

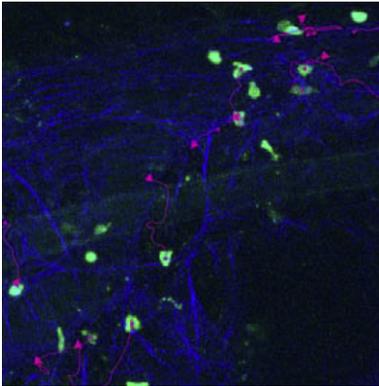
New Roles for Classical Immune Proteins

Traditionally, the functions of classical immune molecules were thought to be restricted to the immune system. However, accumulating evidence demonstrates that some immune proteins contribute to neuronal function. Building upon these observations, McConnell et al. provide direct evidence for a role of MHC I molecules in cerebellar synaptic plasticity and behavior. The authors found that the classical MHC I molecules H2-K^b and H2-D^b are selectively expressed in Purkinje cells and that loss of these proteins led to a lower LTD induction threshold at cerebellar synapses and enhanced motor learning in mice. A recent study by Atwal et al. further expands the role of immune molecules in the nervous system to include the modulation of axonal growth and the regulation of axon regeneration. Three myelin proteins (Nogo, MAG, and OMgP) inhibit axon regeneration. Deletion of their receptor NgR does not fully prevent their inhibitory effects, suggesting that another receptor may be involved. In search of this receptor, the authors discovered that PirB, an MHC I receptor previously implicated in synaptic plasticity, acts as a high-affinity receptor for Nogo, MAG, and OMgP. Blocking both PirB and NgR prevented nearly all of the inhibitory effects of these proteins on axon outgrowth, raising the exciting possibility that targeting the activity of both NgR and PirB in vivo might potentially stimulate axon regeneration.

McConnell et al. (2009). *PNAS* 106, 6784–6789.

Atwal et al. (2008). *Science* 322, 967–970.

T Cells on the Move in the Brain



Migration of T cells (green) along reticular structures (blue). Pink lines indicate migratory paths. Image from Wilson et al.

T lymphocyte entry into the central nervous system is rare except in cases of infection or autoimmunity. In other tissues, pre-existing cellular scaffolds are known to guide lymphocyte migration, but there is no evidence that such structures exist in the brain. To gain insight into the behavior of T lymphocytes in the brain, Wilson et al. monitored the cellular dynamics of CD8⁺ T lymphocytes in mice with toxoplasmic encephalitis, a model of infection-induced CNS inflammation. They discovered two distinct T cell populations: one with relatively constrained migration and one with surprisingly dynamic behavior. Movement of the dynamic T cells was linked to formation of a network of reticular structures that were induced in the brain in areas of inflammation and parasite replication to guide lymphocyte migration. Although a complete understanding of the source and composition of these networks awaits future work, targeting these structures may be an effective means of regulating T cell-mediated inflammation in the CNS.

Wilson et al. (2009). *Immunity* 30, 300–311.

Immune Link to Schizophrenia

It is thought that the immune system may play a role in psychiatric diseases such as depression and schizophrenia. Three recent genome-wide association studies of

schizophrenia highlight chromosomal regions of interest linked to the disease, including a region on chromosome 6 that contains a number of major histocompatibility complex genes. These findings confirm earlier linkage studies suggesting an involvement of this region in the disease and are consistent with the notion that immune proteins may contribute to schizophrenia. Given the presence of other nonimmune genes in this region, however, further research is required to confirm a role for MHC molecules in the disease.

Stefansson et al. (2009). *Nature* 460, 744–747.

The International Schizophrenia Consortium (2009). *Nature* 460, 748–752.

Shi et al. (2009). *Nature* 460, 753–757.

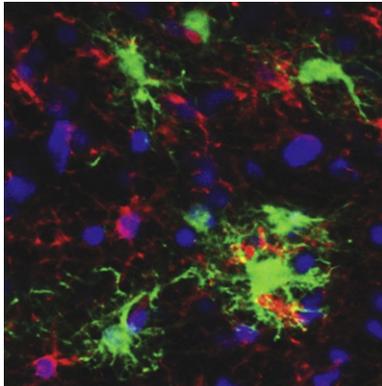
Crossing the Blood-Brain Barrier

The cells of the blood-brain barrier (BBB) form tight intercellular junctions that form a barrier between the body and the brain to prevent access of would-be invaders to the CNS. However, as with all defenses, the BBB has weaknesses and breaches do occur. The question is: how? Two recent studies offer new insights into the mechanisms of invasion through the BBB. Coureuil et al. found that *Neisseria meningitidis*, a pathogen responsible for cerebrospinal meningitis, gains entry to the CNS by adhering to brain endothelial cells and hijacking the intrinsic Par3/Par6/PKC ζ polarity complex. Binding of the bacteria recruited the complex to form ectopic junction-like domains, leading to sequestration of the polarity proteins and, ultimately, destabilization of the BBB junctions. In a separate study, Buonamici et al. investigated the mechanism underlying T cell infiltration during acute lymphoblastic leukemia (T-ALL) following activation of Notch1 signaling, known to be altered in most T-ALL patients. They identified the chemokine receptor CCR7 as an adhesion regulator upregulated by Notch1, and its interaction with the CCL19 ligand was essential for recruitment of leukemia cells to the CNS.

Coureuil et al. (2009). *Science* 325, 83–87.

Buonamici et al. (2009). *Nature* 459, 1000–1004.

Inflammation Mediates Dopaminergic Neuron Death



Activated microglia (Iba1, green), normal and pathological dopaminergic neurons (TH, red), and nuclei (DAPI, blue) in a section from the substantia nigra following Nurr1 knockdown and LPS administration. Image courtesy of C. Glass.

Previous research suggests that inflammation contributes to a number of neurodegenerative diseases, including Parkinson's disease. Nurr1, an orphan nuclear receptor that acts as a constitutively active transcription factor, is known to play a role in the generation and maintenance of dopaminergic neurons, and mutations in this protein have been linked to a familial form of Parkinson's disease. In a recent study, Saijo et al. found that Nurr1 protects dopaminergic neurons from inflammation-induced neurotoxicity by repressing the expression of inflammatory mediators that trigger cell death. Nurr1 recruitment of the CoREST corepressor complex resulted in transcriptional repression of proinflammatory target genes in microglia and astrocytes. Reduction of Nurr1 led to exaggerated inflammatory responses and dopaminergic neuronal death, supporting the concept that suppression of inflammatory signaling in the brain could be a useful therapeutic approach for treatment of Parkinson's disease.

Saijo et al. (2009). *Cell* 137, 47–59.

Immune System Contribution to Epilepsy

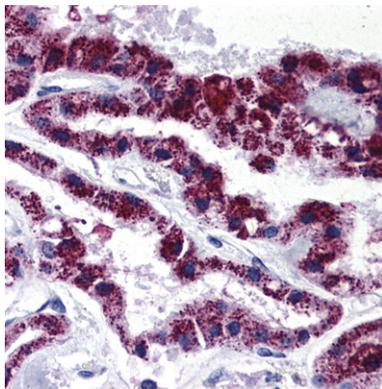
While the molecular mechanisms that contribute to the development of epilepsy are not fully understood, inflammation may play a role, in part by stimulating the breakdown of the blood-brain barrier (BBB). Two recent studies by Fabene et al. and Kim et al. build upon this idea. Kim et al. visualized the activity of CD8⁺ T cells during lymphocytic choriomeningitis virus infection, finding that T cell activation leads to the release of chemokines that subsequently trigger influx of neutrophils and monocytes into the brain, breakdown of the BBB, and development of seizures. In

a complementary study, Fabene et al. found that seizures induced elevated expression of vascular cell adhesion molecules that promote interaction between leukocytes and vascular cells. Blocking leukocyte-vascular interactions prevented BBB leakage and reduced seizures. Together, these findings demonstrate a link between leukocyte-vascular interactions, BBB leakage, and seizure generation. Given the uncertainty regarding the relevance of mouse models to human epilepsy and the potential complications of interfering with immune function, it remains to be seen whether preventing breakdown of the BBB might be a viable therapeutic approach for seizures.

Kim et al. (2009). *Nature* 457, 191–197.

Fabene et al. (2009). *Nature Medicine* 14, 1377–1383.

Two Waves of Lymphocyte Invasion in Autoimmune Disease



CCL20 (fuchsia) expression in choroid plexus epithelial cells from human brain tissue. Original image by A. Elston.

Interleukin 17-producing T cells (T_H-17 cells) are involved in the onset and maintenance of experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis. How and where these T cells gain entry to the CNS to initiate inflammation remains unclear. Recently, Reboldi et al. found evidence for two distinct waves of T cell migration into the CNS during EAE, with distinct molecular requirements and sites of lymphocyte entry. In mice lacking the chemokine receptor CCR6, T_H-17 cells did not migrate into the CNS, and the mice were resistant to developing EAE. Signaling via CCR6, its ligand CCL20 appeared to control the initial infiltration of autoreactive T_H-17 cells into the uninflamed CNS at the choroid plexus. This initial migration of T_H-17 cells triggered activation of parenchymal endothelial cells, leading to recruitment of a second wave of T_H-17 and T_H1 cells that gain entry to the CNS via the BBB in a CCR6-independent manner. This two-wave mode of migration may also be relevant to the development and progression of other autoimmune diseases.

Reboldi et al. (2009). *Nature Immunology* 10, 514–523.

Multiple Antigen Recognition in MS

The pathogenic changes underlying autoimmune disorders are thought to be initiated and driven by T cell populations that recognize and respond to autoantigens. In a recent study aimed at exploring the role of the autoantigen in spontaneous autoim-

munity, Krishnamoorthy et al. studied a transgenic mouse expressing a myelin oligodendrocyte glycoprotein (MOG)-specific T cell receptor. As predicted, the mice developed spontaneous experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, in the presence of MOG. Unexpectedly, the mice also developed EAE in the absence of MOG due to recognition of a non-MOG autoantigen corresponding to an epitope on neurofilament NF-M. The authors refer to the recognition of multiple independent autoantigens by a single T cell population as cumulative autoimmunity and suggest that these additive responses contribute to particularly vigorous immune reactions and may play a role in spontaneously developing autoimmune disorders in humans.

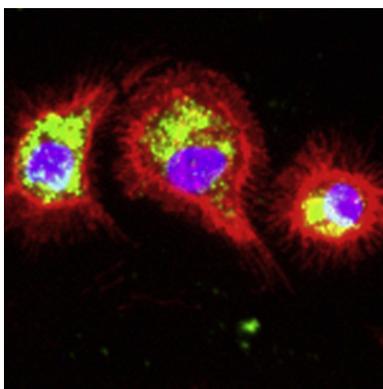
Krishnamoorthy et al. (2009). *Nature Medicine* 15, 626–632.

Maternal Influences on Cognitive Development

During pregnancy, the close interaction between mother and fetus means that maternal exposure to environmental toxins or infections and maternal reactions to these exposures may also be transmitted to the fetus, potentially leading to developmental defects. Such concerns are highlighted by studies linking maternal infection to schizophrenia and autism. In a recent study, Lee et al. examined fetal brain development and cognition in offspring from a maternal systemic lupus erythematosus (SLE) mouse model. Lupus is a chronic autoimmune disorder in which a large proportion of sufferers possess autoantibodies capable of binding DNA and, surprisingly, similar molecular motifs within NMDA receptors. The authors found that these maternal NMDAR-specific autoantibodies reached the developing neocortex of the fetus, inducing neuronal cell death, large-scale disorganization of neocortical structure, and cognitive impairment. While these data suggest an intriguing mechanism by which the maternal immune system could impact cognitive development, it remains to be shown where the attack on NMDARs might occur and what cellular mechanisms are involved.

Lee et al. (2009). *Nature Medicine* 15, 91–96.

Amyloid- β Clearance by the Immune System



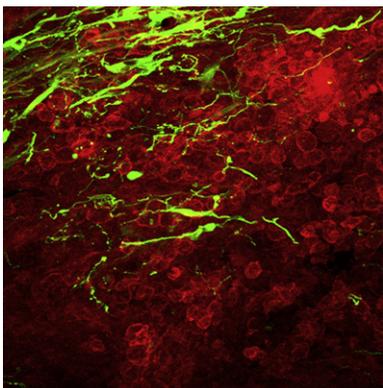
Macrophages (CD11b, red) readily internalize A β 42 (FAM, green). Nuclei are stained with DAPI (blue). Image courtesy of M. Esterman and L. Zhao.

Extracellular amyloid- β (A β) plaques are a cardinal symptom of Alzheimer's disease (AD), and enhancing A β clearance has been explored as a potential therapy. One promising avenue aims to harness the body's own immune system, and recent work from Zhao et al. supports this approach by demonstrating that macrophages can effectively degrade both soluble and insoluble A β in an ex vivo brain preparation. Efficacy of degradation depended on the particular isoform of ApoE expressed, with the E4 variant, which has been linked to AD, being the least efficient and the E2 variant, which reduces AD risk, being the most efficient. Interestingly, macrophage secretion of the MMP-9 extracellular protease known to degrade A β was also correlated with ApoE type, suggesting a possible cellular substrate for genetically determined AD risk factors. In a separate study, Britschgi et al. find that intrinsic antibodies against A β derived from either AD patients or healthy subjects can confer protection on cultured neurons exposed to toxic A β . The antibodies are most reactive to oligomeric and posttranslationally modified toxic forms of A β and, surprisingly, to other peptides associated with autosomal dementia (mutant A β , Abri, and ADan). Interestingly, titers of these antibodies decreased with age and disease progression, perhaps highlighting a point of increased susceptibility in the elderly.

Zhao et al. (2009). *J. Neurosci.* 29, 3603–3612.
Britschgi et al. (2009). *PNAS* 106, 12145–12150.

The Two Faces of Macrophages in Spinal Cord Injury

Following the initial insult of spinal cord injury, activated resident microglia and infiltrating macrophages stage an inflammatory response with reported effects that are paradoxically both regenerative and detrimental. Two recent studies investigated different aspects of this contradiction. Gensel et al. reported that microinjection of zymosan (a robust activator of macrophages) into the spinal cord generates a neurotrophic gradient that promotes axonal growth toward the injection site through an apparent "tunnel" of reactive microglia embedded in the region of inflammation. Increasing proximity to the zymosan focus, however, results in abortive growth, phagocytic uptake of degenerated axonal remnants, and cell death, events likely dependent upon infiltrating macrophages, as selective depletion of circulating monocytes reduced zymosan-associated pathology. Although the resident microglia and infiltrating macrophage populations have been considered functionally identical—that is proinflammatory and destructive—Shechter et al. recently suggested they could have distinct functions after spinal cord injury depending on their origin. By specifically labeling and manipulating the monocyte-derived macrophage population, the authors found that augmentation of this population enhanced motor recovery while elimination resulted in increased lesion size. Interestingly, these infiltrating macrophages seem to regulate activation of the proinflammatory resident microglia through signaling by the anti-inflammatory cytokine IL-10. While these studies represent differing experimental paradigms, they underscore the functional heterogeneity and potential benefits of macrophages and highlight the challenges to dissecting the immune response following spinal cord injury.



Macrophages (OX42, red) activated near the soma of transplanted neurons (EGFP, green) lose their ability to promote axon growth and begin to atrophy. Image courtesy of P. Popovich.

Gensel et al. (2009). *J. Neurosci.* 29, 3956–3968.
Shechter et al. (2009). *PLoS Medicine* 6, e1000113.

Cytokine Signaling and Neuropathic Pain

After nerve damage or other such insults, chronic sensations of pain and pain-hypersensitivity to normally innocuous stimuli often ensue. While the exact origin of this neuropathic pain is uncertain, and perhaps there is no single cause, the general consensus is that interactions between neurons and the resident microglia of the nervous system play a pivotal role, in part through cytokine signaling. Tsuda et al. recently found that microglial activation and subsequent neuropathic pain following nerve injury was due to stimulation of cytokine IFN- γ receptors on microglia. The Lyn tyrosine kinase and the P2X₄ receptor appeared to act as downstream mediators in the response. Signaling through the chemokine receptor CCR2 and its ligand, CCL2, has also been implicated in neuropathic pain, and in a separate study, Jung et al. discovered that in a demyelination model of neuropathic pain, receptor activation occurs primarily in the periphery, including at the injury site and the DRG, explaining the rapid action of peripherally administered CCR2 antagonists. These studies add to the evidence implicating cytokine signaling in neuropathic pain and expand our toehold for therapeutic intervention.

Tsuda et al. (2009). PNAS 106, 8032–8037.

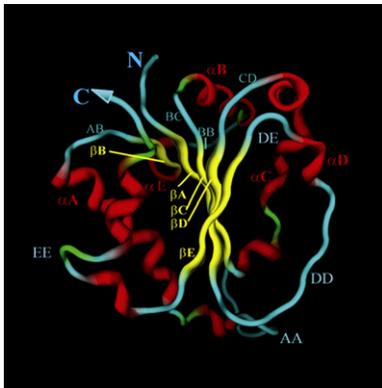
Jung et al. (2009). J. Neurosci. 29, 8051–8062.

The Immunological Synapse Links to Narcolepsy

Hallmarks of narcolepsy include sleep/wake dysfunction and cataplexy, a sudden loss of muscle tone, which have been linked to loss of hypocretin-secreting, hypothalamic neurons that regulate wakefulness. How these neurons are lost remains an open question, although increasing evidence supports an autoimmune etiology in some cases due to a close genetic association between the disorder and the HLA locus, a key component of the immunological synapse. Susceptibility factors beyond the HLA genotype are also thought to play a role, and Hallmayer et al. recently identified a familiar partner. In a genome-wide association study of hundreds of subjects across three ethnic populations, they uncovered evidence that variations in the TRA α -locus are linked to the disorder. As the TRA α -locus codes for the α subunit in a T cell receptor, the HLA partner at the immunological synapse, the study provides further support for an autoimmune origin of narcolepsy.

Hallmayer et al. (2009). Nature Genetics 41, 708–711.

Brain-Specific IL-1 Signaling



Computational model of AcPb TIR domain. β sheets are indicated in yellow, α helices in red, and loops in blue. Image from Smith et al.

Interleukin-1 (IL-1) has a number of physiological roles, and in the CNS, IL-1 signaling can exacerbate neurodegeneration in response to traumatic brain injury, seizure, or acute ischemic insult. The specific mechanisms by which IL-1 acts in the nervous system are not fully understood. By identifying an isoform of the IL-1 receptor accessory protein (termed AcPb) that is expressed exclusively in the CNS, Smith et al. recently provided evidence for a neuronal-specific IL-1 signaling pathway that modulates local inflammatory responses. While AcPb interacts with IL-1 and the IL-1R, AcPb appears to act via noncanonical IL-1 signaling. Although they have intact peripheral immune responses, animals lacking AcPb were more vulnerable to local inflammatory challenge in the CNS and displayed enhanced neuronal degeneration, suggesting that AcPb may promote neuronal survival during neuroinflammation.

Smith et al. (2009). Immunity 30, 817–831.