytes were also present in chronic MS lesions. TCR V[gamma] and V[delta] were analysed by the PCR method using a panel of V[gamma] and V[delta] primers paired with C[gamma] or C[delta] primers in 12 MS brains, as well as in brain samples of ten normal post-mortem cases and three neurological controls. TCR V[gamma]---C[gamma] and V[delta]---C[delta] rearrangements were confirmed using Southern blotting and hybridisation of the PCR products with specific C[gamma] and C[delta] probes. Only one to four rearranged TCR V[gamma] and V[delta] transcripts were detected in each of the 23 brain samples obtained from 12 MS patients, with the majority of [gamma][delta] T cells expressing the V[gamma]2 and V[delta]2 chains. In marked contrast, V[gamma] and V[delta] transcripts could only be found in one of the ten non-neurological control brains analysed. To assess the clonality of V[gamma]2 and V[delta]2 T cell receptor chains in the brain samples of MS patients, we have sequenced the junctional regions of the TCR V[gamma]-N-J[gamma]-C[gamma] and V[delta]-N-D[delta]-N-J[delta]-C[delta] segments amplified from brain tissues, CSF and spleens of two MS patients and from the spleen of two control subjects. The sequence analysis obtained so far shows no compelling evidence of an MS specific expansion of one or more clones expressing particular types of [gamma][delta] T cell receptors. In contrast, a clonal expansion of a different population of TCR [gamma][delta]-bearing T cells was found in the spleen of both an MS patient and one of the control individuals. These results suggests that the [gamma][delta] T cell response at the site ohronic lesions, involve a number of clones, possibly in response to several inflammatory antigenic stimuli. Whether or not [gamma][delta] T cells are involved in the initiation of or in the chronicity of the disease remains to be elucidated.

Jander, S. and G. Stoll (1998). "Differential induction of interleukin-12, interleukin-18, and interleukin-1[beta] converting enzyme mRNA in experimental autoimmune encephalomyelitis of the Lewis rat." Journal of Neuroimmunology **91**(1-2): 93.

<http://www.sciencedirect.com/science/article/B6T03-3V5VDX7-D/2/80b7055b9e70e206cee62e3634637763>

Experimental autoimmune encephalomyelitis (EAE) is a model of autoimmune central nervous system (CNS) disease that is mediated by autoreactive Th1 cells secreting the proinflammatory cytokine interferon (IFN)-[gamma]. Interleukin (IL)-12 in its heterodimeric p35/p40 isoform and the recently described cytokine IL-18 potently induce T cell production of IFN-[gamma]. Interleukin-1[beta] converting enzyme (ICE) is required to convert IL-18 precursor protein into its biologically active mature form. In this study, we used semiquantitative reverse transcriptase-polymerase chain reaction to determine steady state levels of IL-12, IL-18, and ICE mRNA in the spinal cord of Lewis rats at different stages of EAE. In control rats, we found significant IL-18, ICE, and IL-12p35, but not IL-12p40 mRNA expression. IL-18 mRNA increased during the acute stage of EAE together with a marked induction of ICE mRNA. IL-12p35 mRNA levels did not change significantly throughout the course of EAE. Surprisingly, the peak expression of IL-12p40 mRNA was delayed by several days relative to the peak of T cell infiltration and IFN-[gamma] mRNA synthesis. Our data implicate the IL-18/ICE pathway in the amplification of Th1-mediated immune responses in the CNS but suggest a different, so far undefined role of endogenous IL-12 in the late effector phase of EAE.

Kim, J. S., S. C. Gautam, et al. (1995). "Expression of monocyte chemoattractant protein-1 and macrophage inflammatory protein-1 after focal cerebral ischemia in the rat." Journal of Neuroimmunology **56**(2): 127.

<http://www.sciencedirect.com/science/article/B6T03-3YYTF9M-2/2/2d2963a185399a09cb5d5220b36fcc35>

Chemoattractant cytokines, the chemokines, play an important role in early events of inflammation at the site of tissue damage. We examined the expression of mRNA and the protein products of two such chemokines; i.e. monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1[alpha] (MIP-1[alpha]) in the ischemic brain tissue following middle cerebral artery occlusion (MCAo). The mRNA transcripts of MCP-1 and MIP-1[alpha] were detected by Northern hybridization and reverse transcriptase polymerase chain reaction (RT/PCR), respectively, and the anatomic distribution of specific proteins was analyzed by immunohistochemistry. We found that MCP-1 mRNA was not expressed in the brains of normal rats or rats sacrificed 2 h after MCAo. 6 h after the induction of cerebral ischemia, weak expression of both mRNAs was detected in the ischemic tissue. mRNAs were expressed up to 48 h, and were markedly attenuated at 96 h. In the rats subjected to MCA occlusion, MCP-1 immunoreactivity was diffusely expressed and localized to the ischemic area, and was most intense at 48 h after MCA occlusion. Endothelial cells and macrophage-like cells expressed MCP-1 protein in the ischemic brain. The distribution and morphology of MIP-1[alpha] immunoreactive cells were identical with activated astrocytes. We conclude that MCP-1 and MIP-1[alpha] mRNAs and proteins are induced after cerebral ischemia in the rat. They may have a role in promoting inflammatory and/or repair processes in the ischemic brain, possibly by attracting or modulating inflammatory cells in the ischemic area.

Knezevic-Cuca, J., K. B. Stansberry, et al. (2000). "Neurotrophic role of interleukin-6 and soluble interleukin-6 receptors in N1E-115 neuroblastoma cells." Journal of Neuroimmunology **102**(1): 8.

<http://www.sciencedirect.com/science/article/B6T03-3Y9HBD2-2/2/8c2f02e244f65b8cde0a084abafd72b5>

Interleukin 6 (IL-6) plays a role in physiological and pathophysiological processes in neuronal cells. We studied whether IL-6 plays a role in neuroblastoma cells in culture. These studies demonstrate that N1E-115 cells constitutively express IL-6 but not IL-6R. Exogenous IL-6 stimulated neuronal proliferation in a dose-dependent manner. Under serum-free conditions soluble IL-6 receptors (sIL-6R) alone or in combination with IL-6 exerted significant proliferative effects, while IL-6 alone failed to promote cell proliferation. Neutralizing anti-IL-6 antibody caused a 30-40% reduction in IL-6 mediated proliferation. Our results suggest the importance of IL-6/sIL-6R for proliferation and survival of N1E-115 adrenergic neuroblastoma cells.

Kuhlmann, T., M. Glas, et al. (2002). "Investigation of bax, bcl-2, bcl-x and p53 gene polymorphisms in multiple sclerosis." Journal of Neuroimmunology **129**(1-2): 154.

<http://www.sciencedirect.com/science/article/B6T03-4689C4N-2/2/acf5a393657dde644ca220d75d448102>

Clinical course, outcome, radiological features, severity, and histopathology are heterogenous in multiple sclerosis (MS). Since MS is considered to be a polygenic disease, the genetic background may at least partly be responsible for this variability. Some MS cases are histopathologically characterized by a dramatic oligodendrocyte loss that is in part caused by apoptosis. A dysregulated apoptotic elimination of self-reactive T cells may also contribute to disease susceptibility. To analyze genetic differences in the apoptosis regulating factors bcl-2, bax, bcl-x and p53 we investigated polymorphisms of these genes in 105 patients with a relapsing remitting disease course and 99 controls by PCR-SSCP and direct sequencing. We identified so far unpublished sequence alterations in the promotor region of the bcl-x gene, in exon 7 of the p53 gene, and in exon 1 of the bax gene. No differences were observed between MS patients and controls. Additional known polymorphisms were found in intron 3 of the bax gene and in exon 6 of the p53 gene. No significant differences in the frequency of gene sequence variations were found between MS patients and controls. The apoptosis genes studied here therefore appear less likely to be important effector genes in MS.

Lai, J.-P., S. D. Douglas, et al. (1998). "Human lymphocytes express substance P and its receptor." Journal of Neuroimmunology **86**(1): 80.

<http://www.sciencedirect.com/science/article/B6T03-3SY8T41-9/2/daebd5f4ebc8841ef3dcd3420b6936fc>

We present data demonstrating the gene expression of substance P (SP) and its receptor in human peripheral blood-isolated lymphocytes. Using reverse transcribed polymerase chain reaction (RT-PCR) assay, preprotachykinin-A (substance-P) mRNA is detected in human peripheral blood-isolated lymphocytes. Among the [alpha], [beta] and [gamma] transcripts of the SP gene, only the [beta] and [gamma] transcripts are detectable in these cells. These RT-PCR amplified transcripts are recognized by Southern blot assay using a specific SP probe. Direct DNA sequence analysis of the RT-PCR products from lymphocytes also confirmed the structure of these transcripts which are identical to those found in human neuronal cells. At the protein level, human lymphocytes produced endogenous SP as determined by an enzyme immunoassay. Capsaicin, a vanillyl fatty acid amide (ingredient of hot pepper), released preformed SP from lymphocytes. In addition, using RT/nested-PCR analysis, we identified the presence of mRNA for neurokinin-1 receptor (the receptor for SP) in human peripheral blood-isolated lymphocytes,

which was confirmed by Southern blot and DNA sequencing analysis. The demonstration that human lymphocytes express SP and its receptor support the notion that SP is biologically involved in regulating the functions of these cells in an autocrine fashion.

Lai, J.-P., S. D. Douglas, et al. (1998). "Identification of a [delta] isoform of preprotachykinin mRNA in human mononuclear phagocytes and lymphocytes." Journal of Neuroimmunology **91**(1-2): 121.

<http://www.sciencedirect.com/science/article/B6T03-3V5VDX7-J/2/b2b9491ec410b96ceefaaf977379f576>

We have characterized preprotachykinin (PPT-A) gene transcript splicing products and identified a fourth isoform of PPT-A mRNA transcript in human peripheral blood-isolated monocytes and PBL. Using RT-PCR, Southern blot analysis and nucleotide sequencing analysis, we have identified the four isoforms of PPT-A transcripts ([alpha], [beta], [gamma] and [delta]) in human peripheral blood-isolated monocytes and PBL. The [delta]-PPT transcript present in the immune cells lacks exons 4 and 6. The sequences of exons 3, 5 and 7 of [delta]-PPT transcript completely match those of [beta]-PPT transcript. The [alpha]-PPT and [beta]-PPT sequences in these cells are identical to those obtained by Tan and Too (GenBank accession number U37539) and Harmar et al. (Genbank accession number X54469), but differ by a single nucleotide from another entry by Chiwakata et al. (Genbank accession number M68906). In comparison to this latter sequence, there was a C->T change at amino acid position 87 (CCT->CTT) which may result in a Pro to Leu change. Identification of the new SP mRNA transcript in both human CNS and immune cells supports the concept of an important biological link between CNS and immune system.

Lai, J.-P., W.-Z. Ho, et al. (2002). "A non-peptide substance P antagonist down-regulates SP mRNA expression in human mononuclear phagocytes." Journal of Neuroimmunology **128**(1-2): 101.

<http://www.sciencedirect.com/science/article/B6T03-46086CK-1/2/c6e2b0035303983d1751235ad108c96c>

Substance P (SP), a potent modulator of neuroimmunoregulation, exerts its activity by binding to the neurokinin-1 receptor (NK-1R). The SP-NK-1R interaction is important in inflammation and viral infections, including HIV infection of human immune cells. We recently demonstrated that SP modulates HIV replication and that a non-peptide SP antagonist CP-96,345 inhibits HIV replication in human monocyte-derived macrophages (MDM) by affecting the SP-NK-1R interaction. In order to examine the effect of the SP antagonist on SP mRNA expression, MDM was incubated with or without CP-96,345 in the presence or absence of HIV infection. SP mRNA expression in these cells was then determined by real-time PCR technology. The effect of CP-96,345 on chemokine gene expression was also investigated by using a cDNA array assay. CP-96,345 down-regulated SP mRNA expression and antagonized exogenous SP-enhanced SP expression at the mRNA level, suggesting that SP autocrine regulation was interrupted by CP-96,345. CP-96,345 inhibited HIV replication in MDM, associated with down-regulated SP mRNA expression in comparison to HIV infection controls. In parallel with down-regulated SP and CCR5 mRNA expression, cDNA array assays indicated that CP-96,345 treatment also inhibited IL-8 gene expression, while enhancing expression of fractalkine and monocyte chemoattractant protein-3 (MCP-3). Since SP plays an important role in inflammation and viral infections, these studies may have potential applications for therapeutic intervention of inflammation and viral infection of immune cells.

Ledeboer, A., A. Wierinckx, et al. (2003). "Regional and temporal expression patterns of interleukin-10, interleukin-10 receptor and adhesion molecules in the rat spinal cord during chronic relapsing EAE." Journal of Neuroimmunology **136**(1-2): 94.

<http://www.sciencedirect.com/science/article/B6T03-481D7XS-6/2/faf7f318ae98dc163cc89f64ea767164>

Adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) mediate leukocyte infiltration into the CNS, in experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS). Because exogenous interleukin-10 (IL-10) inhibits ICAM-1 and VCAM-1 expression and clinical EAE, we hypothesize that endogenous IL-10 signaling may suppress expression of adhesion molecules. In a rat model of chronic relapsing EAE, expression levels of IL-10 and its receptor (IL-10R1), ICAM-1 and VCAM-1 mRNA in the spinal cord are markedly increased, whereas levels of IL-10 mRNA remain relatively low. The temporal pattern of mRNA and protein expression showed marked differences between spinal cord levels. During relapse, IL-10, IL-10R1, ICAM-1, VCAM-1 mRNA levels and neurological scores show positive correlations. We conclude that endogenous IL-10 is not a crucial factor inhibiting adhesion molecule expression in this model.

Li, Y., S. D. Douglas, et al. (2001). "Substance P enhances HIV-1 replication in latently infected human immune cells." Journal of Neuroimmunology **121**(1-2): 67.

<http://www.sciencedirect.com/science/article/B6T03-448FVSN-3/2/e120ffb63d3a1f11c1363831dd406bb2>

Substance P (SP) is a potent modulator of neuroimmunoregulation. SP receptors are present on human monocytes and T lymphocytes, and SP alters the function of these immune cells. We investigated the effects of SP on HIV-1 replication in latently infected human immune cells. SP significantly enhanced HIV-1 replication in the latently infected promonocytic cell line (U1) and T lymphocyte line (ACH-2) stimulated with tumor necrosis factor (TNF-[alpha]). When added to these cells in combination with TNF-[alpha], SP also enhanced HIV-1 gag gene expression in U1 and ACH-2 cells. This stimulatory effect of SP was associated with the activation of HIV-LTR (long terminal repeat) driven chloramphenicol acetyltransferase (CAT) gene expression, and could be blocked by pretreatment of U1 and ACH-2 cells with an SP receptor antagonist RP-67,580, indicating specific SP receptor-mediated regulation. Furthermore, the addition of SP to the cultures of latently infected peripheral blood mononuclear cells isolated from HIV-1-infected patients enhanced HIV-1 gag gene expression. Thus, SP may play a potentially important role as a positive regulator of HIV-1 replication in latently infected monocytes and lymphocytes. These observations may have significant implications toward understanding the role of neuropeptide SP in the immunopathogenesis of HIV-1 infection and AIDS.

Liu, H.-C., J. K. Anday, et al. (2004). "Dual effects of morphine on permeability and apoptosis of vascular endothelial cells: morphine potentiates lipopolysaccharide-induced permeability and apoptosis of vascular endothelial cells." Journal of Neuroimmunology **146**(1-2): 13.

<http://www.sciencedirect.com/science/article/B6T03-4B4S3HG-1/2/902aea9ea50d23c1cda6c7cd54ab12c2>

Vascular endothelial cells (VEC) provide an essential protective barrier between the vascular system and underlying tissues. Using VEC barrier models of human coronary artery cells and human and rat brain microvascular endothelial cells, we investigated the mechanism by which

morphine affects lipopolysaccharide (LPS)-induced VEC permeability. We demonstrated that co-administration of morphine and LPS induced greater VEC apoptosis and permeability than morphine or LPS alone. The extent of induced apoptosis appeared to be cell-type dependent. Furthermore, RT-PCR analysis revealed that morphine and LPS up-regulated Fas expression. These data suggest potential crosstalk between the signaling pathways that mediate morphine- and LPS-triggered apoptosis in brain VEC.

Maier, C. C., R. D. LeBoeuf, et al. (1993). "The structure of a myelin basic protein-associated idiotope." Journal of Neuroimmunology **46**(1-2): 235.

<http://www.sciencedirect.com/science/article/B6T03-47DKVNK-63/2/34c8e5bc7369ca1dc148997476723333>

A cross-reactive idiotope (CRI) has been previously described on monoclonal antibodies (mAbs) specific for encephalitogenic peptides from myelin basic protein (MBP). The anti-CRI mAb, F25F7, binds an idiotope (Id) localized to the light chains of an anti-MBP peptide 1-9 mAb, denoted F23C6, and an anti-MBP peptide 80-89 mAb, denoted 845D3. It is the purpose of this study to further delineate the CRI being recognized by F25F7. To this end, we have found a structural correlation between the CRI and the antigen, a small synthetic peptide, denoted PBM 9-1, used to elicit the anti-Id mAb. Sequence comparison between the light chain of F23C6 and PBM 9-1 reveals a region of homology in CDR 2/FWK 3. The configuration of this site in the VL, as determined by comparison with a mAb, HyHEL-10, whose structure has been determined and is 97% homologous to the light chain of F23C6, conforms to the rules used to define antigenic determinants or Ids. A synthetic peptide having the F23C6 VL CDR 2/FWK 3 sequence inhibited the binding of F25F7 to F23C6 and 845D3. Taken together, these data suggest the Id recognized by F25F7 is defined, in part, by the PBM 9-1-like sequence of F23C6.

Makarenkova, V. P., G. V. Shurin, et al. (2003). "Lung cancer-derived bombesin-like peptides down-regulate the generation and function of human dendritic cells." Journal of Neuroimmunology **145**(1-2): 55.

<http://www.sciencedirect.com/science/article/B6T03-4B3DT8W-5/2/d16ed0c758f9f3264d818f4596979c80>

Development of tumors is regulated by tumor-derived neuroendocrine factors, including bombesin-like peptides (BLP). We have evaluated neuroendocrine regulation of dendritic cell (DC) maturation and function by both tumor-derived and purified bombesin (BOM), neuromedin B (NMB), gastrin-releasing peptide (GRP), and a BOM antagonist -Phe-bombesin (DPB). BOM, NMB and GRP dose-dependently inhibited maturation of DC assessed as down-regulation of CD40, CD80 and CD86 expression on DC. BOM and GRP also inhibited interleukin-12 (IL-12) production by DC and their ability to activate T cells. DPB partly abrogated immunosuppressive effect of tumor cells on DC. These data are a first evidence for the role of BLP in the regulation of DC maturation and function, demonstrating that BLP inhibit DC maturation and longevity in the lung cancer microenvironment. This suggests a new mechanism of tumor escape and provides new targets for the immunopharmacological correction of immune effectors in cancer.

Matsubara, S., T. Kitaguchi, et al. (2001). "Experimental allergic myositis in SJL/J mouse. Reappraisal of immune reaction based on changes after single immunization." Journal of Neuroimmunology **119**(2): 223.

<http://www.sciencedirect.com/science/article/B6T03-442XPR6-9/2/942b312a2a6e902590e3561b9fedd268>

SJL/J mice have been subjected to immunization with wide varieties of antigens to produce models of autoimmune disorders including experimental myositis. They also have a defect in dysferlin gene and spontaneously develop muscle fiber degeneration, a condition akin to limb-girdle type muscular dystrophy and Miyoshi myopathy. To know whether muscle inflammation of SJL mice after immunization with muscle fractions really represents immune-mediated myositis or no more than an epiphenomenon of muscle degeneration due to dysferlin defect, we studied immunological parameters after immunization with rabbit myosin B fraction. Initial infiltration of macrophages and CD4+ lymphocytes on day 11 was followed by increase in number of CD8+ cells. Such increase was not observed in the nontreated and adjuvant controls. Some infiltrating cells were interferon gamma (IFN- γ) positive. Furthermore, increased expression of the signal transducers and activator of transcription 1 (STAT-1) and interferon regulatory factor 1 (IRF-1) mRNA was shown in the first 2 weeks. These results indicate Th1 system activity in the muscle, rather than simple dysferlin deficiency, particularly 1-3 weeks after immunization. Thus it is concluded that an immune-mediated myositis is taking place at this stage. This model can be helpful in understanding pathomechanisms involved in the early stage of human myositides. It has also important implications concerning immune reactions associated with transplantation or gene therapy for muscular dystrophies.

Matsumoto, Y., G. Kim, et al. (2000). "Characterization of T cell receptor associated with the development of P2 peptide-induced autoimmune neuritis." *Journal of Neuroimmunology* **102**(1): 67.

<http://www.sciencedirect.com/science/article/B6T03-3Y9HBD2-9/2/c724221608fce2ee1ed62e728471e419>

To characterize experimental autoimmune neuritis (EAN)-inducing T cells in more detail, we performed CDR3 spectratyping analysis and found oligoclonal expansion of several V β spectratypes in nerve-infiltrating T cells. V β 5 expansion was observed all the stages examined, whereas V β 8.2 and V β 17 expansion was mainly found at the peak and preclinical stages, respectively. Since V β 5 expansion persists throughout the course of the disease, V β 5+ T cells are judged to be the main effector cells. V β 8.2+ and V β 17+ T cells may also be pathogenic but are not the main effectors because expansion of these spectratypes was found at a limited period of time. Sequence analysis revealed that V β 5, V β 8.2 and V β 17 spectratype-derived TCR clones possess their own dominant sequences in the CDR3 region with no homology among the clones. These findings suggest that polyclonally activated T cells are involved in the formation of the nerve lesion. Furthermore, vaccination with V β 5 DNA, but not with V β 10 DNA, suppressed the development of EAN significantly. Collectively, these findings indicate that determination of autoimmune disease-associated TCR by CDR3 spectratyping provides useful information for designing TCR-based immunotherapy for the disease.

Misko, T. P., J. L. Trotter, et al. (1995). "Mediation of inflammation by encephalitogenic cells: interferon γ induction of nitric oxide synthase and cyclooxygenase 2." *Journal of Neuroimmunology* **61**(2): 195.

<http://www.sciencedirect.com/science/article/B6T03-3YYV2B2-B/2/3e1c7e2d7e5d1107b0ddf10e3a975d1d>

Experimental autoimmune encephalomyelitis (EAE) is a T cell-mediated inflammatory

demyelinating disorder of the central nervous system (CNS) which serves as a prime animal model for the human disease multiple sclerosis. Previous studies from these laboratories demonstrated excess nitric oxide (NO) in the CNS of EAE-affected mice, and amelioration of EAE with a selective inhibitor of the inducible nitric oxide synthase (iNOS). Recent studies from other laboratories have indicated that prostaglandin PGE₂ is increased in CNS tissues of EAE-affected rodents and that EAE is prevented by the inhibition of cyclooxygenase activity. The present study investigated the ability of encephalitogenic lymphoid cells to induce NOS and cyclooxygenase (COX-2) in the murine macrophage line, RAW 264.7. In order to mimic the extracellular milieu present in EAE lesions, conditioned medium (CM) of activated EAE-inducer cells was added to this macrophage line. CM caused a time-dependent increase in nitrite, indicating NO production. Reverse-transcriptase PCR demonstrated iNOS mRNA in RAW 264.7 cells, first detected at 3 h, and Western blots confirmed the induction in RAW cells of the 130-kDa iNOS protein. Production of nitrite by CM-exposed RAW 264.7 cells was blocked by inhibitors of NOS (-N-methylarginine or aminoguanidine) or by antibodies to murine IFN- γ or IL-1 β . CM of activated encephalitogenic cells induced production of PGE₂ by RAW 264.7 cells, as determined by ELISA, and Western blots identified the presence of the 70-80-kDa inducible COX (COX-2) protein. Induction of COX-2 could be inhibited by antibody to IFN- γ . Thus, encephalitogenic cells are capable of inducing the expression of the inflammatory enzymes iNOS and COX-2 in a murine macrophage line via the T cell cytokine IFN- γ , alone or in combination with IL-1 β .

Niino, M., S. Kikuchi, et al. (2003). "Genetic polymorphisms of osteopontin in association with multiple sclerosis in Japanese patients." Journal of Neuroimmunology **136**(1-2): 125.

<http://www.sciencedirect.com/science/article/B6T03-47S6Y27-2/2/b63cf65b11e7e4d06b9f0ae7f6439f01>

Osteopontin (OPN) exhibits pleiotropic functions and abundant transcripts for OPN are present in brains of patients with multiple sclerosis (MS). The aim of this study was to investigate the role of OPN genes in the pathogenesis of MS. Polymorphisms at the 8090th, 9250th and 9583rd positions in OPN were detected by PCR-RFLP from DNAs of 116 MS Japanese patients and 124 healthy controls. The C/C genotype at the 8090th position in exon 6 was more prevalent in MS than in control (p=0.01) and A/A (age; 25.2 \pm 8.9 years, p=0.01) genotypes. There were no significant correlations between OPN gene polymorphisms and disease progression. Our results suggest that the 8090th polymorphism might be associated with susceptibility to MS, while the 9583rd polymorphism might be associated with age of onset of MS.

Omari, K. I. M. and K. Dorovini-Zis (2001). "Expression and function of the costimulatory molecules B7-1 (CD80) and B7-2 (CD86) in an in vitro model of the human blood-brain barrier." Journal of Neuroimmunology **113**(1): 129.

<http://www.sciencedirect.com/science/article/B6T03-41Y28FP-G/2/d5a182e24ffe4bbb2470d32971e36a9e>

The interaction of B7 molecules with their ligand provides important accessory signals for optimal T cell activation and proliferation. In this study the in vitro expression of B7-1 and B7-2 by human brain microvessel endothelial cells (HBMEC) was investigated by semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR) and immunocytochemistry. In addition, the contribution of B7 molecules to T cell proliferation on cerebral endothelial cells was studied by coincubating purified CD4⁺ T cells with resting or cytokine activated HBMEC. Untreated cultures constitutively expressed B7-2 RNA and surface protein, but lacked B7-1 expression. Treatment with TNF- α and IFN- γ upregulated B7-2 and induced de novo expression of B7-1.

Monoclonal blocking antibodies to B7-1 or B7-2 and human CTLA-4Ig chimeric protein significantly reduced the ability of HBMEC to support [alpha]-CD3-induced proliferation of CD4+ T lymphocytes. Expression of B7 glycoproteins and the ability to provide secondary signals for T cell proliferation suggest a potential role of the human cerebral endothelium in T cell activation during the early stages of central nervous system inflammation.

Omari, K. M. and K. Dorovini-Zis (2003). "CD40 expressed by human brain endothelial cells regulates CD4+ T cell adhesion to endothelium." Journal of Neuroimmunology **134**(1-2): 166.

<http://www.sciencedirect.com/science/article/B6T03-47CXW39-2/2/7eada645c7068bf95570aeb37140eaf8>

Recent evidence suggests that interactions between CD40 on antigen presenting cells (APC) and CD40L on T cells generate signals that result in the activation of APC. In this study, the expression and function of CD40 was investigated in primary cultures of human brain microvessel endothelial cells (HBMEC). Results revealed constitutive expression of CD40 on untreated HBMEC. Stimulation with TNF-[alpha], IFN-[gamma], LPS or combination of TNF-[alpha] and IFN-[gamma] significantly upregulated CD40. The majority of CD40 molecules were localized on the apical surface of EC. Incubation of HBMEC with soluble CD40L resulted in increased expression of the adhesion molecules E-selectin, VCAM-1 and ICAM-1. Consequently, the adhesion of both resting and anti-CD3 activated CD4+ T lymphocytes to CD40L treated HBMEC was significantly increased compared to unstimulated EC. The expression of CD40 by cerebral endothelium, and endothelial cell activation following binding of CD40 to its ligand, CD40L, suggest a potential mechanism by which activated CD40L expressing T cells could enhance adhesion and migration of inflammatory cells across the blood-brain barrier (BBB) to sites of inflammation in the human central nervous system (CNS).

Palma, C. and S. Manzini (1998). "Substance P induces secretion of immunomodulatory cytokines by human astrocytoma cells." Journal of Neuroimmunology **81**(1-2): 127.

<http://www.sciencedirect.com/science/article/B6T03-3S4PGS1-H/2/cf62cd33062e1a6661c493fd9e912715>

In human astrocytoma cell lines, substance P (SP) stimulated interleukin (IL)-8, IL-6, granulocyte macrophage colony-stimulating factor and leukemia inhibitory factor protein secretion. These SP effects were blocked by a specific NK1 tachykinin receptor antagonist. Further, SP stimulation increased the half-life of IL-6 and IL-8 messenger RNAs, suggesting that the synthesis of these cytokines is also regulated post-transcriptionally. SP-induced cytokine release was inhibited by staurosporine and phorbol 12-myristate 13-acetate desensitization suggesting protein kinase C involvement. The demonstration that SP affects cytokine production in glioma cells might be of relevance for the biology of such tumors.

Palma, C., F. Urbani, et al. (1995). "Interleukin-6 production by U373 MG, a human astrocytoma cell line: different pathways involved in substance P and lipopolysaccharide activation." Journal of Neuroimmunology **59**(1-2): 155.

<http://www.sciencedirect.com/science/article/B6T03-3YYTVJM-K/2/07176691abda11a44b8feb2e534caf73>

Substance P (SP) and lipopolysaccharide (LPS) stimulated interleukin-6 (IL-6) gene expression, as well as IL-6 protein secretion in the human astrocytoma cell line U373 MG. Staurosporine, an inhibitor of protein kinase C (PKC), entirely blocked SP- but not LPS-induced IL-6 release. In addition, the down regulation of PKC inhibited the SP response and only marginally altered LPS activation. Differently from SP, LPS-induced IL-6 release was markedly reduced by W7, a calmodulin antagonist. Moreover, SP interacted in a synergistic manner with LPS. Thus, neural (SP) and bacterial (LPS) mediators stimulate U373 MG IL-6 release via distinct, though not antagonistic, activation pathways.

Petitto, J. M. and Z. Huang (1995). "Molecular cloning of the coding sequence of an interleukin-2 receptor [alpha] subunit cDNA in murine brain." Journal of Neuroimmunology **59**(1-2): 135.

<http://www.sciencedirect.com/science/article/B6T03-3YYTVJM-H/2/b54e85b6fcf908dd0ca891bb412fad69>

Interleukin-2 (IL-2) has various trophic and neuromodulatory actions in the mammalian central nervous system (CNS). The interleukin-2 receptor [alpha] (IL-2R[alpha]) is an accessory subunit of the IL-2 receptor heterotrimer complex which is essential for 'high' affinity IL-2 binding. Although an IL-2R[alpha] (or IL-2Ra-like) epitope has been localized in brain by immunohistochemistry, it was unknown whether the IL-2R[alpha] subunit expressed in-brain was derived from the same or a different gene than the lymphocyte IL-2R[alpha]. Therefore, in the present study, the cDNA comprising the full length coding region was cloned and sequenced from saline-perfused forebrain. The brain IL-2R[alpha] cDNA was found to be 100% homologous with the corresponding lymphocyte IL-2R[alpha] cDNA sequence. IL-2R[alpha] mRNA was expressed at very low levels in saline-perfused forebrain of non-challenged BALB/c mice as well as in saline-perfused forebrain from severe combined immunodeficiency (SCID) mice. The present data, demonstrating IL-2R[alpha] gene expression in both well-perfused normal and SCID mouse forebrain from which no CD3[gamma] gene expression was detected by PCR, provides evidence that the IL-2R[alpha] clones isolated are from resident brain cells and not from blood lymphocytes (e.g. T lymphocytes). Thus, these findings demonstrate that the protein coding sequence of the mouse brain IL-2R[alpha] is derived from the same gene coding sequence as the lymphocyte IL-2R[alpha], and indicate that previously reported differences in the size of their respective mRNA transcripts appear to be due to differences in untranslated regions.

Petitto, J. M., Z. Huang, et al. (1994). "Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: Evidence of low levels of mRNA expression and [¹²⁵I]NPY binding sites." Journal of Neuroimmunology **54**(1-2): 81.

<http://www.sciencedirect.com/science/article/B6T03-47DKSSM-13/2/387a5ebe6f988fcbc17da518f07694d5>

The present study addressed the question of whether the effects of neuropeptide Y (NPY) on parameters of cellular immune activity are mediated by the direct action of this neuropeptide on lymphocyte NPY receptors. A partial cDNA corresponding to bp 3-585 of the NPY-Y1 receptor coding sequence was cloned from rat splenic lymphocytes and found to have 100% nucleotide sequence homology with that segment of the NPY-Y1 receptor in brain. Basal levels of NPY-Y1 mRNA expression and [¹²⁵I]NPY binding sites of rat splenic lymphocytes were markedly lower than in frontal cortex. These data provide the first direct evidence that cells of the immune system possess NPY receptors, and suggest that further study will be necessary to determine their physiological significance.

Piraino, P. S., T. A. Yednock, et al. (2002). "Prolonged reversal of chronic experimental allergic encephalomyelitis using a small molecule inhibitor of [alpha]4 integrin." Journal of Neuroimmunology **131**(1-2): 147.

<http://www.sciencedirect.com/science/article/B6T03-46WV6NX-5/2/d20dbd5381c8a439d0c599c6e358282f>

CNS leukocytic invasion in experimental allergic encephalomyelitis (EAE) depends on [alpha]4[beta]1 integrin/vascular cell adhesion molecule-1 (VCAM-1) interactions. A small molecule inhibitor of [alpha]4[beta]1 integrin (CT301) was administered to guinea pigs in the chronic phase (>d40) of EAE for 10, 20, 30 or 40 days. CT301 elicited a rapid, significant improvement in the clinical and pathological scores that was maintained throughout the treatment period. A progressive loss of cells in the spinal cord of treated animals confirmed the resolution of inflammation associated with clinical recovery. Therefore, prolonged inhibition of [alpha]4[beta]1 integrin caused a sustained reversal of disease pathology in chronic EAE and may be similarly useful in MS.

Poluektova, L., T. Moran, et al. (2001). "The regulation of alpha chemokines during HIV-1 infection and leukocyte activation: relevance for HIV-1-associated dementia." Journal of Neuroimmunology **120**(1-2): 112.

<http://www.sciencedirect.com/science/article/B6T03-449TY7W-G/2/4e3b51812120860e70b47c74102e8f2c>

Cellular immunity against human immunodeficiency virus type 1 (HIV-1)-infected brain macrophages serves to prevent productive viral replication in the nervous system. Inevitably, during advanced disease, this antiretroviral response breaks down. This could occur through virus-induced dysregulation of lymphocyte trafficking. Thus, we studied the production of non-ELR-containing [alpha]-chemokines and their receptor (CXCR3) expression in relevant virus target cells. Macrophages, lymphocytes, and astrocytes secreted [alpha]-chemokines after HIV-1 infection and/or immune activation. Lymphocyte CXCR3-mediated chemotactic responses were operative. In all, [alpha]-chemokine-mediated T cell migration continued after HIV-1 infection and the neuroinflammatory events operative during productive viral replication in brain.

Reiseter, B. S., G. T. Miller, et al. (1998). "Treatment of murine experimental autoimmune encephalomyelitis with a myelin basic protein peptide analog alters the cellular composition of leukocytes infiltrating the cerebrospinal fluid." Journal of Neuroimmunology **91**(1-2): 156.

<http://www.sciencedirect.com/science/article/B6T03-3V5VDX7-P/2/516c59d6881d06c6ef64fe9006bf325e>

Experimental autoimmune encephalomyelitis (EAE) can be effectively treated during disease exacerbation by administration of a peptide corresponding to the major T cell epitope of myelin basic protein (MBP), but the mechanism by which T cell tolerance leads to clinical improvement is not well-defined. Acute exacerbations of EAE are accompanied by an infiltration of blood-borne leukocytes into the brain and spinal cord, where they mediate inflammation and demyelination. To investigate peptide effects on infiltrating cells, we collected cerebrospinal fluid (CSF) from (PL/JxSjL)F1 mice with MBP-induced EAE. Pleiocytosis by lymphocytes, neutrophils, and macrophages was seen throughout the course of relapsing-remitting disease. A single

administration of the MBP peptide analog, Ac1-11[4Y], reduced disease severity, accompanied by a dramatic and selective loss of neutrophil pleiocytosis. A longer course of peptide therapy resulted in complete recovery from clinical signs of disease, and decreased pleiocytosis by all cell types. Clinical severity throughout the course of disease and therapy was directly related to the degree of infiltration by neutrophils and macrophages, and the clinical improvement following peptide therapy was accompanied by decreased central nervous system (CNS) expression of chemoattractants for these cell types. These observations support a model of disease exacerbation mediated by phagocytic cellular infiltration under the ultimate control of T cell-derived factors, amenable to treatment by down-regulation of the T cell activation state.

Ringheim, G. E., K. L. Burgher, et al. (1995). "Interleukin-6 mRNA expression by cortical neurons in culture: Evidence for neuronal sources of interleukin-6 production in the brain." Journal of Neuroimmunology **63**(2): 113.

<http://www.sciencedirect.com/science/article/B6T03-4002J1P-2/2/128eb0f2ac84f4279cd746e0cad090b1>

In this study, we investigated the capacity of murine cortical neurons to express interleukin-6 (IL-6) mRNA and protein in culture. Using in situ hybridization techniques, IL-6 mRNA was localized to neuronal cells in these cultures. Moreover, IL-6 mRNA expression as measured by in situ and PCR was shown to be upregulated by the proinflammatory cytokines interleukin-1[beta] (IL-1[beta]) and tumor necrosis factor-[alpha] (TNF-[alpha]). This was consistent with the dose and time-dependent increases in IL-6 secreted protein observed from cultures stimulated with IL-1[beta] and TNF-[alpha]. Taken together, the data suggest that neurons are capable of participating more directly in the CNS cytokine network than previously thought and may play an important role in the inflammatory response activities in the brain.

Rinner, I., K. Kawashima, et al. (1998). "Rat lymphocytes produce and secrete acetylcholine in dependence of differentiation and activation." Journal of Neuroimmunology **81**(1-2): 31.

<http://www.sciencedirect.com/science/article/B6T03-3S4PGS1-4/2/37cf97457a69535fa892f82f0abb6ce4>

Previous data from this laboratory suggested for the first time that immune cells of the immune system of different species are capable to synthesize the neurotransmitter acetylcholine. In the present study we detected the RNA message for choline acetyltransferase in thymic, splenic and peripheral blood lymphocytes of rats using RT-PCR. Furthermore, using a sensitive radioimmunoassay, we measured acetylcholine in thymic, splenic and peripheral blood lymphocytes. T-cells were found to contain about three times the amount of acetylcholine as compared to B-cells, and CD4+ cells showed significantly higher levels as compared to CD8+ cells. Mitogenic stimulation with PHA increased the acetylcholine levels in lymphoid cells as well as the release into the supernatants.

Rosche, B., S. Cepok, et al. (2004). "The role of the Polio Virus Receptor and the Herpesvirus entry mediator B genes for the development of MS." Journal of Neuroimmunology **156**(1-2): 171.

<http://www.sciencedirect.com/science/article/B6T03-4D4D5VY-1/2/d50cc01ad92cea05ca6032c1eff9f0d2>

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS). Although the cause of MS is still uncertain, it is well accepted that both genetic and environmental factors are important for the development of disease. In this study, we focused on the Polio Virus Receptor (PVR) and Herpesvirus entry mediator B (HVEB) receptor genes, which are located on chromosome 19q13, a region previously linked to MS. Both receptors are expressed in the brain and immune system and play an important role for inter-cellular adhesion and entry of neurotropic viruses to the brain. We identified four new polymorphisms in the PVR gene, which were located in the promoter region and three different exons. All exonic polymorphisms altered the amino acid sequence of the receptor. No new polymorphisms were found in the HVEB gene, but we confirmed a previously identified intronic polymorphism. We analyzed the frequency of the polymorphisms by RFLP analysis in sporadic MS patients, MS families, and healthy controls and determined the surface expression of HVEB and PVR on peripheral blood monocytes. We did not find differences in the frequency of the polymorphisms or surface expression between MS patients and controls. Overall, our findings do not support a role of HVEB and PVR genes in the development of MS.

Roupe van der Voort, C., C. J. Heijnen, et al. (2000). "Stress induces increases in IL-6 production by leucocytes of patients with the chronic inflammatory disease juvenile rheumatoid arthritis: a putative role for [alpha]1-adrenergic receptors." Journal of Neuroimmunology **110**(1-2): 223.

<http://www.sciencedirect.com/science/article/B6T03-41C2RJC-W/2/17d44ec4c8811b10166b07f41bd657ca>

Juvenile rheumatoid arthritis (JRA) is characterized by chronic inflammation of the joints. In the present study we demonstrate that exposure of JRA patients to a noradrenergic stressor (cold pressor test) results in enhanced LPS-induced IL-6 production by peripheral blood cells of these patients. Healthy, age-matched controls had the same rise in norepinephrine, but do not respond with changes in IL-6 production after exposure to the cold pressor test. Moreover, PBMC of patients with JRA express mRNA encoding [alpha]1-adrenergic receptors (AR), predominantly of the [alpha]1d-AR subtype. In contrast, we could not detect mRNA encoding for [alpha]1-AR in PBMC of healthy controls. The results of this study suggest that expression of [alpha]1-AR mRNA in PBMC during chronic inflammation is associated with altered responses of the immune system to stress.

Roupe van der Voort, C., A. Kavelaars, et al. (1999). "Neuroendocrine mediators up-regulate [alpha]1b- and [alpha]1d-adrenergic receptor subtypes in human monocytes." Journal of Neuroimmunology **95**(1-2): 165.

<http://www.sciencedirect.com/science/article/B6T03-3W4B1W0-M/2/3ce0eaf25fca4acc3d71a5e0c63d5a7b>

[beta]2- and [alpha]2-adrenergic receptors (AR) are thought to be the main AR subtypes to exert the effects of catecholamines on the immune system. However, in the present study, we demonstrate that another subtype of AR can be induced in human monocytes. Expression of [alpha]1b- and [alpha]1d-AR mRNA can be obtained by culturing freshly isolated human peripheral blood monocytes with the neuroendocrine mediators dexamethasone or the [beta]2-AR agonist terbutaline. Using the human monocytic cell line THP-1, we demonstrate that increased levels of [alpha]1b- and [alpha]1d-mRNA are accompanied by increased levels of receptor protein as determined by Western blot analysis and radioligand binding assays. This study describes for the first time regulated expression of [alpha]1-AR subtypes in human monocytes.

Roupe van der Voort, C., A. Kavelaars, et al. (2000). "Noradrenaline induces phosphorylation of ERK-2 in human peripheral blood mononuclear cells after induction of [alpha]1-adrenergic receptors." Journal of Neuroimmunology **108**(1-2): 82.

<http://www.sciencedirect.com/science/article/B6T03-40R5BF6-C/2/7f8f3b439bfff5ea69989c29fc7c53c5>

[alpha]1-Adrenergic receptors (ARs) are not expressed by peripheral blood mononuclear cells (PBMCs) of healthy human individuals. However, in the present study we show that [alpha]1-ARs can be induced in lymphocytes after culturing with either the mitogen PHA or the glucocorticoid dexamethasone. Moreover, incubation of these activated PBMCs with noradrenaline (NA) results in enhanced phosphorylation of ERK-2, a kinase involved in the activation of many immune functions. Similar induction of [alpha]1-AR mRNA with concomitant NA-induced activation of ERK-2 occurs in monocytes after culture with LPS. Our results demonstrate that functional [alpha]1-ARs can be induced on PBMCs and that these [alpha]1-ARs mediate NA-induced activation of ERK-2.

Roy, S., R. G. Charboneau, et al. (1999). "Morphine synergizes with lipopolysaccharide in a chronic endotoxemia model." Journal of Neuroimmunology **95**(1-2): 107.

<http://www.sciencedirect.com/science/article/B6T03-3W4B1W0-C/2/d135b0b84fd31c2d702400ce37fcbb24>

Emergent or elective surgical procedures may be complicated by sepsis, resulting in critical illness that can lead to organ failure and death. The opioid drug, morphine is widely used to alleviate pain in post-surgical patients; however, it is well documented that chronic treatment of mice with morphine affects the proliferation, differentiation and function of immune cells. Thus, morphine might be expected to exacerbate the effects of sepsis, which also compromises the immune system. To test this notion, we investigated the effect on several immune functions of a clinical dose of morphine (4 mg/kg) superimposed upon a lipopolysaccharide (LPS)-induced infection model. Our results show that this relatively low dose of morphine, though generally having no effects on immune parameters by itself, significantly augmented LPS responses. A clinical dose of morphine (4 mg/kg body weight) superimposed upon an animal model of sepsis resulted in a significant increase in mortality at 48 h. In the absence of the drug, most septic animals died after 96 h. Phenotypic responses such as, decreased thymic cellularity, compromised mitogenic response and inhibition of IL-2 synthesis that are evident at 48-72 h after LPS injection appear as early as 24 h in animals that receive morphine in addition to LPS. In addition, our results show that in T cells there is a shift from TH1 type cytokine elaboration to a TH2 type cytokine elaboration in animals that receive both LPS and morphine.

Sato, S., S. L. Reiner, et al. (1997). "Central nervous system cytokine mRNA expression following Theiler's murine encephalomyelitis virus infection." Journal of Neuroimmunology **76**(1-2): 213.

<http://www.sciencedirect.com/science/article/B6T03-3PSB1XD-Y/2/aeffadb4e512d063b5dc934a0010bbe3>

DA strain of Theiler's murine encephalomyelitis virus (TMEV) produces a biphasic disease with an initial self-limited acute gray matter polioencephalomyelitis in all strains of mice followed by, in the case of certain susceptible strains of mice, a chronic inflammatory demyelination of the spinal

cord with a persistent virus infection. A pathogenic role for T-helper 1 (Th1) cells during the demyelinating phase of disease has been proposed. We characterized the cytokine mRNA expression in the brain and spinal cord of susceptible and resistant strains of mice during the early encephalomyelitic disease and the late demyelination, using a semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR) assay. At the time of the encephalomyelitis, both resistant and susceptible mice expressed proinflammatory cytokine mRNAs followed by T-cell derived mRNAs; susceptible mice expressed more IL-12 p40 mRNA than resistant mice. During this early disease, there was no significant difference in Th1 cytokine mRNA expression in the brain and spinal cord among the four strains and relatively little Th2 type cytokine upregulation above levels seen in mock-infected controls. During the late demyelinating disease, susceptible but not resistant mice had evidence of viral genome and a continuous expression of Th1 type cytokine mRNAs. The expression of Th2 cytokine mRNAs varied among the different strains and did not correlate with susceptibility or resistance. The results indicate the complexity of cytokine mRNA expression following TMEV infection and the dependence of the expression on disease pathology, the time following infection and the genetics of the host.

Schaecher, K. E., J.-M. Goust, et al. (2001). "The effects of calpain inhibition upon IL-2 and CD25 expression in human peripheral blood mononuclear cells." *Journal of Neuroimmunology* **119**(2): 333.

<http://www.sciencedirect.com/science/article/B6T03-442XPR6-R/2/32a66410440e29c426f84df9f0015f0e>

Calcium is an important contributor to T cell activation; it is also the major factor in the activation of the calcium-activated neutral proteinase, calpain. For this reason, we wanted to investigate if calpain has a role in T cell activation and what aspects of this activation calpain affects. As measured by semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), calpain inhibition decreased interleukin-2 (IL-2) and CD25 mRNA expression in a dose-dependent manner, at early time points following the initial activation, and over extended periods of time in activated human peripheral blood mononuclear cells (PBMCs). Using an enzyme-linked immuno-sorbent assay (ELISA) specific for human IL-2, we found that calpain inhibition decreased IL-2 secretion in a dose-dependent manner, shortly after activation, and continuously over time. Inhibiting calpain caused a dose-dependent inhibition of CD25 cell surface expression and also inhibited expression shortly after activation and for at least 48 h. This study showed that calpain has an integral role in the synthesis of the two important T cell activation factors, IL-2 and CD25.

Schwarz, H., P. M. Villiger, et al. (1994). "Neuropeptide Y is an inducible gene in the human immune system." *Journal of Neuroimmunology* **51**(1): 53.

<http://www.sciencedirect.com/science/article/B6T03-476HJ7V-12/2/4c93ee2395ce3483427fcc6e784c3be8>

This study reports on neuropeptide Y (NPY) mRNA expression in human peripheral blood mononuclear cells (PBMC) and lymphoid tissues. By reverse transcription polymerase chain reaction (RT-PCR) it is shown that activated human PBMC of normal blood donors expressed the NPY gene. The PCR products had the expected size and Northern blotting demonstrated the presence of the 0.8-kb NPY mRNA. To define the subpopulations of mononuclear cells expressing this neuropeptide, purified monocytes, B cells and T cells were stimulated with specific activators. Monocytes and in vitro matured macrophages expressed NPY mRNA in response to phorbol myristate acetate (PMA). B lymphocytes expressed NPY mRNA following stimulation with antibody to surface immunoglobulin and PMA. In order to analyze whether these

cell types express NPY under physiological conditions in vivo, human bone marrow, tonsil and thymus were analyzed. In situ hybridization of bone marrow revealed a small number of cells containing high levels of NPY mRNA which was also detected in RNA extracts of human thymus and tonsil. In summary, NPY is an inducible gene in human lymphocytes and monocytes and it is expressed at sites where these cells are activated in vivo.

Sciacca, F. L., C. Ferri, et al. (2000). "Association study of a new polymorphism in the PECAM-1 gene in multiple sclerosis." Journal of Neuroimmunology **104**(2): 174.

<http://www.sciencedirect.com/science/article/B6T03-3YS33NS-B/2/0e7bb4c477810d5342fd1251f9f3aa10>

Genetic polymorphisms of immunorelevant genes may modulate occurrence or clinical features of multifactorial diseases. PECAM-1 is an adhesion molecule crucial for transmigration of cells from blood to tissues, but its genetic contribution to multifactorial diseases has never been investigated. We have identified and characterized a tetranucleotide repeat polymorphism within the third intron of PECAM-1. In a cohort of healthy controls (HC), we found 10 alleles. An assessment of the association of this polymorphism with multiple sclerosis (MS) showed similar allele and genotype frequencies in HC and MS patients as well as in MS patients differing for the gravity of their disease course. We conclude that although potentially able to affect organ-specific autoimmune diseases, this new PECAM-1 polymorphism, does not seem to contribute to the genetic background of MS.

Sedqi, M., S. Roy, et al. (1996). "Expression cloning of a full-length cDNA encoding delta opioid receptor from mouse thymocytes." Journal of Neuroimmunology **65**(2): 167.

<http://www.sciencedirect.com/science/article/B6T03-3W496PR-B/2/bd214dd7346ef81c9cd6e57fbff89d3c>

A delta opioid receptor complementary DNA (cDNA) was cloned by expression of cDNA library from activated thymocytes in Cos 7 cells. The deduced amino acid sequence of this receptor was similar to that described in the brain. As analyzed by southern blot hybridization, the delta opioid receptor transcripts are constitutively expressed in unactivated thymocytes. In addition, neither [kappa] nor [mu] opioid receptor transcripts were detected in thymocytes, suggesting tissue-specific opioid receptor gene expression in the immune system. The studies represent the first report of a full-length opioid receptor in the immune system.

Selmaj, K., C. Kowal, et al. (2000). "Naked DNA vaccination differentially modulates autoimmune responses in experimental autoimmune encephalomyelitis." Journal of Neuroimmunology **111**(1-2): 34.

<http://www.sciencedirect.com/science/article/B6T03-41J66JG-5/2/c2d1bce2466dedd2629dc569c1cbaf96>

Vaccination with naked DNA represents a therapeutic strategy currently under consideration in multiple sclerosis (MS). In this study, we tested the potential therapeutic effect of vaccination with a naked DNA construct encoding proteolipid protein (pRc/CMV-PLP) upon the outcome of subsequent sensitization for experimental autoimmune encephalomyelitis (EAE) actively-induced in SJL mice with PLP139-151 peptide in adjuvant. Intramuscular vaccination with the naked DNA

pRc/CMV-PLP construct led to PLP expression in local muscle tissue that persisted for about 8 weeks. Early sensitization for EAE (4 weeks after DNA vaccination) caused recipient mice to develop a severe, exacerbated form of disease (in comparison to control mice), while late sensitization (>10 weeks) resulted in a milder, ameliorated form. In the groups sensitized 10 weeks post-DNA vaccination led to peripheral tolerance as evidenced by a decrease in T cell proliferation and cytotoxic T cell response, no Th2 response, and no increase in apoptosis. These data are novel in that they demonstrate a differential effect of DNA vaccination and have important implications for its use as a mechanism to enhance or modulate immune reactivity.

Shahabi, N. A., Y. Daaka, et al. (1999). "Delta opioid receptors expressed by stably transfected Jurkat cells signal through the map kinase pathway in a ras-independent manner." Journal of Neuroimmunology **94**(1-2): 48.

<http://www.sciencedirect.com/science/article/B6T03-3VNPV73-5/2/661a1db953b9c8a9bbdf0073e3480e3e>

Delta opioid receptors (DOR) are G-protein coupled 7-transmembrane receptors (GPCR), expressed by thymic and splenic T cells, that modulate interleukin (IL)-2 production and proliferation in response to concanavalin A or crosslinking the TCR. Mitogen-activated protein kinases (MAPKs) are involved in mediating intracellular responses to TCR crosslinking. In addition, MAPKs can be activated by signaling cascades that are initiated by the release of G-proteins from GPCRs. To determine whether DORs expressed by T cells signal through the MAPKs, extracellular-regulated kinases (ERKs) 1 and 2, two delta opioid peptides, deltorphin and [-Ala2,-Leu5]-enkephalin (DADLE), were studied in Jurkat cells that had been stably transfected with DOR (DOR-Ju.1). These peptides rapidly and dose-dependently induced ERK phosphorylation; pretreatment with naltrindole (NTI), a selective DOR antagonist, abolished this. Pertussis toxin (PTX) also inhibited phosphorylation, indicating the involvement of the Gi/o proteins. Herbimycin A, a protein tyrosine kinase (PTK) inhibitor, reduced the DADLE-induced ERK phosphorylation by 68%. ERK phosphorylation was inhibited by Bisindolylmaleimide 1 (GF109203X), an inhibitor of PKC, and by pretreatment with PMA prior to DADLE. A GTP/GDP exchange assay was used to assess the potential role of Ras in the pathway leading to ERK phosphorylation; DADLE failed to stimulate GTP/GDP exchange in comparison to PMA. Additional studies showed that DADLE stimulated an increase in *cfos* mRNA; this was reduced by the inhibitor of MAPK/ERK kinase (MEK), PD98059. Therefore, in DOR-Ju.1 cells, DOR agonists stimulate ERK phosphorylation in a Ras independent and PKC-dependent manner; PTKs appear to be involved. MAPKs mediate the increase in *cfos* mRNA induced by DOR agonists.

Sharp, B. M., N. Shahabi, et al. (1997). "Detection of basal levels and induction of delta opioid receptor mRNA in murine splenocytes." Journal of Neuroimmunology **78**(1-2): 198.

<http://www.sciencedirect.com/science/article/B6T03-3R7J7TN-T/2/30b2caf1bc1a471b250fc774b93494c6>

Activation of delta opioid receptors (DOR) modulates calcium mobilization, interleukin-2 production, chemotaxis and proliferation of T-lymphocytes. Recent reports indicate that lymphocytes and mononuclear cells may express mRNA transcripts for DOR. The investigations reported herein show that low levels of DOR were consistently detected by RT-PCR amplification of RNA from freshly obtained Balb/c murine splenocytes, both weanling and adult. Culturing cells without stimulation increased DOR levels and concanavalin A apparently reduced this; DOR was preferentially expressed in a T-cell-enriched fraction. Thus, the expression of DOR mRNA by unactivated splenocytes is modulated by culture and con A in the T-cell fraction.

Shrikant, P., C. Il Yup, et al. (1994). "Regulation of intercellular adhesion molecule-1 gene expression by tumor necrosis factor-[alpha], interleukin-1[beta], and interferon-[gamma] in astrocytes." Journal of Neuroimmunology **51**(2): 209.

<http://www.sciencedirect.com/science/article/B6T03-476WCJ3-X7/2/10c3570a28de34dab7faadb50d3e5e68>

Intercellular adhesion molecule-1 (ICAM-1) is a cell surface glycoprotein which can be induced on astrocytes, the major glial cell of the central nervous system (CNS). In this study, we examined the effect of three proinflammatory cytokines, tumor necrosis factor-alpha (TNF-[alpha]), interleukin-1 beta (IL-1[beta]), and interferon-gamma (IFN-[gamma]), on the expression of ICAM-1 by primary rat astrocytes. Astrocytes constitutively express ICAM-1 mRNA and protein, which is enhanced by treatment with TNF-[alpha], IL-1[beta] and IFN-[gamma]. TNF-[alpha] is the most potent inducer of ICAM-1 expression, followed by IL-1[beta], then IFN-[gamma]. Kinetic analysis demonstrated optimum ICAM-1 mRNA expression after a 1-h exposure to TNF-[alpha], 2 h exposure to IL-1[beta], and 4 h exposure to IFN-[gamma]. Peak ICAM-1 protein expression was detected 12-16 h after treatment with TNF-[alpha] or IL-1[beta], and after a 24-h exposure to IFN-[gamma]. Nuclear run-on analysis demonstrated that the ICAM-1 gene is transcribed under basal conditions in astrocytes, and that both TNF-[alpha] and IL-1[beta] enhance transcriptional activation of the ICAM-1 gene. ICAM-1 mRNA stability studies determined that basal ICAM-1 mRNA has a half-life of about 1 h, and that TNF-[alpha], IL-1[beta] and IFN-[gamma] have a modest effect on stabilization of basal ICAM-1 mRNA expression. These results indicate that under inflammatory conditions in the CNS, such as multiple sclerosis (MS) and experimental allergic encephalomyelitis (EAE), astrocytes can be induced to express the adhesion molecule ICAM-1, which can contribute to inflammatory events within the CNS.

Sierra-Honigmann, A. M., S. A. Rubin, et al. (1993). "Borna disease virus in peripheral blood mononuclear and bone marrow cells of neonatally and chronically infected rats." Journal of Neuroimmunology **45**(1-2): 31.

<http://www.sciencedirect.com/science/article/B6T03-476WCFH-W1/2/a38e1296003ebdc5af5e57da7ccb38ff>

Borna disease virus (BDV) establishes a persistent infection in cells of the nervous system in rats. The response, or lack thereof, of the immune system to BDV infection of neurons is responsible for the presence or absence, respectively, of Borna disease. We recently demonstrated transmission of BDV by bone marrow cells from neonatally infected rats. Our findings suggested the possibility of a heretofore unsuspected interaction between BDV and the immune system, that of direct effects of BDV infection on the cells of the immune system. This report enlarges upon the previous findings and confirms the presence of BDV RNA in bone marrow cells of neonatally infected rats, using a reverse transcription-polymerization chain reaction-enzyme immunosorbent assay (RT-PCR-EIA). In addition, we detected BDV RNA in peripheral blood mononuclear cells of neonatally infected rats, and in rats inoculated as adults in the chronic, but not the acute, stage of infection. In addition, the RT-PCR-EIA technique identified BDV RNA in cerebrospinal fluid, nasal secretions, saliva, urine and stool. BDV-sequences were not detected in the plasma of infected animals nor in the body fluids and tissues of normal rats.

Skorupa, A. F., S. C. G. Brezinski, et al. (2001). "Expression of Golli mRNA during development in primary immune lymphoid organs of the rat." Journal of Neuroimmunology **119**(1): 64.

<http://www.sciencedirect.com/science/article/B6T03-43T7TV1-8/2/1e290e509c09a562efdfb4492b89a213>

The gene-of-the-oligodendrocyte lineage (Golli)-MBP transcription unit contains three Golli-specific exons together with eight exons of the "classical" myelin basic protein (MBP) gene, yielding alternatively spliced proteins which share amino acid sequence with MBP. Unlike MBP, a late antigen expressed only in the nervous system, Golli gene products are expressed pre- and post-natally at many sites. In this study, we determined the sequence of Golli in rat by RT-PCR and 5' RACE and showed that Golli sequences are expressed in primary lymphoid organs as early as e16.5, which could explain the anergic rat T cell response we previously observed in Golli-induced meningitis.

Stinissen, P., J. Zhang, et al. (1998). "[gamma][delta] T cell responses to activated T cells in multiple sclerosis patients induced by T cell vaccination." Journal of Neuroimmunology **87**(1-2): 94.

<http://www.sciencedirect.com/science/article/B6T03-3TCFKBS-D/2/7d104c3ce2ce497a7136eaa09c53491d>

To explore the hypothesis that [gamma][delta] T cells may regulate activated [alpha][beta] T cells, we studied [gamma][delta] T cell responses to [alpha][beta] T cell clones in Multiple Sclerosis (MS) patients who received attenuated autologous autoreactive T cells. We recently conducted a pilot study of T cell vaccination with myelin basic protein reactive T cells in MS. Since T cell vaccination upregulates the anti-vaccine T cell responses, we evaluated [gamma][delta] T cell reactivity towards the vaccine in the vaccinated patients. Lymphocytes were stimulated in vitro with irradiated vaccine cells and the responding lines were checked for the presence of [gamma][delta] T cells. Our data demonstrate that in the majority of vaccinated MS patients [gamma][delta] T cells expand upon stimulation with the vaccine cells. The responding [gamma][delta] T cells were predominantly V[delta]1+/V[gamma]1+, and represented diverse clonal origins. The [gamma][delta] T cells could not inhibit in vitro proliferation of the vaccine T cells and displayed low cytotoxic reactivity towards the vaccine clones. However, they produced high levels of IL2, TNF[alpha] and IL10. These results indicate that [gamma][delta] T cells can be stimulated by activated [alpha][beta] T cells, and that these [gamma][delta] T cell responses are upregulated after T cell vaccination. These findings suggest that [gamma][delta] T cells are involved in peripheral mechanisms to control activated autoreactive T cells.

Storto, M., U. de Grazia, et al. (2000). "Expression of metabotropic glutamate receptors in murine thymocytes and thymic stromal cells." Journal of Neuroimmunology **109**(2): 112.

<http://www.sciencedirect.com/science/article/B6T03-416BXKJ-8/2/77eb587eee3257eb4dd9fa07a1292290>

RT-PCR combined with immunoblotting showed the expression of group-I (mGlu1 and 5) and group-II (mGlu2 and 3) metabotropic glutamate receptors in whole mouse thymus, isolated thymocytes and TC-1S thymic stromal cell line. Cytofluorimetric analysis showed that mGlu-5 receptors were absent in CD4-/CD8- but present in more mature CD4+ CD8+ and CD4+CD8- thymocytes. mGlu-1a receptors showed an opposite pattern of expression with respect to mGlu5, whereas mGlu2/3 receptor expression did not differ between double negative and double positive cells. mGlu receptors expressed in both thymic cell components were functional, as indicated by measurements of polyphosphoinositide hydrolysis or cAMP formation. These data suggest a possible role for mGlu receptor signalling in the thymus.

Szczepanik, A. M., S. Funes, et al. (2001). "IL-4, IL-10 and IL-13 modulate A[beta](1-42)-induced cytokine and chemokine production in primary murine microglia and a human monocyte cell line." Journal of Neuroimmunology **113**(1): 49.

<http://www.sciencedirect.com/science/article/B6T03-41Y28FP-6/2/53671e21c5a94a9775f9364e7a06b2fe>

A hallmark of the immunopathology associated with Alzheimer's disease (AD) is the presence of activated microglia surrounding senile plaque deposits of [beta]-amyloid (A[beta]) peptides. A[beta] peptides have been shown to be potent activators of microglia and macrophages, but little is known about endogenous factors that may modulate their responses to amyloid. We investigated whether the 'anti-inflammatory' cytokines IL-4, IL-10 and IL-13 could regulate A[beta]-induced production of the inflammatory cytokines IL-1[alpha], IL-1[beta], TNF-[alpha], IL-6 and the chemokine MCP-1. A[beta](1-42) time- and dose-dependently induced the production and secretion of these inflammatory proteins in the human THP-1 monocyte cell line and in primary murine microglia, similar to what was observed for lipopolysaccharide (LPS) stimulated cells. IL-10 was found to suppress all A[beta] and LPS-induced inflammatory proteins measured (IL-1[alpha], IL-1[beta], IL-6, TNF-[alpha] and MCP-1) in both cell types with the exception of LPS-induced MCP-1 in THP-1 cells where no change was observed. In contrast to the inhibition observed for IL-10, both IL-4 and IL-13 enhanced MCP-1 secretion. IL-4 and IL-13 reduced IL-6 secretion, but effects on IL-1[alpha], IL-1[beta] or TNF-[alpha] were dependent on cell type and stimulus conditions. Additional experiments using RT-PCR showed that IL-4, IL-10 and IL-13 mRNA is found to be present in human brain tissue. These results show that IL-4, IL-10, and IL-13 differentially regulate microglial responses to A[beta] and may play a role in the inflammation pathology observed surrounding senile plaques.

van der Meulen, M. F. G., D. F. van Wichen, et al. (2002). "Evidence for heterogeneity of T cell expansion in polymyositis and inclusion body myositis." Journal of Neuroimmunology **133**(1-2): 198.

<http://www.sciencedirect.com/science/article/B6T03-473MDJN-8/2/62fb9bfc2d78098e014bddcf8d4a5a7f>

V[beta] usage of muscle-infiltrating T lymphocytes in polymyositis (PM) and sporadic inclusion body myositis (s-IBM) was correlated with clinical and histopathological features. Immunohistochemical analysis was combined with complementarity-determining region 3 (CDR3) length analysis in nine muscle biopsies of eight PM patients and six biopsies of five s-IBM patients. V[beta] usage was heterogeneous in seven patients. Four of these patients had definite PM with endomysial located T cell infiltrates, but T cells specifically surrounding and invading individual non-necrotic fibers were not found. In two s-IBM patients, V[beta] 2 usage was increased. In one of them, a repeat biopsy showed a heterogeneous V[beta] usage. We conclude that clonal expansion of muscle-infiltrating T cells could only be detected in part of the patients. Explanations may be that clonal expansion does not take place in all disease phases and that PM is a heterogeneous disease with respect to pathogenesis.

van Sorge, N. M., W. L. van der Pol, et al. "Severity of Guillain-Barre syndrome is associated with Fc[gamma] Receptor III polymorphisms." Journal of Neuroimmunology **In Press, Corrected Proof** <http://www.sciencedirect.com/science/article/B6T03-4FNDRX7-1/2/3be0aafac7e642d89d6a15eb0ea3822a>

Macrophages and ganglioside-specific IgG are involved in the pathogenesis of Guillain-Barre syndrome (GBS). Leukocyte IgG receptors (Fc[gamma]R) confer potent cellular effector functions to the specificity of IgG. The efficacy of IgG-mediated cellular inflammatory responses is determined by functional polymorphisms of three Fc[gamma]R subclasses (Fc[gamma]RIIa: H131/R131; Fc[gamma]RIIIa: V158/F158; Fc[gamma]RIIIb: NA1/NA2). Fc[gamma]R genotype distributions were determined in a Dutch, and British cohort of GBS patients and controls. In addition, a meta-analysis incorporating all previously published data, encompassing a total of 345 GBS patients and 714 healthy controls, was performed. Results suggest that Fc[gamma]RIII genotypes may represent mild disease-modifying factors in GBS.

Vandenbroeck, K., G. Martino, et al. (1997). "Occurrence and clinical relevance of an interleukin-4 gene polymorphism in patients with multiple sclerosis." Journal of Neuroimmunology **76**(1-2): 189.

<http://www.sciencedirect.com/science/article/B6T03-3PSB1XD-V/2/9689c82c112f673f33b3397b3975017e>

An epistatic gene interaction has been advocated to explain disease susceptibility in multiple sclerosis (MS). Cytokine genes are possible candidates due to the central role played by cytokines in the regulation of the immune-mediated pathogenetic process leading to central nervous system demyelination in these patients. Since interleukin (IL)-4 gene polymorphisms have been associated with immune-mediated diseases, we have analysed the relationship between a variable number of tandem repeat polymorphism of the IL-4 gene and clinical and physiological features of 256 sporadic MS patients and 146 healthy controls. Genotype frequencies were similar between the MS group and healthy controls. However, in MS patients a positive and significant correlation ($r=0.91$; $p<0.001$) was found between the carriage rate of the IL-4 B1 allele (from 0.21 to 0.36) and age of disease onset. No association was found between IL-4 alleles and disease progression, sex or ethnic background of the patients. Our results show that the IL-4 B1 allele is associated with late onset of MS and therefore might represent a modifier of age of onset rather than a susceptibility factor for patients with MS.

Yamabe, T., G. Dhir, et al. (1994). "Cytokine-gene expression in measles-infected adult human glial cells." Journal of Neuroimmunology **49**(1-2): 171.

<http://www.sciencedirect.com/science/article/B6T03-476HK1W-7D/2/bb5d439bf483a77e9c61e55e06575557>

The expression of interleukin (IL)-1[beta], IL-6 and tumor necrosis factor (TNF) [alpha] transcripts in cultured human glial cells was examined using reverse transcription followed by polymerase chain reaction (PCR) amplification and Southern blot quantitation. Microglial cultures derived from brain biopsy specimens from three different individuals expressed transcripts for the three cytokines under basal culture conditions. This expression was enhanced in response to measles virus (MV) infection (IL-1[beta], 2.2-8.8-fold; IL-6, 2.5-8.4-fold; TNF[alpha], 2.2-3.2-fold). Neither IL-1[beta] nor TNF[alpha] transcripts were detectable in undissociated brain tissue from two individuals, suggesting that the basal expression of these cytokines in culture may have been induced by tissue dissociation or by the culture conditions. Oligodendrocytes did not express cytokine transcripts under basal culture conditions, and IL-1[beta] and IL-6 but not TNF[alpha] transcripts could be induced by MV. Similarly, meningeal fibroblasts expressed IL-1[beta] and IL-6 but not TNF[alpha] in response to MV-infection, suggesting that the production of TNF[alpha] is more cell type-restricted than either IL-1[beta] or IL-6. The results indicate that adult human microglia can participate in the inflammatory response to MV infection in the CNS by producing cytokines that contribute to inflammation and demyelination. In addition, besides their role in myelination, oligodendrocytes can potentially influence immunoreactivity in the CNS by producing

IL-1[β] and IL-6.

Yamakuni, H., N. Kawaguchi, et al. (2002). "ATP induces leukemia inhibitory factor mRNA in cultured rat astrocytes." Journal of Neuroimmunology **129**(1-2): 43.

<http://www.sciencedirect.com/science/article/B6T03-468VMH4-2/2/8c2a1e213354cd968c18c909df8a7b36>

Leukemia inhibitory factor (LIF) is a cytokine involved in the survival and differentiation of the neural cells in the central and peripheral nervous systems. In the present study, we examined the effects of various neurotransmitter receptor agonists on LIF mRNA expression in cultured rat astrocytes, microglia and neurons to elucidate the cell types producing LIF and to clarify the neurotransmitter(s) regulating the mRNA expression. The results demonstrated that the expression of LIF mRNA was intensely induced by ATP in the cultured astrocytes. Experiments using ATP, UTP and related compounds showed the involvement of P2Y2 and P2Y4 purinoceptors in the expression induced by ATP.

Ye, S.-M. and R. W. Johnson (2001). "Regulation of interleukin-6 gene expression in brain of aged mice by nuclear factor [κ]B." Journal of Neuroimmunology **117**(1-2): 87.

<http://www.sciencedirect.com/science/article/B6T03-43B8BRH-B/2/90a66f194977ab7f9d558cd84f4e66f8>

Interleukin-6 (IL-6) is increased in brain of aged mice. The purpose of this study was to determine if binding of nuclear factor [κ]B (NF[κ]B) to the IL-6 promoter is responsible for the age-related increase in brain IL-6. In an initial study, the effect of age on IL-6 in brain was verified as IL-6 protein was increased in brain of aged mice compared to adult and juvenile mice. Competitive RT-PCR showed that IL-6 mRNA concentration was at least 4-fold higher in aged brain compared to adult brain. Next, binding of the transcription factor NF[κ]B to the IL-6 promoter in brains of 1-, 6-, and 24-month-old mice was determined. Electrophoretic mobility shift assay showed that NF[κ]B activity was increased in aged brain compared to adult and juvenile brain. Moreover, glial cells cultured from aged mice showed more NF[κ]B DNA-binding activity and more IL-6 mRNA and protein expression than glia from adults. However, incubating glia from aged mice in the presence of [κ]B decoy inhibited these effects of age. The same was observed in vivo as intracerebroventricular injection of [κ]B decoy in aged mice decreased NF[κ]B activity and IL-6 mRNA and protein in brain. These results show that the DNA-binding activity of NF[κ]B is increased in the brain of aged mice and that at least one consequence is increased expression of IL-6.

Zwijnenburg, P. J. G., T. van der Poll, et al. (2003). "Interleukin-18 gene-deficient mice show enhanced defense and reduced inflammation during pneumococcal meningitis." Journal of Neuroimmunology **138**(1-2): 31.

<http://www.sciencedirect.com/science/article/B6T03-487KRJ5-1/2/0f8e8c2a2389462364c7bb736263d52f>

To determine the role of endogenous interleukin-18 (IL-18) in pneumococcal meningitis, meningitis was induced in IL-18 gene-deficient (IL-18^{-/-}) and wild-type (WT) mice by intranasal inoculation of *Streptococcus pneumoniae* with hyaluronidase. Induction of meningitis resulted in

an upregulation of both pro- and mature IL-18 in brain tissue in WT mice. IL-18^{-/-} and WT mice were equally susceptible to develop meningitis after intranasal infection, yet IL-18^{-/-} mice showed a prolonged survival and a suppressed inflammatory response, as reflected by a less profound inflammatory infiltrate around the meninges and lower concentrations of cytokines and chemokines in brain tissue. These findings suggest that endogenous IL-18 contributes to a detrimental inflammatory response during pneumococcal meningitis and that elimination of IL-18 may improve the outcome of this disease.