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Review

Immune Proteins in Brain Development and Synaptic Plasticity

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Many proteins first identified in the immune system are also expressed in the developing and adult nervous system. Unexpectedly, recent studies reveal that a number of these proteins, in addition to their immunological roles, are essential for the establishment, function, and modification of synaptic connections. These include proinflammatory cytokines (e.g., TNFα, IL-6), proteins of the innate immune system (e.g., complement C1q and C3, pentraxins, Dscam), members of the major histocompatibility complex class I (MHCI) family, and MHCI-binding immunoreceptors and their components (e.g., PIRB, Ly49, DAP12, CD3ζ). Understanding how these proteins function in neurons will clarify the molecular basis of fundamental events in brain development and plasticity and may add a new dimension to our understanding of neural-immune interactions in health and disease.

Introduction

The "one gene-one protein" model has long been discarded in the face of evidence that numerous cellular processes, including differential splicing and posttranslational modification, can allow a single gene to encode multiple distinct protein products. These modifications vastly increase the number of protein functions that can be encoded by a limited DNA genome. More recently, it has become apparent that even identical proteins can have more than one role in different tissues, cell types, or subcellular domains (Cirulli and Yebra, 2007; Radisky et al., 2009; Wegrzyn et al., 2009). In this way, one protein can control multiple, apparently unrelated phenotypic features, a feature termed pleiotropy. Pleiotropy is an emerging concept in proteomics and may provide an unexpected mechanism for the coordination of disparate cellular functions (Radisky et al., 2009).

A large number of proteins that were first discovered in the immune system have since been detected in the healthy, uninfected nervous system, raising the possibility that these proteins have pleiotropic functions in neurons (Boulanger et al., 2001). Indeed, accumulating evidence indicates that several immune proteins have novel, nonimmune functions in the brain. These include proinflammatory cytokines (e.g., TNFα, IL-6), proteins of the innate immune system (e.g., complement C1q and C3), proteins of the adaptive immune system (e.g., members of the major histocompatibility complex class I [MHCI] family), and MHCI-binding immunoreceptors and their components (e.g., PIRB, Ly49, DAP12, CD3ζ). Similarly, a smaller number of proteins that were first discovered in the nervous system have since been found to have immunological functions (e.g., Dscam, semaphorins). Rather than provide an exhaustive overview of proteins that have both immune and neuronal functions, this review focuses on recent evidence that specific immune proteins are required for normal brain development and synaptic plasticity. In the past I have described some of these as immune proteins "moonlighting" in the brain (Boulanger et al., 2001). However, "moonlighting" implies that the brain is not the site of their "day job." Referring to them as immune proteins, while necessary for clarity, may create a similar conceptual barrier. The current research suggests that these terms may need to be revised to reflect evidence that immune and neural roles of these proteins are essential to different cellular and systems functions and may in fact be equally significant.

Expression of Immune Proteins in the Nervous System

Immune responses in the brain are blunted and often have slower kinetics (reviewed in Carson et al., 2006), giving rise to the idea that the central nervous system is "immune privileged." Although the brain's relative isolation from the immune system was originally thought to stem, in part, from a lack of key immune proteins in neurons, numerous studies have since revealed that many of these immune proteins are expressed in both neuronal and nonneuronal cell types in the central and peripheral nervous system. However, the expression of these proteins in the nervous system is often spatially and temporally regulated in a manner that is more consistent with nonimmunological roles.

One striking example is proteins of the MHCI, key players in adaptive immunity. The MHCI is a large family of proteins that are expressed on the surface of most nucleated cells in the body. Cell-surface MHCI presents peptides derived from intracellular proteins for immune surveillance, permitting immune recognition of foreign ("nonself") antigens generated by transplanted, infected, and cancerous tissues. MHCI mRNA (Figure 1A) and protein (Figures 3A and 3C) are expressed in subsets of neurons and are spatially and developmentally regulated. In the mammalian brain, MHCI expression is particularly high in regions undergoing activity-dependent plasticity, including the developing visual system and adult hippocampus and cerebellum (Corriveau et al., 1998; Huh et al., 2000; Letellier et al., 2008; McConnell et al., 2009). Furthermore, different members of the MHCI gene family are expressed in the brain

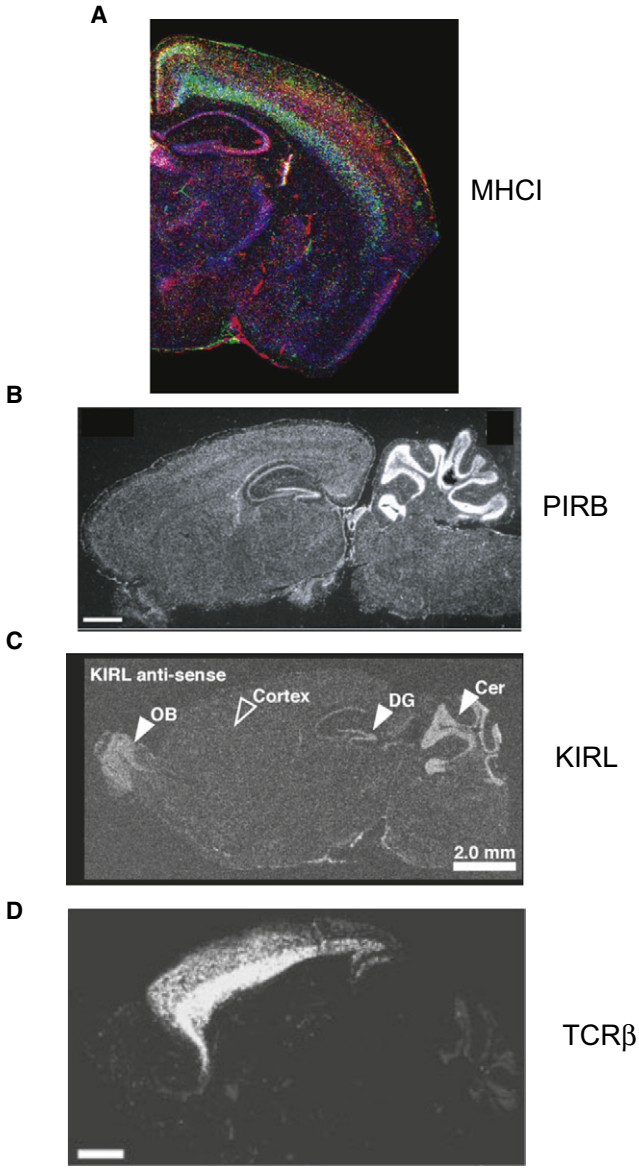


Figure 1. Expression of mRNA Encoding MHCI and Immunoreceptors for MHCI in Healthy Adult Rodent Brain

S^{35} labeling using antisense probes against specific MHCI mRNAs or mRNAs encoding particular MHCI immunoreceptors in sections of adult mouse brain (in B–D, light areas indicate silver grains).

(A) Pseudocolored in situ hybridization showing mRNA encoding three different MHCI genes in three overlayed serial coronal sections of adult mouse brain. Red, H2-D; blue, T22; green, Qa-1. Reprinted with permission from Boulanger et al. (2001).

(B) Paired immunoglobulin-like receptor B (PIRB) mRNA detected in a sagittal section. Scale, 1 mm. Reprinted with permission from Syken et al. (2006), copyright 2006 National Academy of Sciences, USA.

(C) Killer cell immunoglobulin-like receptor-like gene (KIRL) mRNA detected in a sagittal section. Olfactory bulb (OB), hippocampal dentate gyrus (DG), and cerebellum (CB). Modified with permission from Bryceson et al. (2005).

(D) Unrecombined T cell receptor beta subunit (TCRβ) mRNA detected in a sagittal section. Reprinted with permission from Syken and Shatz (2003).

in distinct, characteristic patterns (Huh et al., 2000; Lidman et al., 1999) (Figure 1A). MHCI protein is enriched in synaptic fractions (Huh et al., 2000), and in hippocampal neurons in vitro, MHCI protein is detected in dendrites, where it colocalizes with the postsynaptic marker PSD-95 (Goddard et al., 2007) (Figure 3A).

Immunoreceptors for MHCI have also been detected in the adult mammalian brain (Figures 1B–1D), including the immunoglobulin-like receptor B (PIRB) (Syken et al., 2006), the killer cell immunoglobulin-like receptor-like (KIRL) receptor (Bryceson et al., 2005), and unrecombined T cell receptor beta subunit (TCRβ) (Syken and Shatz, 2003). Recombination-activating gene 1 (RAG1), which is required for somatic recombination of TCR genes in lymphocytes, is widely expressed in embryonic and postnatal neurons and is coexpressed with RAG2 in olfactory sensory neurons (OSNs) (Chun et al., 1991; Jessen et al., 2001). It is as yet unknown if more of the dozens of known MHCI immunoreceptors are expressed in the brain, but it is notable that MHCI is much more widely expressed than any of the immunoreceptors examined to date (Figure 1 shows expression of just three of the more than 50 MHCI mRNAs expressed in mouse).

Proteins of the innate immune system are also expressed in neurons in patterns consistent with nonimmunological roles. C1q and C3, components of the classical complement cascade, are expressed in a punctuate pattern in the developing (but not adult) brain, and a subset of C1q protein colocalizes with synaptic markers in the early postnatal retina. Like MHCI, expression of C1q in the developing visual system peaks during the period of activity-dependent remodeling (Stevens et al., 2007). Interleukin- (IL-) 6 and IL-6 receptor mRNAs are also coexpressed in neurons and are developmentally regulated in rat brain, with highest levels of both detected in adult hippocampus (Gadient and Otten, 1994).

Neurons themselves express immune proteins, but they can also be affected by secreted and cell-surface immune proteins produced by infiltrating immune cells (e.g., lymphocytes), microglia (the resident CNS macrophage), and other resident neuroglia (e.g., astrocytes, oligodendrocytes). Indeed, although neurons can produce tumor necrosis factor- (TNF)- α, glia are the source of the endogenous TNFα that affects synaptic scaling (see below): wild-type (WT), TNFα-expressing neurons plated on WT glia show robust synaptic scaling in response to activity blockade with tetrodotoxin (TTX), while WT neurons plated on glia purified from TNFα knockout mice do not (Stellwagen and Malenka, 2006). Similarly, although the immunoreceptor component DAP-12 is detected in microglia, but not neurons, genetic ablation of DAP-12 modifies neuronal glutamate receptor expression and synaptic plasticity (Roumier et al., 2004). Neurons can also be induced to express immune proteins as the result of interactions with glia. For example, retinal ganglion cells (RGCs) upregulate proteins of the complement cascade in response to astrocytes (Stevens et al., 2007).

Immune Proteins in Normal Brain Development

The expression of immune proteins in the early postnatal brain suggests that these proteins may be involved in developmental processes in the central nervous system. Numerous immune proteins are expressed in neuronal stem cells, suggesting that

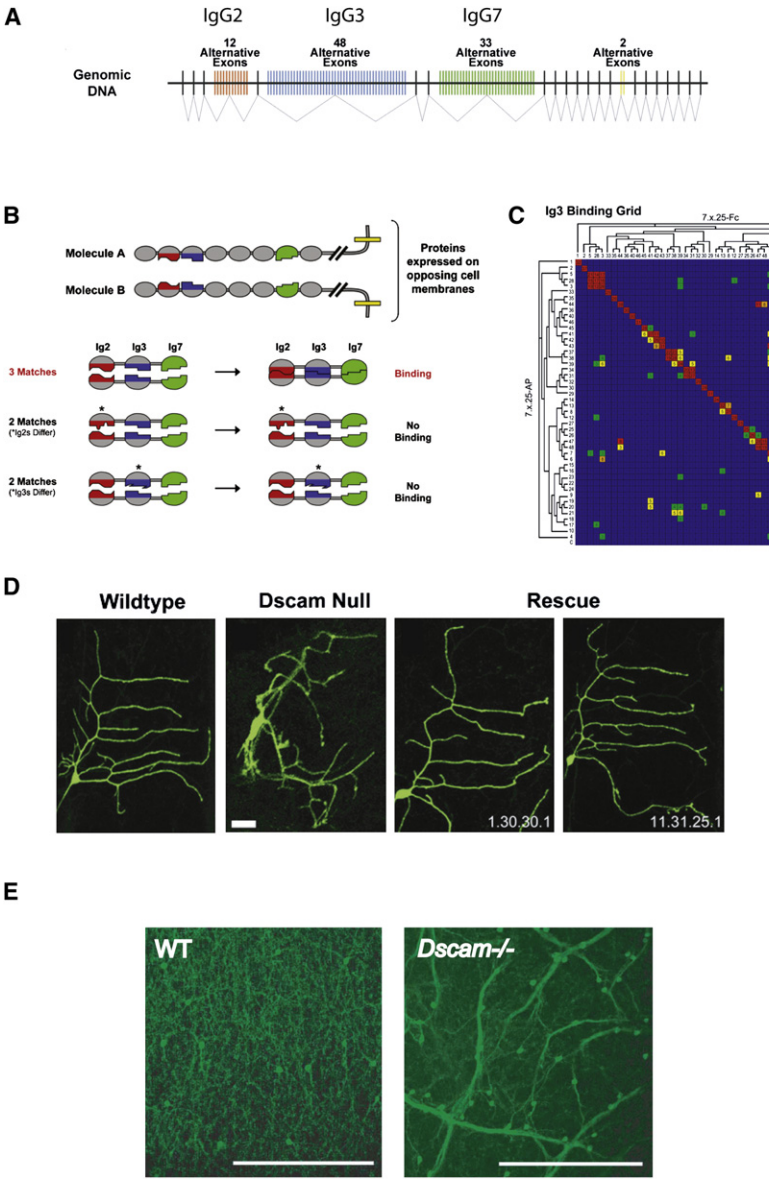


Figure 2. Dscam Encodes Diverse Proteins that Display Homophilic Binding and Mediate Normal Self-Avoidance between Sister Neurites or between Neurites of a Single Cell Type

(A) Constant and variable regions in the Dscam gene in *Drosophila*. Differential splicing of exons 4, 6, 9, and 17 can produce up to 38,016 distinct Dscam mRNA isoforms. Modified with permission from Wojtowicz et al. (2004).

(B) Schematic illustration of the molecular basis of Dscam homophilic interactions. In most cases, matching at all three variable domains is required for binding. Modified with permission from Sawaya et al. (2008).

(C) Homophilic binding between Dscam isoforms that vary only at the IgG3 domain. Ig3 domains are arranged according to their sequence relatedness, as shown in the dendrograms, and binding is indicated as fold over background by a color scale and the number in each block. Red diagonal line indicates that binding is preferentially homophilic. Reprinted with permission from Wojtowicz et al. (2007).

(D) Loss of Dscam in single *Drosophila* neurons causes extensive dendritic self-crossing of sister branches of the same cell, resulting in tangled and disorganized dendritic fields in dendritic arborization (da) class I neurons. This phenotype is rescued by expression of either of two specific Dscam isoforms (1.30.30.1 or 11.31.25.1) in single neurons in an otherwise Dscam null background. Scale, 10 μm. Modified with permission from Hughes et al. (2007).

(E) Whole adult (6–8 week) wild-type (WT, left) or *Dscam*$^{-/-}$ (right) mouse retinas stained with anti-TH. Dopaminergic amacrine cell neurites arborize evenly, while in mice lacking DSCAM, amacrine cell neurites are bundled in thick fascicles. Modified with permission from Fuerst et al. (2008).

innate immune response, possibly through their ability to bind directly to bacteria; soluble Dscam is secreted into the hemolymph in flies, and loss of Dscam specifically in hemocytes impairs phagocytosis of bacteria (Watson et al., 2005).

In addition to its expression in immune cells, Dscam and DSCAM are also expressed in the invertebrate and vertebrate nervous system, respectively. In flies, a single neuron can express more than one Dscam isoform (Neves et al., 2004; Zhan et al., 2004), and although the mechanisms that drive alternative splicing remain unclear, it appears that the process is largely stochastic but can be biased by cell type (Neves et al., 2004). The Dscams examined to date participate in homophilic interactions between their highly diverse extracellular domains (Wojtowicz et al., 2004, 2007) (Figures 2A–2C). Remarkably, both the presence and absence of homophilic Dscam interactions may be used to specify neuronal wiring. In *Drosophila*, homophilic binding between Dscams triggers repulsion between sister dendrites, leading to dendritic self-avoidance (Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007) (Figure 2D), and triggers repulsion between sister axons, leading to axon tiling (Millard et al., 2007). Although heterophilic binding between Dscam

immune signaling could influence neurogenesis (see Carpentier and Palmer, 2009 [this issue of *Neuron*]). In addition, immune proteins have been implicated in later neurodevelopmental events, including multiple steps in the establishment and maturation of synaptic connections.

Neurite Guidance and Synapse Formation

The high molecular diversity of some immune protein families makes them attractive candidates for mediating specific intercellular recognition events during the establishment of precise neuronal connectivity. One such family of proteins is the *Drosophila* Dscams, and their vertebrate homologs, the DSCAMs (Down Syndrome Cell Adhesion Molecules). In *Drosophila*, alternative splicing of the immunoglobulin (Ig) domains of Dscam can permit the generation of up to 38,016 Dscam isoforms (Schmucker et al., 2000) (Figure 2A). Although Dscam was first identified in neurons, in invertebrates, Dscams are thought to function in the

isoforms occurs very rarely, if at all (Wojtowicz et al., 2004), the absence of homophilic binding may be an important cue for developing circuits. This is perhaps analogous to "missing self" recognition in the immune system, in which cells that have downregulated cell-surface MHCI in an attempt to evade immune surveillance fail to bind to MHCI receptors on the surface of NK cells, triggering NK cell-mediated lysis. Support for a neuronal role for a lack of homophilic Dscam interactions comes from a series of elegant experiments in which the diversity of the Dscams was genetically reduced, either by generating alleles that reduce the maximum possible diversity to 22,176 isoforms (Chen et al., 2006), by using homologous recombination to reduce the repertoire of extracellular domains to a single isoform (Hattori et al., 2007), or by reintroducing single Dscam isoforms into individual Dscam null mutant neurons on an otherwise wild-type background (Chen et al., 2006). In all three cases, the likelihood of ectopic homophilic interactions was increased, and in all three cases connectivity defects were observed, consistent with the possibility that Dscam-mediated "missing self" recognition is important for proper neuronal wiring in *Drosophila*. These techniques all share the caveat that the eliminated isoforms may have included one or a pool of isoforms that are essential for connectivity and that this, rather than the overall reduction of Dscam molecular diversity, gave rise to the defects. Indeed, Chen et al. (2006) argue that changes in the projections of neurons expressing a single Dscam isoform support the possibility that neurons use particular isoforms for specific aspects of neuronal branching patterns. However, while much evidence indicates that homophilic Dscam-mediated self-recognition interactions are important for self-avoidance, instructive functional differences between individual isoforms have not yet been demonstrated.

Dscams and/or DSCAMs have also been implicated in commissural axon guidance (Ly et al., 2008), laminar specificity of axonal arborization in the retina (Yamagata and Sanes, 2008), and targeting of olfactory neuron axons to the correct glomeruli (Hummel et al., 2003; Zhan et al., 2004) (reviewed in Schmucker and Chen, 2009). Despite the fact that the enormous isoform diversity of Dscam appears to be unique to arthropods, recent genetic analyses of DSCAM in the vertebrate brain reveal an intriguing conservation of molecular function in specifying neural wiring. In the mouse, as in the fly, DSCAM is required for prevention of neurite fasciculation (Figure 2E) as well as for normal mosaic spacing of cell bodies (Fuerst et al., 2008), forms of self-avoidance within a single cell type. It is as yet unclear how DSCAM affects vertebrate wiring in the absence of massive isoform diversity, but in some systems it may function as a repulsive cue (Fuerst et al., 2008) or as a kind of molecular "non-stick coating" (R. Burgess, personal communication), in either case preventing synapses from forming between DSCAM-expressing cells. Conversely, separate studies on the role of DSCAM in retinal lamination in the mouse (Yamagata and Sanes, 2008) suggest that DSCAMs can act as attractive or adhesive cues. These differences in the way DSCAMs behave in a given cell type or species suggest that DSCAMs, like many guidance molecules, can function as either attractants or repellents, depending on the cellular context (Yamagata and Sanes, 2008).

A smaller family of immune-related proteins, the neuronal pentraxins, have been implicated in the regulation of synapse number, most likely by controlling synapse formation. In the humoral immune response, pentraxins are secreted proteins that mark cells for phagocytosis and degradation. Two neuronal pentraxins have been identified to date: neuronal pentraxin 1, or NP1, which was identified based on its ability to bind to the snake venom toxin taipoxin (Schlimgen et al., 1995), and neuronal activity-regulated pentraxin, or Narp (also known as NP2), which was identified as an immediate-early gene that is induced by physiological levels of electrical activity (Tsui et al., 1996). While they are not identical to other pentraxins, the C-terminal domains of the neuronal pentraxins NP1 and Narp are homologous to the classic innate immune system pentraxins. Neuronal pentraxins are detected at excitatory synapses and regulate excitatory synapse number. Narp overexpression increases the number of excitatory synapses (O'Brien et al., 1999; Xu et al., 2003), while dominant-negative Narp decreases the number of excitatory synapses (O'Brien et al., 2002). Both neuronal pentraxins are secreted and form large, covalently linked heteromultimers with themselves and the recently identified transmembrane neuronal pentraxin receptor (NPR), and formation of this complex synergistically enhances their synapse-promoting function (Xu et al., 2003). The NPR may also serve a dominant-negative function when it is cleaved following mGluR1/5 activation, releasing the pentraxin domain. This causes the pentraxin domain to accumulate in endosomes along with AMPARs. This simultaneous relocalization of AMPARs and the NPR pentraxin domain from the cell surface to an intracellular compartment is required for the induction of mGluR1/5-dependent LTD (Cho et al., 2008), suggesting that neuronal pentraxin signaling may be involved in the weakening as well as the formation of synapses.

It is likely that neuronal pentraxins regulate synapse number by promoting excitatory synapse formation, since neuronal pentraxins are sufficient to induce clustering of AMPA receptors in both neuronal and nonneuronal cells (O'Brien et al., 1999; Xu et al., 2003), and dominant-negative Narp decreases the ability of axons to induce GluR1 clusters on contacted dendrites (O'Brien et al., 2002). However, pentraxins are also required for normal developmental synapse remodeling (see below), a process that requires both the formation of appropriate synapses and the removal of inappropriate synapses. In light of the finding that the neuronal pentraxin receptor is involved in the functional weakening of synapses (Cho et al., 2008), it will be of interest to determine if neuronal pentraxins regulate synapse number through changes in synapse elimination as well as synapse formation.

Developmental Synapse Refinement

Proteins of both the innate and adaptive immune system have been identified that are essential for activity-dependent synapse refinement in the developing brain (Table 1), a key step in establishing the precision of adult circuits. MHCI was first implicated in mammalian brain development when it was identified in an unbiased screen for genes involved in the activity-dependent remodeling of retinal ganglion cell (RGC) axons projecting to the developing lateral geniculate nucleus (LGN) (Corriveau et al., 1998). These retinogeniculate projections are initially exuberant, with inputs from the two eyes overlapping in the LGN at birth. During the first two postnatal weeks, these retinal

Table 1. Activity-Dependent Plasticity in the Developing and Adult Visual System of Mice with Altered Expression of Specific Immune Proteins

Activity-Dependent Synapse Elimination		
Developmental Retinogeniculate Remodeling		
Manipulation	Phenotype	Reference
MHCI-deficient ($\beta 2\ m^{-/-}TAP^{-/-}$)	enlarged ipsilateral projection (P30)	Huh et al., 2000
$CD3\zeta^{-/-}$	enlarged ipsilateral projection (P30)	Huh et al., 2000
$C1q^{-/-}$	increased ipsilateral/contralateral overlap (P30)	Stevens et al., 2007
$C3^{-/-}$	increased ipsilateral/contralateral overlap (P30)	Stevens et al., 2007
$C1q^{-/-}$	more low-amplitude functional inputs (P30)	Stevens et al., 2007
PIRB-TM	ipsilateral projection normal (P30)	Syken et al., 2006
Visual Cortical Plasticity *during* Critical Period (Deprivation-Induced)		
$TNF\alpha^{-/-}$	no increase in strength of response to open eye (P26–P30); decrease in deprived eye normal	Kaneko et al., 2008
PIRB-TM	enhanced expansion of cortical representation of open eye (P19–P25)	Syken et al., 2006
$NgR^{-/-}$	normal expansion of cortical representation of open eye (P24)	McGee et al., 2005
Visual Cortical Plasticity *after* Critical Period (Deprivation-Induced)		
$TNF\alpha^{-/-}$	normal critical period for MD-induced plasticity (P33)	Kaneko et al., 2008
PIRB-TM	extended critical period for MD-induced plasticity (P22–P31, P31–P36, P100–P110)	Syken et al., 2006
$NgR^{-/-}$	extended critical period for MD-induced plasticity (P45, P120)	McGee et al., 2005
Nogo A$^{-/-}$	extended critical period for MD-induced plasticity (P45, P120)	McGee et al., 2005

Retinogeniculate remodeling is impaired in MHCI-deficient animals, CD3ζ-deficient animals, and complement C1q- or C3-deficient animals, but not PIRB-deficient animals. Deprivation-induced visual cortical plasticity is enhanced *during* the critical period in PIRB-deficient animals, but not NgR-KO animals; the critical period is *extended* in mice lacking either PIRB, NgR, or NogoA, but not in mice lacking TNFα.

inputs undergo activity-dependent remodeling to segregate into eye-specific regions, establishing the mature pattern of connectivity necessary for binocular vision. MHCI mRNA is highly expressed in the developing cat and mouse LGN during retinogeniculate remodeling (Corriveau et al., 1998; Huh et al., 2000), and furthermore, developmental refinement of retinal axons is impaired in MHCI-deficient ($\beta 2\ m^{-/-}TAP^{-/-}$) mice, such that inappropriate projections that would normally be eliminated instead persist (Huh et al., 2000). Thus, in the developing brain, MHCI is required for the normal developmental elimination of inappropriate projections, perhaps analogous to its role in the immune system, where it permits recognition and removal of unwanted cells expressing "nonself" antigens. Although MHCI genes are expressed in the adult cerebellum (Figure 3C), subsequent studies have found that MHCI is not required for normal activity-dependent remodeling of climbing fiber-Purkinje cell projections (Letellier et al., 2008; McConnell et al., 2009). This may reflect mechanistic differences in remodeling in these brain regions or may indicate that the MHCI genes found in these two brain regions are functionally specialized in terms of their role in remodeling.

Proteins of the classical complement cascade (encoded in the MHC class III region) are also required for retinogeniculate remodeling and seem to act in the final stages of this process (Stevens et al., 2007). In the immune response, complement proteins bind to bacteria and other foreign material that has been marked for phagocytosis and clearance. C1q, the initiating protein in the classical complement cascade, is produced by astrocytes as well as by astrocyte-stimulated neurons. C1q is expressed widely in the postnatal brain, and C1q-deficient (as well as C3-deficient) mice show an impairment in retinogeniculate synapse elimination. Interestingly, the impairment is of a similar magnitude (Stevens et al., 2007) to that seen in MHCI-deficient mice (Huh et al., 2000). In C1q-deficient animals, each LGN neuron receives a higher number of functional inputs than in WT, as measured electrophysiologically, confirming the anatomical failure of synapse elimination. Most LGN neurons receive one strong input and multiple weak inputs in C1q-deficient animals, versus the single strong input seen in WT animals at this age (Stevens et al., 2007). This suggests that loss of C1q prevents structural, but not functional, weakening of retinal inputs during development. Thus, C1q may be involved in eliminating synapses that have already lost the competition; if so, it is permissive but not instructive for synapse elimination, similar to its role in the immune system.

Neuronal pentraxins have also been implicated in developmental synapse refinement, since in mice lacking both NP1 and Narp, retinal ganglion cell axons fail to show normal eye-specific segregation at early ages (P10) (Bjartmar et al., 2006). It is possible that neuronal pentraxins mark synapses for degradation, in a manner analogous to their function in the innate immune system. Of note, some nonneuronal pentraxins can bind directly to C1q, resulting in either inhibition or activation of the classical complement cascade, depending on the context (Nauta et al., 2003). If neuronal pentraxins interact with C1q, which remains to be determined, the lack of remodeling in both C1q- and neuronal pentraxin-deficient mice could potentially reflect a failure of a late stage in remodeling in which

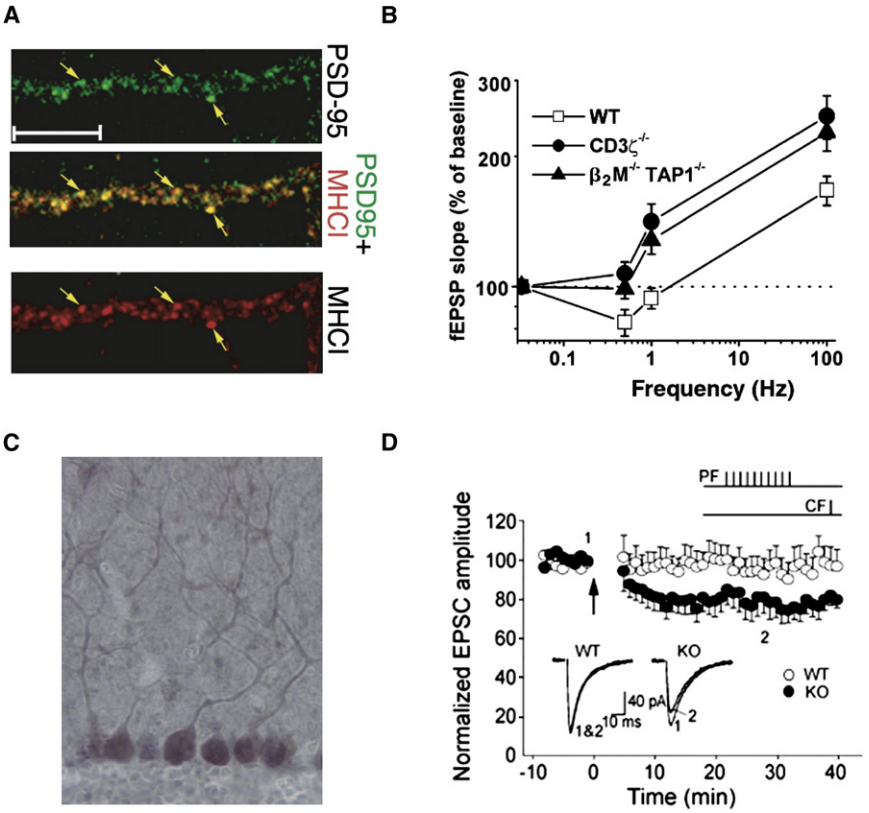


Figure 3. Activity-Dependent Synaptic Plasticity in Two Regions of the Adult Mammalian CNS Requires Normal Expression of MHCI

(A) MHCI protein (red) is expressed in dendrites and colocalizes with PSD-95 (green) in hippocampal neurons in vitro. Scale bar, 10 μm. Modified with permission from Goddard et al. (2007), copyright 2007 National Academy of Sciences, USA. MHCI mRNA is also seen in CA1 pyramidal cells (Figure 1A).

(B) Hippocampal frequency-dependent synaptic plasticity is shifted in favor of potentiation in MHCI-deficient (β2 $m^{-/-}$TAP1$^{-/-}$) or CD3ζ-deficient mouse hippocampal slices. Reprinted with permission from Huh et al. (2000).

(C) MHCI protein is expressed in Purkinje cell dendrites and throughout the molecular layer. Scale bar, 20 μm.

(D) The threshold for pairing-induced LTD at parallel fiber-Purkinje cell synapses is reduced in MHCI-deficient mice lacking the classical MHCI genes K^b and D^b ("KO").

(C) and (D) modified with permission from McConnell et al. (2009).

the remains of the "losing" axons are degraded and phagocytosed through a single, immune-like mechanism. However, there are significant differences in both the timing and magnitude of the remodeling deficit in C1q- versus neuronal pentraxin-deficient mice: for example, loss of neuronal pentraxin causes a larger-magnitude deficit in eye-specific segregation that resolves by P30, while loss of C1q causes a smaller deficit that is attenuated but still measurable at P30 (Bjartmar et al., 2006; Stevens et al., 2007). In the future, it will be important to determine if neuronal pentraxins and C1q contribute to synapse remodeling via partially or fully mechanistically distinct processes.

Glutamatergic transmission was absent in cultured retinal ganglion cells from neuronal pentraxin mutants, while ganglion cell activity was elevated in intact retinas (Bjartmar et al., 2006), suggesting that these proteins may affect refinement indirectly, by modifying the activity that drives it. In contrast, both MHCI-deficient and C1q-deficient animals show normal retinal waves (Huh et al., 2000; Stevens et al., 2007), suggesting they do not fail to generate the activity that drives remodeling but rather are unable to translate it into appropriate activity-dependent changes in connectivity.

Immune Proteins as Regulators of Basal Synaptic Transmission

A number of immune proteins have been detected at mature synapses (Boulanger et al., 2001), and some have been found to regulate synaptic transmission (Table 2). A prominent example is the proinflammatory cytokine TNFα. TNFα is released by glia, and exogenous TNFα can promote the cell surface accumulation of AMPA-type glutamate receptors (AMPARs) in hippocampal neurons in vitro. Since AMPARs carry the majority of excitatory glutamatergic current at resting membrane potentials, this TNFα-mediated increase in cell surface AMPARs should regulate synaptic transmission, and indeed, exogenous TNFα rapidly induces an increase in the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs) in hippocampal neurons in vitro (Beattie et al., 2002; Stellwagen et al., 2005). This result is consistent with a postsynaptic increase in receptor sensitivity, which should increase both mEPSC amplitude and frequency, as previously subthreshold events are pulled out of the noise by more sensitive detectors. Also consistent with a postsynaptic locus of action, TNFα affects mEPSC frequency when applied postsynaptically, but not presynaptically (Beattie et al., 2002). Endogenous TNFα is required for maintenance of normal cell surface levels of AMPARs, since application of a soluble form of the TNFα receptor 1 (sTNFR1), which acts as a TNFα antagonist, causes a drop in cell surface AMPARs and a corresponding decrease in both the frequency and amplitude of mEPSCs in hippocampal neurons in vitro. Furthermore, this drop in AMPAR level is mimicked by anti-TNFα antibodies. When applied to hippocampal slices, sTNFR1 causes a drop in the AMPA/NMDA ratio, a drop in AMPAR surface expression, and a drop and the frequency of mEPSCs (Beattie et al., 2002; Stellwagen et al., 2005), all suggesting a role for TNFα in maintaining AMPAR-mediated transmission. In contrast to its facilitating effects on excitatory synaptic transmission, exogenous TNFα decreases inhibitory synaptic strength (Stellwagen et al., 2005), revealing that endogenous TNFα could potentially coordinate changes in excitation and inhibition, for example, during synaptic scaling (see below).

In vitro and slice experiments in the mammalian hippocampus indicate that MHCI regulates several features of presynaptic

Table 2. Manipulations of Immune Protein Signaling Modify Basal Synaptic Transmission in Mouse Hippocampal Neurons

Basal Synaptic Transmission		
Manipulation	Phenotype	Reference
MHCI-deficient ($\beta 2\ m^{-/-}TAP^{-/-}$)	mEPSC frequency increased, fEPSP amplitude normal	Goddard et al., 2007; Huh et al., 2000
$CD3\zeta^{-/-}$	fEPSP amplitude normal	Huh et al., 2000
Exogenous TNFα	mEPSC frequency increased, EPSP enhanced, inhibition decreased, AMPA/NMDA ratio increased	Beattie et al., 2002; Stellwagen et al., 2005; Stellwagen and Malenka, 2006
Soluble TNFR (sTNFR, TNFR1)	mEPSC frequency decreased (in vitro, slices), mEPSC amplitude decreased (in vitro only), AMPA/NMDA ratio decreased	Beattie et al., 2002
$TNFR^{-/-}$	population spike/stimulus strength I/O function normal	Albensi and Mattson, 2000

nerve terminals at excitatory synapses. Cultured hippocampal neurons from mice lacking most cell surface MHCI ($\beta 2\ m^{-/-}TAP^{-/-}$) have slightly larger synapsin-immunoreactive presynaptic puncta (Goddard et al., 2007). In apparent contrast, another group found that treatment of cortical neurons in vitro with antibodies against two specific MHCI proteins (anti-K^b or anti-D^b) reduced the number (but did not affect the size) of synapsin puncta (Zohar et al., 2008). Thus, both studies agree that changes in MHCI expression or function may modify synapsin immunoreactivity, though they differ in terms of the parameters affected (number versus size of synapsin puncta) and the sign of the modification. This difference could be due to the cell types used or the use of antibodies (which may have gain-of-function effects by mimicking ligand binding) versus MHCI-deficient transgenics.

Furthermore, MHCI-deficient hippocampal neurons in culture have a higher frequency of mEPSCs, a parameter that is responsive to changes in the presynaptic release of neurotransmitter, and the size of glutamate vesicular transporter (vGlut)-immunoreactive puncta is increased. Electron micrographs of adult hippocampal slices show that MHCI-deficient presynaptic terminals contain 10% more synaptic vesicles (Goddard et al., 2007). However, fEPSP amplitudes are normal in CA1 of the hippocampus of MHCI-deficient mice (Huh et al., 2000), arguing against a blanket increase in the probability of glutamate release in this circuit. Mice specifically lacking only the classical MHCI proteins K^b and D^b show enhanced presynaptic glutamate release at climbing fiber (CF)-Purkinje cell (PC) synapses in the cerebellum (McConnell et al., 2009). In contrast to the changes in presynaptic parameters, two postsynaptic parameters are normal in MHCI-deficient hippocampus: mEPSC amplitude, which is responsive to changes in the expression or function of postsynaptic glutamate receptors, and expression of the postsynaptic scaffolding protein PSD-95 are both normal. These results together suggest that MHCI selectively affects the basal properties of the presynaptic terminal. It remains unknown if these changes in presynaptic structure and function in MHCI-deficient neurons are due to differences in the details of synapse formation or elimination or rather reflect a later failure to homeostatically adjust presynaptic parameters in response to changing postsynaptic activity during early development (see below).

Like changes in MHCI, changes in a component of some MHCI receptors have been associated with regulation of glutamatergic transmission. DAP12 is a transmembrane adaptor protein that is involved in signal transduction by a number of immunoreceptors, including the natural killer (NK) cell receptors KIR2DS and NKG2D, both of which bind to MHCI (Tomasello et al., 1998). Although DAP12 is known for its role in activating NK cells, transgenic loss-of-function mutation of DAP12 reduces levels of GluR1 and GluR2 in the PSD fraction, increases the inward rectification of synaptic AMPARs (Roumier et al., 2004), and increases the AMPA/NMDA ratio (Roumier et al., 2008). Consistent with a role for DAP12 in synaptic function, human mutations in DAP12 cause a presenile dementia known as Nasu-Hakola disease (Paloneva et al., 2000). Similarly, antibodies against the MHCI receptor Ly49 increased the size of synapsin puncta, much like genetic loss of MHCI, although Ly49 antibodies also increased the number of synapsin puncta, which is unchanged in MHCI-deficient neurons in vitro (Goddard et al., 2007; Zohar et al., 2008).

While MHCI clearly modifies some aspects of presynaptic structure and function, it does not seem to be involved in determining the *number* of excitatory synapses in hippocampal neurons in vitro, since average number of synapsin- or PSD-95-immunoreactive puncta is unchanged in cultured MHCI-deficient neurons (Goddard et al., 2007). In contrast, MHCI might regulate synapse number in the developing LGN in vivo, since activity-dependent retinal ganglion cell axon remodeling is impaired in MHCI-deficient mice (Huh et al., 2000).

Mutant mice lacking the complement protein C1q show an increase in the intensity of immunostaining for both the presynaptic marker vGLUT2 and the postsynaptic marker PSD-95 in the P16 lateral geniculate nucleus (LGN) (Stevens et al., 2007). However, it remains to be determined if this is due to a change in the expression of these markers at individual synapses, as is seen in MHCI-deficient neurons (Goddard et al., 2007), or is secondary to an increase in synapse number, perhaps due to a failure of synapse elimination in the LGN at this age (Stevens et al., 2007) (see above). Studies that further examine if immune proteins regulate synapse number will need to take into account the fact that synapse counts from a snapshot at a single developmental time point are the product of both synapse formation and synapse elimination. This is particularly important since MHCI and C1q/C3 both modify synapse elimination in some projections (Huh et al., 2000; Stevens et al., 2007).

In addition to its regulation of the properties of excitatory connections, MHCI was recently identified in a screen for targets of the transcription factor Npas4, which controls the number of inhibitory GABA-releasing synapses that contact excitatory

Table 3. Effects of Specific Immune Proteins on Acute and Homeostatic Synaptic Plasticity in the Adult Mouse Hippocampus

Synaptic Plasticity		
HFS-LTP		
Manipulation	Phenotype	Reference
MHCI-deficient (β2 $m^{-/-}TAP^{-/-}$)	LTP enhanced	Huh et al., 2000
$CD3\zeta^{-/-}$	LTP enhanced	Huh et al., 2000
Exogenous IL-6	LTP inhibited, PTP inhibited	Tancredi et al., 2000
Exogenous TNFα	LTP inhibited	Tancredi et al., 1992; but see Stellwagen and Malenka, 2006
$TNFR^{-/-}$	LTP normal	Albensi and Mattson, 2000
$TNF\alpha^{-/-}$	LTP normal	Stellwagen and Malenka, 2006
LFS-LTD		
MHCI-deficient (β2 $m^{-/-}TAP^{-/-}$)	LTD abolished	Huh et al., 2000
$CD3\zeta^{-/-}$	LTD abolished	Huh et al., 2000
$TNFR^{-/-}$	LTD impaired	Albensi and Mattson, 2000; but see Stellwagen and Malenka, 2006
$TNF\alpha^{-/-}$	LTD normal	Stellwagen and Malenka, 2006
Homeostatic Plasticity: Reduced Activity (TTX)		
MHCI-deficient (β2 $m^{-/-}TAP^{-/-}$)	no increase in mEPSC amplitude, no increase in PSD-95 puncta size, nor further increase in synapsin immunoreactivity (occluded?)	Goddard et al., 2007
$TNF\alpha^{-/-}$	no increase in mEPSC amplitude	Stellwagen and Malenka, 2006
Soluble TNFR	no increase in mEPSC amplitude, no decrease in mIPSC amplitude	Stellwagen and Malenka, 2006
Homeostatic Plasticity: Increased Activity (Picrotoxin)		
$TNF\alpha^{-/-}$	normal decrease in mEPSC amplitude	Stellwagen and Malenka, 2006

HFS-LTP, high-frequency-stimulation-induced long-term potentiation; LFS-LTD, low-frequency-stimulation-induced long-term depression.

neurons (Lin et al., 2008). However, it remains unknown if MHCI affects the establishment, maintenance, or function of GABAergic connections. A number of proinflammatory cytokines, including IL-1β (Zeise et al., 1992) and TNFα (Stellwagen et al., 2005), have been shown to regulate inhibitory synaptic transmission.

Immune Proteins in Structural and Functional Plasticity of Synapses

In addition to their role in the establishment of appropriate connectivity and synaptic properties, several immune proteins have been implicated in the later structural and functional plasticity of synapses. This includes developmental plasticity (e.g., the activity-dependent elimination of developing synapses, see above), as well as modification of the efficacy of mature synapses. Plasticity at all ages falls into two broad categories: acute, synapse-specific forms of associative plasticity (e.g., LTP and LTD), which are thought to contribute to synapse refinement and learning and memory (Kessels and Malinow, 2009), and slower, more global forms of nonassociative plasticity that arise in response to chronic changes in activity (homeostatic plasticity or synaptic scaling), which are thought to stabilize neuronal networks. These two forms of plasticity likely go hand-in-hand in most circuits, since LTP and LTD can easily saturate synaptic transmission and destabilize networks without homeostatic compensation (Turrigiano, 2008). Intriguingly, some of the same immune proteins are required for both acute and homeostatic plasticity in the developing and adult brain, suggesting that they are part of a shared mechanistic program for plasticity that operates on very different timescales.

Acute Synaptic Plasticity

Immune proteins have been implicated in the functional plasticity of mature synapses (Table 3). MHCI is required for normal activity-dependent synaptic plasticity in both the adult hippocampus (Huh et al., 2000) and adult cerebellum (McConnell et al., 2009) (Figures 3B and 3D). MHCI protein is expressed in the dendrites of hippocampal neurons in vitro (Goddard et al., 2007), and in hippocampal slices from mice lacking cell surface MHCI, LTP induced by tetanic stimulation is approximately twice the magnitude of that induced in WT. Plasticity induced by lower-frequency stimulation is also affected: LTD in response to 1 Hz or 0.5 Hz stimulation is abolished in MHCI-deficient hippocampus (Huh et al., 2000), although it remains unknown if LTD could be induced in these mutants at even lower stimulation frequencies. Thus, endogenous MHCI in the adult hippocampus inhibits LTP and either permits or promotes LTD. A component of many MHCI immunoreceptors, CD3ζ, is also required for LTD and limits LTP in the adult hippocampus (Huh et al., 2000) (Figure 3B). Transgenic mice lacking another immunoreceptor component, DAP12, have enhanced pairing-induced hippocampal LTP (Roumier et al., 2004), although their responses to tetanic stimulation have not yet been determined.

Although published results remain inconsistent, LTD may be abolished in mice lacking the TNF receptor (Albensi and Mattson, 2000), and exogenous TNFα may inhibit LTP (Tancredi et al., 1992), indicating that TNFα, like MHCI, could inhibit LTP and either permit or promote LTD (Table 3). The inconsistencies in the results to date could be due to differences in experimental measures (for example, some studies monitored the slope of the fEPSP, while others monitored the amplitude of the population spike) or may indicate that TNFα is not part of the core mechanism of LTP or LTD, but instead modifies the threshold for the induction of some forms of plasticity. Since TNFα is a proinflammatory cytokine and can regulate MHCI expression, any effects TNFα may have on plasticity could potentially be mediated by changes in MHCI. In fact, several other proinflammatory cytokines, including interleukin- (IL-) 6 (Bellinger et al., 1995; Li et al., 1997; Tancredi et al., 2000), IL-1β (Cunningham et al., 1996; Katsuki et al., 1990), IL-2 (Tancredi et al., 1990), IL-18 (Curran and O'Connor, 2001), IL-8 (Xiong et al., 2003), and interferon-α and -β (D'Arcangelo et al., 1991; Mendoza-Fernandez et al., 2000), also inhibit hippocampal LTP, consistent with the possibility they may converge on a common pathway. Although exogenous IL-6 inhibits LTP in hippocampal slice, IL-6 levels are dramatically upregulated by LTP induction in vivo (Balschun et al., 2004; Jankowsky et al., 2000), and application of an anti-IL-6 antibody 90 min after tetanus prolonged LTP and improved long-term memory (Balschun et al., 2004).

MHCI and its receptors have also been implicated in synaptic plasticity in the adult cerebellum. The classical MHCI molecules H2-K^b and H2-D^b are normally expressed in cerebellar Purkinje cells (PCs), and in $K^{b-/-}D^{b-/-}$ mice, the threshold for LTD at parallel fiber (PF)-PC synapses is reduced (Figures 3C and 3D), although the extent of LTP induced at these synapses is normal. In addition, climbing fiber (CF)-PC paired-pulse facilitation (PPF) is enhanced in these animals. $K^{b-/-}D^{b-/-}$ mice also perform better on the rotarod, a behavioral test that is thought to require plasticity in the cerebellum; they learn the task more effectively and remember it for longer, suggesting the MHCI-dependent change in cerebellar plasticity may have functional consequences (McConnell et al., 2009). PF-PC PPF (but not CF-PC PPF) is enhanced in mice lacking CD3ε, an invariant subunit of the T cell receptor (TCR), and rotarod performance is impaired in these mice (Nakamura et al., 2007), in contrast to what is seen in $K^{b-/-}D^{b-/-}$ mice.

Proteins of the innate immune system have also been implicated in long-term functional plasticity in invertebrates. For example, at mature *Aplysia* synapses, blockade of Dscam either pre- or postsynaptically interferes with the redistribution of glutamate receptors in response to serotonin treatment, which is likely the cause of the observed impairment of serotonin-induced long-term facilitation (LTF) after Dscam blockade (Li et al., 2009).

Adult Plasticity in the Mammalian Visual Cortex

Activity-dependent functional plasticity is thought to underlie many examples of activity-dependent structural plasticity of the mature CNS, and in support of this model, some of the same immune molecules have been implicated in both processes. The role of immune molecules in adult structural plasticity has primarily been characterized in the mammalian visual cortex (Table 1). In this system, loss of visual input to one eye—due to monocular deprivation or enucleation—is associated with a weakening and pruning of inputs from the deprived eye as well as a gradual strengthening and expansion of inputs from the open eye (Mioche and Singer, 1989; Shatz and Stryker, 1978; Wiesel, 1982; Wiesel and Hubel, 1965). TNFα is not required for the weakening of inputs from the deprived eye but is essential for the later strengthening of open eye inputs (Kaneko et al., 2008). It is proposed that this strengthening is a homeostatic response to the earlier, competitive weakening of deprived-eye inputs, implying that TNFα may be required for some forms of homeostatic plasticity (see below). An MHCI-binding protein, PIRB, has also been implicated in deprivation-induced plasticity in the mammalian visual cortex. In mice expressing a form of PIRB in which the transmembrane domain has been removed, preventing PirB-mediated intracellular signaling (PIRB-TM mice), the deprivation-induced expansion of the open eye's territory is more robust and can be induced well after the close of the developmental critical period (Syken et al., 2006). While the depression of responses to the closed eye was not examined in PIRB-TM mice, this result suggests that PIRB may *limit* the same process that TNFα *enhances*, that is, the delayed, homeostatic strengthening of connections from the open eye.

Homeostatic Plasticity (Synaptic Scaling)

In hippocampal neurons in vitro, chronic, long-term reduction of excitatory synaptic activity (e.g., with tetrodotoxin [TTX]) normally causes an increase in synaptic transmission, while a chronic increase in activity (e.g., by application of picrotoxin, a blocker of $GABA_A$-mediated inhibition) causes a decrease in synaptic transmission. These changes keep the activity of networks relatively constant in the face of ongoing acute plasticity, keeping excitation and inhibition in balance and preventing runaway excitation that can lead to epileptic activation and excitotoxicity (Turrigiano, 2008). Although the molecular mechanisms underlying homeostatic plasticity remain largely unknown, it is notable that TNFα and MHCI, both immune proteins, are two of only a handful of molecules that have been implicated in activity-dependent synaptic scaling (Table 3).

One important prediction regarding molecular mediators of homeostatic plasticity is that they should be regulated in response to long-term changes in network activity. Indeed, blocking activity with TTX reduces the expression of MHCI in the prenatal LGN in vivo (Corriveau et al., 1998) and in hippocampal neurons in vitro (Goddard et al., 2007), while increasing activity with kainic acid increases MHCI expression in the dentate gyrus in vivo (Corriveau et al., 1998). Thus, MHCI is bidirectionally regulated by changes in activity, with increases in activity adding to the normal constitutive expression of MHCI. In contrast, TNFα may be released in response to a *drop* in activity (Stellwagen and Malenka, 2006). The activity-dependent availability of these factors, both of which regulate synaptic transmission and plasticity (see above), may provide a mechanism for homeostatic modifications.

In support of this possibility, MHCI and TNFα are both required for synaptic scaling. In WT hippocampal neurons in vitro, chronic TTX treatment causes an increase in both presynaptic synapsin and postsynaptic PSD-95 immunoreactivity. In MHCI-deficient neurons, however, neither synapsin nor PSD-95 scale up in

response to TTX (Goddard et al., 2007). It is important to note that synapsin-immunoreactive puncta are already enlarged prior to TTX treatment in MHCI-deficient neurons, suggesting that presynaptic scaling may be occluded by prior saturation of synapsin expression. Postsynaptic PSD-95, however, is indistinguishable from WT at rest, and therefore the failure of PSD-95 immunoreactivity to scale up in response to TTX likely reflects a requirement for MHCI in postsynaptic homeostatic plasticity.

TNFα has also been implicated in the homeostatic plasticity of postsynaptic parameters. Conditioned medium from TTX-treated cultures is sufficient to increase synaptic AMPAR levels and mEPSC amplitude, indicating that a soluble factor released by TTX-treated cells is sufficient to transfer these forms of scaling from one culture to another. This factor may be secreted TNFα, since acute application of TNFα alone increases AMPAR levels at the cell surface in a manner that mimics TTX (Beattie et al., 2002; Stellwagen et al., 2005). More tellingly, soluble TNFR, which scavenges endogenous TNFα, blocks the ability of conditioned medium or TTX treatment to induce scaling of AMPARs and mEPSCs. This suggests that TNFα released into the culture medium during activity blockade is required for the homeostatic delivery of AMPARs to the cell surface. sTNFR also prevents the decrease in the amplitude of miniature inhibitory postsynaptic currents (mIPSC) caused by TTX, revealing that TNFα mediates scaling of both excitation and inhibition in response to TTX. However, TNFα does not mediate the *reduction* in excitatory synaptic strength produced by *increased* neuronal activity, suggesting that while TNFα is required for scaling up of excitatory synapses, other factors are responsible for scaling them down (Stellwagen and Malenka, 2006).

Homeostatic synaptic scaling could occur in a cell-autonomous manner to maintain a steady level of overall synaptic drive in the face of input-specific plasticity, or could be driven by functional matching of pre- and postsynaptic elements at individual synaptic contacts. TNFα-mediated scaling is not cell-autonomous, since glia are the source of endogenous TNFα that drives scaling in neurons (Beattie et al., 2002). It is tempting to speculate that MHCI might be involved in coordinating pre- and postsynaptic properties, since presynaptic synapsin puncta are enlarged, but postsynaptic PSD-95 puncta are unaffected, in MHCI-deficient neurons (Goddard et al., 2007), indicating an unusual uncoupling of pre- and postsynaptic parameters.

Plasticity in Response to Neuronal Injury

In many regions of the adult CNS, nerve transection, crush, or lesion is followed by a secondary loss of inputs onto the cell body and dendrites of the damaged cell (synaptic stripping). This retrograde wave of synapse loss may represent a form of homeostatic plasticity or may involve the inappropriate reactivation of mechanisms of developmental synapse elimination. Indeed, immune molecules that are involved in normal, developmental synapse elimination and homeostatic plasticity have also been implicated in injury-induced plasticity. One week after peripheral transection of sciatic motoneurons, significant detachment of inputs onto the cell body of the axotomozed motoneuron is normally observed. In mice lacking either β2 m or TAP, both of which have reduced levels of MHCI on the cell surface, synaptic stripping is enhanced in vivo. Thus, endogenous MHCI minimizes secondary synapse loss after injury in this model. Of note, the neuroprotective effect of MHCI is relatively selective for axon terminals that, based on morphological criteria, are putatively inhibitory (Oliveira et al., 2004). This MHCI-mediated preservation of inhibitory terminals might prevent further synapse loss by reducing the risk of excitotoxicity.

In this same injury model, later regeneration of the axotomized neurons themselves is also slightly impaired in MHCI-deficient animals (Oliveira et al., 2004). This is interesting in light of the fact that one MHCI receptor, PIRB, has recently been found to mediate some of the regeneration-inhibiting effects of myelin-derived proteins on cerebellar granule neurons in vitro (Atwal et al., 2008). Thus, MHCI is required for the small basal level of axonal regeneration, while PIRB, a putative MHCI receptor, is required for the opposing inhibition of regeneration. There are several possible explanations for this apparent contrast. Mechanisms of regeneration may vary for different cell types in vitro versus in vivo; MHCI may inhibit constitutive, regeneration-inhibiting signaling by PIRB; or PIRB and MHCI may function independently to regulate regeneration. Peripheral nerve regeneration can also be inhibited by IL-1 receptor antagonists (Guenard et al., 1991), indicating that endogenous IL-1, like MHCI, promotes nerve regeneration after injury. These results all point to potential mechanisms whereby inflammatory signaling may regulate synapse loss and regeneration following nerve injury.

The contributions of brain immune molecules in disease pathogenesis and progression, injury responses, and pain are discussed in detail elsewhere in this issue. Clearly, immune responses to neuronal injury and disease can cause neuroinflammation and/or autoimmunity (see Bhat and Steinman, 2009 [this issue of *Neuron*]) and thereby exacerbate damage. However, the fact that immune proteins also have normal functions in brain development and plasticity adds two novel, nonimmune dimensions to their potential role in pathogenic processes.

First, changes in the expression or function of immune proteins could lead to interruption of their *normal* functions in brain development and plasticity (loss of function), potentially disrupting the establishment and modification of brain circuitry. For example, high levels of circulating proinflammatory cytokines during infection and inflammation lead to sickness behavior, including deterioration of cognition. Elevated cytokine levels could potentially contribute to changes in cognition by disrupting their normal function in the forms of synaptic plasticity thought to underlie some forms of learning and memory (Balschun et al., 2004).

Second, altered expression or activation of these proteins could lead to inappropriate reactivation of their normal brain functions (gain of function). Immune proteins that are essential for the normal developmental pruning and elimination of synapses (e.g., C1q, MHCI) are upregulated in some disease states, and aberrant re-expression of these proteins could contribute to pathological synapse loss. For example, C1q is expressed at low levels in the adult retina, but is re-expressed in a mouse model of glaucoma (Stevens et al., 2007). Similarly, neuronal MHCI is upregulated with age in some cell populations (Edstrom et al., 2004), and reactivation of MHCI-dependent synapse remodeling and synaptic plasticity (Huh et al., 2000) could contribute to age-related synapse loss, as well as to changes in synaptic plasticity that could give rise to age-related memory impairments. Thus determining how immune proteins

contribute to normal development and plasticity may identify novel immune-mediated features of a wide variety of neuropathological states.

Search for Cellular Mechanisms

An outstanding question is how, on a molecular level, immune proteins perform their nonimmune functions in the development and plasticity of the brain. While in most cases a great deal is known about immune protein signaling pathways in cells of the immune system, almost nothing is known yet about how these proteins receive, transduce, or respond to signals in neurons.

Immune Signaling Cascades in the Brain

One possibility is that these proteins use signaling mechanisms in the brain that are either similar or identical to those employed in the immune system, with either related or distinct outcomes. Such immune signaling mechanisms may be cell-autonomous within a single neuron, or may involve interactions with other neurons or glia. Fortunately, the experimental tools (e.g., transgenics, antibodies, constructs) used to study these proteins in the immune system are ready-made to test these possibilities in the brain.

To date, there is preliminary evidence that similar signaling cassettes may be used by some proteins in both the nervous and immune systems. For example, activity-dependent synaptic remodeling is similarly impaired in mice lacking either C1q, the initiating protein in the complement cascade, or C3, a downstream component, suggesting that C1q may affect remodeling through interactions with other proteins of the complement cascade. Strikingly, the function of C1q and C3 in the brain also appears functionally analogous to their function in the immune system: the clearance of cellular material that has been marked for destruction (Stevens et al., 2007). Outside the brain, the complement cascade trigger assembly of the membrane attack complex (MAC), which leads to cell lysis. It remains to be determined if the MAC is involved in the removal of inappropriate axons in the developing visual system. Outside the CNS, complement-mediated attack is targeted to damaged or foreign cells by a large number of highly specific triggers and regulators. It is unclear if complement is as selectively targeted in the nervous system. Some C1q is detected in areas where pre- and postsynaptic markers are not apposed in the developing LGN, putatively sites of either nascent or degenerating synapses (Stevens et al., 2007). If C1q is indeed enriched at synapses that have been tagged for removal, it will be important to identify the regulatory proteins that underlie this specificity and attract complement proteins to these synapses and not their neighbors.

PIRB is another immune protein that may use overlapping signaling pathways in the immune system and the nervous system. PIRB an immunoreceptor that is phosphorylated in immune cells upon ligand binding, triggering recruitment of the downstream phosphatases Shp-1 and Shp-2. PIRB isolated from brain is also phosphorylated, and is associated with Shp-1 and Shp-2 (Syken et al., 2006), suggesting that these immunoreceptors may employ at least some of the familiar immune signaling cascade in neurons. However, it is unknown if this phosphorylation and subsequent recruitment of Shp phosphatases is required for PIRB's effects on brain development and responses to neuronal injury.

PIRB is one of many receptors for MHCI. MHCI proteins have small intracellular domains and, in their immune capacity, bind to cell surface and/or soluble proteins to generate their cellular effects. Dozens of receptors for classical and nonclassical MHCI proteins have been identified outside the nervous system (e.g., Natarajan et al., 2002). It is possible that neuronal MHCI can bind to one or more of these classical immunoreceptors expressed on the surface of CNS cells. Several lines of evidence support this possibility. First, immunoreceptors that bind to MHCI have been detected in neurons (Figure 1), including mouse PIRB (Atwal et al., 2008; Syken et al., 2006), KIR-like genes (Bryceson et al., 2005), members of the mouse Ly49 family (Zohar et al., 2008), the invariant TCR subunits CD3ζ (Barco et al., 2005; Huh et al., 2000) and CD3ε (Nakamura et al., 2007), and mRNA encoding unrearranged TCRβ chain (Nishiyori et al., 2004; Syken and Shatz, 2003). Second, not only are these receptors expressed, but at least one, PIRB, binds to neurons in a manner that is responsive to MHC levels (Syken et al., 2006). Third, knockouts of specific immunoreceptor proteins phenocopy some of the effects of loss of MHCI. For example, retinogeniculate remodeling is similarly impaired in MHCI-deficient and CD3ζ-deficient mice, suggesting that MHCI may regulate this remodeling via a CD3ζ-containing receptor (Huh et al., 2000). Similarly, antibodies against either the MHCI proteins K^b and D^b or the MHCI receptor Ly49 have effects on neuron survival and neurite outgrowth in cortical neurons in vitro; however, the two antibodies have opposite effects, with anti-MHCI promoting outgrowth and reducing survival, and anti-Ly49 reducing outgrowth and enhancing survival (Zohar et al., 2008).

Despite the detection of several MHCI receptors in the CNS, recent experiments suggest that additional mediators of MHCI and immunoreceptor functions in the nervous system remain to be identified. For example, although retinogeniculate remodeling is impaired in MHCI-deficient mice (Huh et al., 2000), retinogeniculate remodeling is normal in mice lacking functional PIRB (Syken et al., 2006), indicating that MHCI binding to PIRB is not required for normal remodeling of these projections. In fact, although MHCI and PIRB are coexpressed in neurons, and MHCI affects PIRB binding to neurons, there is little evidence to date that the known effects of MHCI on brain development or plasticity are mediated by this immunoreceptor, since MHCI-deficient animals and PIRB-TM animals do not share any published phenotypes (see Tables 1–3). Conversely, there are hints that neurons may express other ligands for PIRB, since genetic ablation of MHCI reduces, but does not eliminate, the saturable binding of alkaline phosphatase-labeled PIRB to the cell surface of either mouse embryo fibroblasts or cultured cortical neurons (Syken et al., 2006). Further experiments (e.g., examining hippocampal LTP and LTD in PIRB-TM mice, and examining visual cortical plasticity in MHCI-deficient mice) will help clarify the molecular relationships between MHCI and the multiple immunoreceptors expressed in neurons.

Immune proteins may participate in signaling cascades that are composed of the same molecular players as in the immune system, but respond differently to modulatory cues, and have very different readouts, in neurons. For example, TNFα is a proinflammatory cytokine that causes *up*regulation of MHCI in nonneuronal cells, but instead causes *down*regulation of MHCI

mRNA in early postnatal rat hippocampus (Sourial-Bassillious et al., 2006). Thus, although TNFα is a regulator of MHCI expression within and outside the CNS, at least at early ages, the sign of the regulation differs. Similarly, mGluR5 is expressed in T cells, but unlike in neurons, where mGluR5 activation is usually coupled to phospholipase C (PLC) (Pin and Duvoisin, 1995), mGluR5 is coupled to stimulation of adenylate cyclase in T cells (Pacheco et al., 2004).

The idea that immune proteins in the brain may employ classical immune signaling cascades makes it relevant to consider that many of these molecules converge on shared signaling pathways in the immune response, and may do so in the brain as well. MHCI in neurons and astrocytes can be regulated by TNFα (Lavi et al., 1988; Neumann et al., 1997; Sourial-Bassillious et al., 2006), raising the possibility that some of the effects of TNFα could be mediated by changing MHCI levels in neurons. Consistent with this possibility, LTD is abolished in mice lacking either the TNF receptor (Albensi and Mattson, 2000) or cell surface MHCI (Huh et al., 2000), and exogenous TNFα inhibits LTP (Tancredi et al., 1992), while loss of MHCI promotes LTP (Huh et al., 2000). The possible role of MHCI in mediating these effects of TNFα could be tested by examining LTP and LTD after applying TNFα to MHCI-deficient neurons. However, not all of the effects of TNFα are likely mediated by MHCI, since TNFα modifies AMPAR trafficking and AMPAR-mediated currents (Beattie et al., 2002), while changes in MHCI levels do not affect basal excitatory fEPSP amplitude, which is primarily AMPAR-mediated at resting membrane potentials (Huh et al., 2000). Activation of the complement cascade can indirectly regulate MHCI expression outside the CNS, and loss of either C1q, C3 (Stevens et al., 2007), or MHCI (Huh et al., 2000) alone can each impair retinogeniculate remodeling. Again, it is as yet unknown if these molecules act in a single common pathway, or have parallel, potentially additive effects on remodeling at these synapses.

Novel, Nonimmune Pathways

In addition to acting through familiar binding partners and signal transduction pathways, it is also possible that immune proteins have neuronal effects through novel interactions with proteins that have no known immune function. A precedent for nonimmunological binding partners for MHCI has been identified outside the nervous system. X-ray crystallography has demonstrated that the MHCI-like protein HFE can bind to the dimeric transferrin receptor (TfR), an interaction that regulates TfR function and iron homeostasis. Disruption of this normal interaction between HFE and the TfR is the likely cause of the common iron-loading disorder hereditary hemochromatosis (Bennett et al., 2000). Studies of a particular nonclassical MHCI, M10, are also consistent with non-immune-protein interactions for MHCI in neurons. M10 proteins appear to be expressed exclusively in neurons of the mammalian vomeronasal organ (VNO), where they associate with V2R pheromone receptors and are required for normal delivery of V2Rs to the dendritic tips of VNO sensory neurons. In mice lacking most if not all cell surface MHCI proteins, pheromone-mediated behavior is impaired, suggesting that MHCI-dependent V2R trafficking is required for normal pheromone sensing in vivo (Ishii et al., 2003; Ishii and Mombaerts, 2008; Loconto et al., 2003). It has further been proposed that MHCI-associated peptides may function as chemosensory signals (Leinders-Zufall et al., 2004). MHCI is known to bind to a wide array of cell surface and soluble proteins and peptides outside the CNS, and it seems likely that a similar diversity of protein interactions with MHCI is exploited for distinct functions in the brain.

Diversity and Specificity of Signaling

A tantalizing feature of many proteins of the immune system is their remarkable diversity. Different immune proteins generate diversity at many levels, including large gene families, somatic recombination, alternate mRNA splicing, high allelic diversity, and the binding to diverse peptides. In the immune system, at least some of this diversity is harnessed for a complex and precise molecular recognition system, but for the most part it remains unknown if this diversity is exploited in the neuronal functions of immune proteins. For example, vertebrate TCRs undergo somatic recombination to form a virtually unlimited repertoire of receptors, which permits precise, specific recognition of small MHCI-presented peptides that differ by only a few amino acids. Similarly, members of the MHCI family are among the most polymorphic in the genome, with hundreds of possible alleles, with each allele conferring the ability to present and thereby recognize different populations of peptides. The binding of MHCI-presented peptides to somatically recombined TCRs permits tremendous diversity and specificity of protein interactions. However, it remains unknown if MHCI presents peptides on the surface of neurons, and if so, if the identity of these peptides affects the neuronal functions of MHCI. In *Drosophila*, Dscams can undergo alternate splicing to produce thousands of distinct transcripts, and recent studies suggest at least some of this diversity is important for neuronal intercellular recognition events during brain development (Chen et al., 2006; Hattori et al., 2007). Intriguingly, although DSCAM does not appear to undergo alternative splicing in mammals, there is evidence that it is still able to participate in molecular recognition events between neurons (Fuerst et al., 2008), though the mechanism remains unclear.

In contrast to TCRs, some Ly49 receptors and the leukocyte immunoglobulin-like receptors (LILR) -B1 and -B2 interact with MHCI proteins relatively promiscuously, with little or no specificity for particular MHCI alleles, genes or MHCI-associated peptides (Natarajan et al., 2002). Both precise and promiscuous forms of molecular recognition might have a place in the developing and adult brain; for example, diverse, specific molecular interactions could be involved in the establishment of appropriate neuronal connectivity, while promiscuous interactions could help ensure that basic cellular events in development and plasticity occur normally in the face of massive allelic, peptide, or mRNA splicing variability. MHCI proteins are able to participate in both precise (e.g., presented antigenic peptide) and relatively promiscuous (e.g., CD8) interactions by using different regions of the protein to mediate binding to diverse versus static partners. It will be of interest to determine if immune proteins also spatially segregate the domains used for their neuronal and immunological functions, thereby allowing them to be shaped by potentially antagonistic evolutionary pressures.

Future Directions and Conclusions

For many of the immune proteins mentioned here, a careful examination of neuronal mRNA and protein expression patterns

is in order, including a developmental time series. Developmental expression patterns may provide important clues to the function of specific immune proteins. There is some evidence that overall developmental changes in immune protein expression may differ in the CNS as compared to the periphery. For example, while MHCI is downregulated in the periphery with age (a change that is thought to contribute to peripheral immunoscenescence, or breakdown of the immune response), in the CNS the opposite is seen: MHCI levels, which are relatively low in the uninfected adult CNS, increase with age (e.g., Edstrom et al., 2004). For diverse protein families, such as MHCI and Ly49, an important clue about the functional role of this diversity in neurons will be to determine how the members differ in their expression, and if more than one member can be expressed by a single cell. In some cases, these studies will require the development of new antibodies against fix-insensitive epitopes or against neuron-specific isoforms of immune proteins. Similarly, reagents need to be developed to reliably discriminate the many members of large immune protein families such as the MHCI proteins, the Ly49 receptors, and the Dscams, which are comprised of dozens to thousands of members. These reagents will help build a more complete picture of the functions of these proteins in normal development and plasticity, and allow semi-quantitiative evaluation of changes in immune protein expression in the context of disease states and injury.

A second, related area in need of attention is the regulation of expression of these immune proteins in the context of the nervous system. Although much is known about the regulation of immune proteins in the periphery during inflammation, relatively little is known about how these proteins are regulated in neurons, particularly under nonpathological conditions. Neuronal expression of MHCI is dynamic during brain development and is spatially restricted throughout life (Corriveau et al., 1998; Huh et al., 2000), and this tight regulation may be important to its neuronal functions. Regulation of immune protein expression in neurons may also be necessary in order to minimize potentially destructive engagement of these molecules in the brain during the course of their immune functions. In particular, control of the cell surface population of MHCI proteins may be critical for both its normal neuronal functions and avoidance of pathological engagement of its immune functions, leading to autoimmunity. Neuronal MHCI is regulated by increases and decreases in electrical activity (Corriveau et al., 1998; Neumann et al., 1995) and by the neuronal transcription factors CREB (Barco et al., 2005), Npas4 (in inhibitory neurons) (Lin et al., 2008), and MeCP2 (in the neuron-derived cell line N2A) (Miralves et al., 2007), revealing that the level and pattern of MHCI expression can be responsive physiologically relevant neuronal cues.

In addition to these novel neuronal regulators, it is also of interest whether MHCI and other polyfunctional immune proteins retain their responsiveness to classical inflammatory cues. If so, immune signaling in the periphery could trigger changes in neuronal expression of these molecules, and thereby impact brain development and plasticity. MHCI expression in the CNS, as in the periphery, is regulated by pro- and antiinflammatory cytokines (e.g., Fujimaki et al., 1996; Linda et al., 1998; Neumann et al., 1995, 1997; Wong et al., 1984, 1985). However, it remains to be determined if the sign and magnitude of the regulation differ in neurons or if regulation varies with developmental age or CNS cell type, although preliminary evidence suggests this may be the case (Edstrom et al., 2004; Sourial-Bassillious et al., 2006). Cytokines are regulated by a variety of insults, including ischemia (Amantea et al., 2009) and maternal immune challenge (see Deverman and Patterson, 2009 [this issue of *Neuron*]), raising the possibility that cytokine-driven changes in MHCI and other immune effectors may mediate some effects of these insults on the developing and adult brain. Similarly, MHCI is upregulated in neurons following injury (i.e., facial or sciatic nerve transaction) (Maehlen et al., 1989; Streit et al., 1989; Zanon and Oliveira, 2006), and the presence of MHCI at the cell surface helps limit postinjury synapse loss and may promote regeneration (Oliveira et al., 2004). Molecular crosstalk between immune and neuronal signaling, mediated by pleiotropic molecules that function in both systems, may contribute to the pathogenesis and progression of both neurodevelopmental and neurodegenerative disorders. Thus understanding how immune proteins are regulated by inflammatory signals will provide important clues to how peripheral immune signaling may affect brain structure and function.

Just as it is important to identify upstream regulators of immune proteins in the brain, it is essential to identify their downstream effectors. This third area of active research involves determining the cellular and molecular mechanisms whereby these immune proteins perform their nonimmunological functions in the brain. This research can use as a starting point what is known about the downstream signaling of these proteins in the immune system. However, unbiased screen-based experiments will also be important for the discovery of novel, neuron-specific signaling pathways for immune proteins in the brain.

One exciting feature of the study of pleiotropic proteins is that findings about one function can provide insight into the mechanisms of other functions. For most of the molecules discussed here, including MHCI, classical MHCI immunoreceptors, complement, and cytokines, immune functions are far better-characterized than neuronal functions. For these molecules, their relatively extensive immunological literature may contain important clues as to their neuronal functions. Conversely, some molecules are best known for their neuronal functions, but are also expressed by immune cells and have less well-characterized functions in the immune response. These include neuropilin 1 (Sarris et al., 2008; Tordjman et al., 2002), agrin (Khan et al., 2001), semaphorins (Suzuki et al., 2008), $GABA_A$ receptors (Tian et al., 1999), and Dscam. Although Dscam is expressed in immune tissues, and loss of Dscam impairs the ability of flies (Watson et al., 2005) and mosquitos (Dong et al., 2006) to fight bacterial infections, almost nothing is known about how it performs these immune functions. In particular, although immune-competent cells possess the capacity to produce thousands of Dscam isoforms (Watson et al., 2005), it is as yet unclear what, if any, function their incredible isoform diversity serves in the immune system. In contrast, much more is known about the circuit and cellular functions of Dscam in the CNS, and about the role (Chen et al., 2006; Hattori et al., 2007) and even the structural basis (Meijers et al., 2007; Sawaya et al., 2008) of isoform-specific Dscam interactions on the surface of neurons. Thus neuronal studies could provide a framework for imagining how Dscam might help fight pathogens.

Accumulating evidence indicates that the same molecules can perform both immunological and neurological functions in a single organism. It will be important to determine how these distinct functions coexist, and the pressures they exert on one another. Shared molecular machinery could help coordinate neuronal and immune responses of the disparate systems in which these proteins function, linking changes in the timing and magnitude of the two responses. It also increases the risk of potentially pathological molecular crosstalk. Given that the precisely tuned functioning of the immune system and the nervous system are both critical for survival, adaptations may have arisen to minimize such crosstalk, which if unchecked could promote autoimmunity, hamper efforts to fight off infections or cancer, or induce major motor or cognitive impairments. One speculative idea is that the immune privilege of the brain, long taken to be evidence that neurons lack key immune proteins, is instead necessary to preserve the distinct neuronal functions of these proteins. In this model, rather than being evidence of a lack of immune proteins, CNS immune privilege is the opposite: a specialization that is due to the expression and functional importance of immune proteins in normal brain development and plasticity.

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