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SIGNALING MECHANISMS IN SYNAPSE ASSEMBLY

Role of immune molecules in the establishment and plasticity of glutamatergic synapses

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Abstract

An increasing number of studies support an unexpected role for immune molecules in regulating healthy brain functions during development and in adulthood. Here we review the roles of specific immune molecules (including cytokines, components of the complement cascade, and members of the major histocompatibility complex class I family and their receptors) in the formation and plasticity of glutamatergic synapses. These findings add a new dimension to our understanding of neural–immune interactions, and suggest novel molecular mechanisms that may underlie the modification of glutamatergic synapses in both normal and pathological states.

Introduction

The initial idea that the central nervous system (CNS) is an immune-privileged environment devoid of immune signaling has been significantly modified over the years. It is now understood that immune signaling is a prominent feature of many pathological brain conditions. In addition, accumulating evidence suggests that specific immune proteins are, unexpectedly, key regulators of normal brain functions. These recent studies show that many canonical immune molecules are expressed in the nervous system, and play important but non-immunological roles in neurodevelopment and synaptic plasticity [reviewed in Boulanger (2009)]. These include molecules of the innate immune system (e.g. pro-inflammatory cytokines and components of the complement cascade) as well as the adaptive immune system [e.g. members of the major histocompatibility complex class I (MHCI) family of molecules and their receptors].

Many of the studies to date support the idea that immune proteins participate in the establishment and later plasticity of excitatory synaptic connections. In the mammalian CNS, fast excitatory synaptic transmission is primarily mediated by the neurotransmitter glutamate. Glutamatergic synaptic transmission mediates information processing during sensory and motor function, and the plasticity of glutamatergic synaptic transmission is thought to underlie certain forms of learning and memory. Given the central role of glutamatergic synaptic transmission in brain development and behavior, it is not surprising that dysregulation of glutamatergic transmission has been associated with many disorders of the CNS, including major depression, schizophrenia, and certain forms of epilepsy, and with excitotoxic cell damage following ischemia and traumatic brain injury (Morimoto *et al.*, 2004; Lang *et al.*, 2007; Hashimoto, 2009). The focus of this review is to highlight the roles of specific immune molecules in the establishment and plasticity of mature glutamatergic circuitry.

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Immune molecules in the establishment of mature glutamatergic circuitry

Remodeling of the developing retinogeniculate projection

Early in mammalian brain development, many populations of neurons form exuberant axonal projections onto sets of target cells. Because of this initial overproduction of contacts, axon pruning and accompanying synapse elimination are essential for the establishment of mature patterns of brain circuitry in these pathways (Katz & Shatz, 1996). Such remodeling has been relatively well studied in the developing mammalian visual system, where retinal ganglion cell (RGC) axons initially form an excess of glutamatergic synapses onto thalamic relay neurons in the dorsal lateral geniculate nucleus (LGN) (Fig. 1A). In mice, the removal of these surplus connections occurs during the first two postnatal weeks, and requires spontaneous activity in the RGCs, which occurs during this period in the form of waves of activity that propagate across the retina (Fig. 1B). Initially, RGC axons project onto neurons in the LGN in an overlapping pattern, such that each LGN neuron is innervated by multiple RGCs from both eyes. During the remodeling process, appropriate synaptic connections are strengthened and inappropriate ones are weakened and removed, such that, by the end of the second postnatal week, each individual LGN neuron receives input from only one or two RGC axons (Chen & Regehr, 2000; Huberman, 2007; Kano & Hashimoto, 2009). This remodeling process also gives rise to the eye-specific layering of the retinal

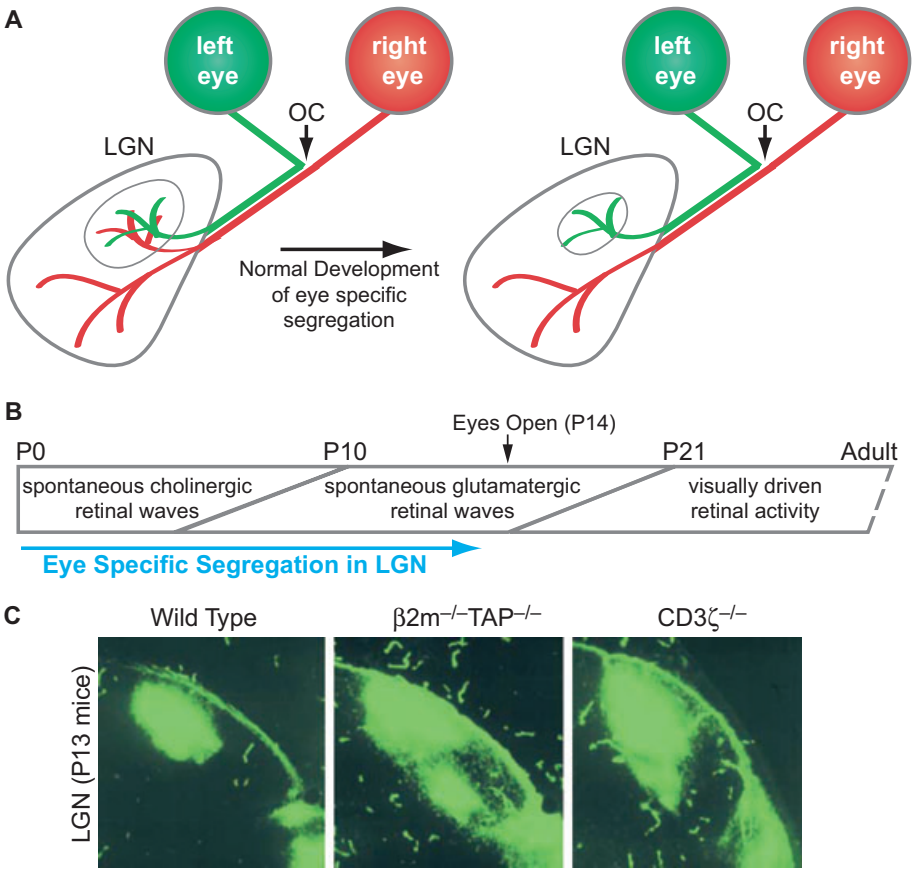

FIG. 1. Activity-dependent remodeling in the mouse LGN during visual system development. (A) Schema illustrating activity-dependent remodeling in the mouse LGN. Early in development, axons from both eyes project to the LGN in an overlapping pattern (left side). During the first two postnatal weeks, spontaneous activity arising in the retinas causes segregation of inputs from the two eyes into non-overlapping domains in the LGN (right side). (B) Timeline illustrating changes in the electrical activity arising from the retina during early postnatal mouse development. (C) MHCI-deficient $\beta 2m^{-/-}TAP^{-/-}$ mice have impaired activity-dependent remodeling of retinal afferents in the LGN, as illustrated by the expansion of territory still occupied by labeled ipsilaterally projecting RGC axons (green) in the LGN at this age. A similar phenotype is seen in mice with normal MHCI expression that lack the immunoreceptor component CD3ζ (modified with permission from Huh *et al.*, 2000). OC, optic chiasm.

projection that typifies the adult LGN. Although much work remains to be done to fully describe the cellular and molecular mechanisms underlying synaptic remodeling in the developing LGN, several studies have identified an unexpected role for immune molecules, including MHCI, in this process.

The MHCI family (human leukocyte antigen in humans) is a large, polymorphic group of transmembrane molecules comprising over 50 members in mice. The MHCI molecules are divided into 'classical' (class Ia) and 'nonclassical' (class Ib) subgroups (Bjorkman & Parham, 1990; Amadou *et al.*, 1999). Classical MHCI molecules are expressed on almost all nucleated cells of the body, and are crucial components of the adaptive immune system. In this capacity, classical MHCI proteins present peptides derived from intracellular proteins on the cell surface for surveillance by circulating immune cells. Whereas a subset of the nonclassical MHCI proteins perform limited immune functions, many nonclassical MHCIs are expressed in a restricted pattern and have no known immune function.

The first evidence that MHCI might have a non-immune role in the brain came when MHCI was identified in an unbiased screen for candidate molecules involved in activity-dependent remodeling in the developing cat LGN. In this screen, prenatal blockade of sodium-based action potentials with tetrodotoxin (TTX) – which prevents remodeling of RGC axons (Shatz & Stryker, 1988; Sretavan *et al.*, 1988) – was associated with a striking decrease in MHCI mRNA expression in the LGN (Corriveau *et al.*, 1998). This result revealed, for the first time, that MHCI expression can be regulated by the endogenous neuronal activity that drives remodeling, and suggested that MHCI immune molecules might play an unexpected role in the development of the CNS. Subsequent studies revealed that MHCI mRNA and proteins are expressed in many regions of the developing and adult brain (Fig. 2A and D), and that MHCI levels are highly dynamic during development (Corriveau *et al.*, 1998; Lidman *et al.*, 1999; Linda *et al.*, 1999; Huh *et al.*, 2000; McConnell *et al.*, 2009). MHCI mRNA levels are high in the mouse LGN during RGC remodeling, and decrease dramatically after remodeling is complete; MHCI levels are high in adults in brain regions known to be sites of ongoing synaptic plasticity (e.g. hippocampus and cortex) (Corriveau *et al.*, 1998).

To determine whether MHCI molecules are required for the developmental remodeling of RGC axons, anterograde tracing experiments were conducted to label RGC axons in MHCI-deficient ($\beta 2m^{-/-}TAP^{-/-}$) animals. These double-knockout (KO) mice lack two genes necessary for stable cell surface expression of nearly all MHCI molecules: those encoding β_2-microglobulin (β2M), the light chain associated with most MHCI heavy chains, and the transporter associated with antigen processing (TAP1), which is required to load

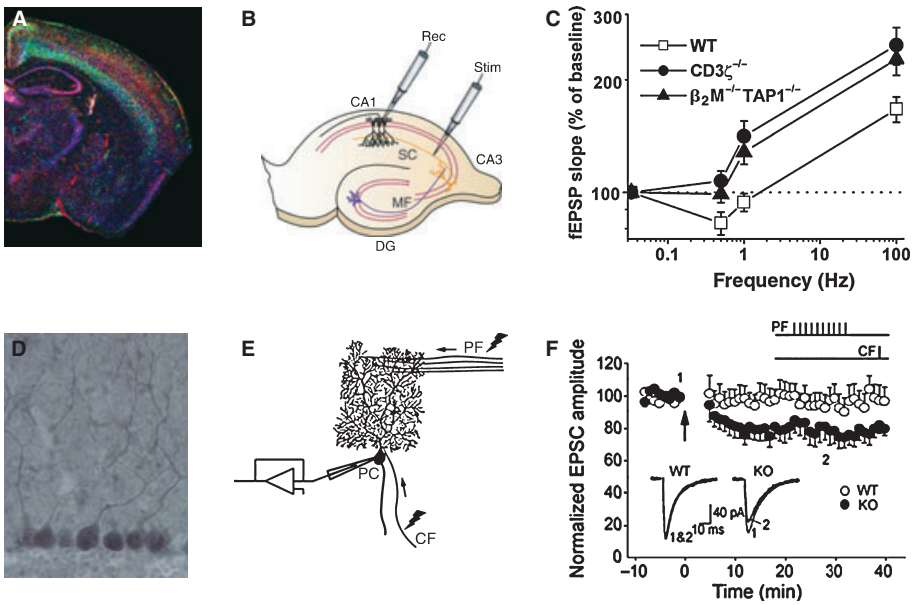

FIG. 2. Expression of MHCI molecules in the hippocampus and cerebellum, and their role in hippocampal and cerebellar synaptic plasticity. (A) Pseudocolored S^{35} *in situ* hybridization showing expression of mRNA encoding three different MHCI proteins [H2-D (red), T22 (blue), and Qa-1 (green)] in merged serial coronal sections from adult mouse brain (reprinted with permission from Boulanger *et al.*, 2001). (B) Schematic representation of a coronal slice of rodent hippocampus showing typical electrode placements used to study synaptic plasticity at CA3–CA1 synapses. SC, Schaffer collaterals; DG, dentate gyrus; MF, mossy fibers; Stim, stimulating electrode; Rec, recording electrode (reprinted with permission from Citri & Malenka, 2008). (C) Frequency-dependent plasticity curve recorded at CA3–CA1 synapses in WT, MHCI-deficient ($\beta2m^{-/-}TAP1^{-/-}$) and CD3ζ-deficient mouse hippocampal slices. LTP is enhanced and LTD is abolished in both MHCI-deficient and CD3ζ-deficient animals (reprinted with permission from Huh *et al.*, 2000). fEPSP, field EPSP. (D) Immunohistochemistry showing MHCI protein expression in WT PCs. (E) Schematic representation of the electrode placements used to record LTD at PF–PC synapses using paired stimulation of CFs and the PFs. (F) Sample traces and averaged data for PF LTD recorded in WT and MHCI-deficient ($K^{b-/-}D^{b-/-}$; KO in the figure) cerebellar slices using the electrode configuration depicted in E. LTD was induced by pairing presynaptic PF stimulation trains (10 stimuli at 100 Hz) with single CF activation (50 ms following PF train) at 0.1 Hz for 5 min, in current-clamp mode. The arrow indicates the starting point of the 5-min induction protocol. The magnitude of PF LTD for this stimulation protocol is larger in MHCI-deficient animals (D–F reprinted with permission from McConnell *et al.*, 2009).

peptides onto MHCI. In $\beta2m^{-/-}TAP^{-/-}$ mice, cell surface expression of most MHCI proteins is reduced or abolished (Ljunggren *et al.*, 1995; Dorfman *et al.*, 1997). In MHCI-deficient $\beta2m^{-/-}TAP^{-/-}$ animals, RGC axons reach the LGN, but remodeling is incomplete, and as a result, immature, overlapping retinal projections from the two eyes persist in the mature LGN (Fig. 1C) (Huh *et al.*, 2000). In a recent study, similar experiments in mice that lack only the classical MHCI molecules H2-K and H2-D ($K^{b-/-}D^{b-/-}$ mice) yielded similar results (Datwani *et al.*, 2009). These studies demonstrate that MHCI molecules, and perhaps classical MHCI molecules in particular, are required for the developmental establishment of appropriate patterns of excitatory connectivity in the LGN (Table 1).

One central question raised by these studies is how MHCI molecules convey information in neurons. The MHCI proteins are primarily transmembrane proteins with small cytoplasmic domains. Outside of the CNS, MHCI molecules transduce adaptive immune signals by binding to a variety of cell surface immunoreceptors, including T cell receptors (TCRs) and NK cell receptors, expressed on the surface of circulating immune cells (Bromley *et al.*, 2001). At present, it is unknown whether MHCI uses the same or related receptors to transduce signals in the brain. In support of this possibility, mRNA encoding an immature, unrecombined form of the TCR β-subunit (TCRβ) has been detected in both the developing and adult brain (Syken & Shatz, 2003). However, although high levels of TCRβ mRNA were found in the mouse LGN during retinogeniculate remodeling, TCRβ protein has not yet been detected in the brain. Furthermore, RGC axons undergo normal remodeling in the LGNs of mice expressing a truncated, nonfunctional form of TCRβ, suggesting that MHCI does not affect retinogeniculate remodeling by binding to a TCRβ-containing receptor (Syken & Shatz, 2003). CD3ζ, a transmembrane component of the TCR, is also expressed in the brain and enriched in the developing LGN, and $CD3\zeta^{-/-}$ mice show a defect in retinogeniculate remodeling that is similar to that seen in MHCI-deficient $\beta2m^{-/-}TAP^{-/-}$ mice (Fig. 1C and Table 1) (Huh *et al.*, 2000; Baudouin *et al.*, 2008; Xu *et al.*, 2010). However, as no CD3ζ-containing receptor for MHCI has been identified in neurons, it remains to be determined whether the phenotypes in CD3ζ-deficient animals are attributable to changes in neuronal MHCI signaling or, instead, reflect MHCI-independent functions of CD3ζ.

In addition to the TCR, many other immunoceptors are capable of binding MHCI molecules to mediate immune responses, and some of these have recently been detected in neurons (Bryceson *et al.*, 2005; Syken *et al.*, 2006; Atwal *et al.*, 2008; Zohar *et al.*, 2008). For example, paired immunoglobulin-like receptor B (PirB), the mouse homolog of the human LILR receptor, is expressed in neurons (Syken *et al.*, 2006; Atwal *et al.*, 2008). However, there is no detectable expression of PirB mRNA in the LGN at the time of retinogeniculate remodeling, and RGC axon remodeling occurs normally in animals expressing a truncated, nonfunctional form of PirB (Syken *et al.*, 2006). Together, these results suggest that MHCI molecules are critical to the normal developmental remodeling of glutamatergic retinal afferents, but probably do not signal through the classical TCR or PirB, but instead may bind to an as yet unidentified receptor.

Molecules of the innate immune system have also been implicated in retinogeniculate remodeling. Outside of the CNS, activation of the complement cascade pathway plays a role in immune-mediated

TABLE 1. Activity-dependent structural plasticity phenotypes

	Mouse model studied	LGN remodeling	CF–PC synapse elimination	OD plasticity
Innate immune system				
Complement	Clq^{-}	Impaired[1]	ND	ND
	$C3^{-/-}$	Impaired[1]	ND	ND
Cbln1	$Cbln1^{-/-}$	ND	Impaired[2]	ND
Neuronal pentraxins	$NP1/2^{-/-}$	Impaired[3]	ND	ND
TNF-α	TNF-$\alpha^{-/-}$	ND	ND	Reduced[4]
Adaptive immune system				
MHCI	$\beta 2m^{-/-}TAP^{-/-}$	Impaired[5]	Normal[6,7]	Enhanced[8]
	$K^bD^{b-/-}$	Impaired[8]	Normal[6,7]	Enhanced[8]
CD3ζ	$CD3\zeta^{-/-}$	Impaired[5,9]	ND	ND
PirB	PirB-TM	Normal[10]	ND	Enhanced[10]

[1]Stevens *et al.* (2007); [2]Hirai *et al.* (2005); [3]Bjartmar *et al.* (2006); [4]Kaneko *et al.* (2008); [5]Huh *et al.* (2000); [6]Letellier *et al.* (2008); [7]McConnell *et al.* (2009); [8]Datwani *et al.* (2009); [9]Xu *et al.* (2010); [10]Syken *et al.* (2006). ND, not determined.

clearance of pathogens, infected cells, and cellular debris via phagocytosis. A recent screen implicated components of the complement cascade, namely C1q and its downstream target, C3, in retinogeniculate remodeling (Stevens *et al.*, 2007). C1q mRNA and protein are strongly expressed in the retina and LGN during remodeling, and C1q expression declines after remodeling is complete. Anterograde tracing experiments show that $C1q^{-/-}$ mice have impaired eye-specific segregation of RGC axons in the LGN that is similar in magnitude to that seen in MHCI-deficient animals (Huh *et al.*, 2000; Stevens *et al.*, 2007; Datwani *et al.*, 2009). $C3^{-/-}$ animals also show similar remodeling impairment in the LGN, suggesting that C1q could potentially affect synapse elimination by engaging all or part of the classical complement pathway. Electrophysiological recordings demonstrate that the failure of anatomical remodeling in C1q-deficient animals is accompanied by the retention of multiple functional glutamatergic RGC axon inputs onto LGN neurons.

The neuronal pentraxins (NPs) NP1 and NP2/Narp are members of a family of neuron-specific, innate immune-related proteins that have also been shown to play a role in visual system development. NP1/2-deficient mice show impaired eye-specific segregation of RGC afferents in the LGN at postnatal day (P) 10. Although this segregation defect resolves by P30, the spatial arrangement of the eye-specific territories remains abnormal even in adult NP1/2-deficient animals (Bjartmar *et al.*, 2006).

To understand when and how these different immune or immune-related molecules contribute to the activity-dependent remodeling of retinal projections, it is helpful to briefly review what is known about the remodeling process at a mechanistic level. Pioneering experiments using ocular TTX injections have demonstrated that RGC remodeling into eye-specific layers requires spontaneous retinal activity that occurs before the onset of vision (Shatz & Stryker, 1988; Sretavan *et al.*, 1988). Subsequent studies have shown that this spontaneous activity is organized into waves of action potentials that travel across the developing retina. In mice, retinal waves are cholinergic during the first postnatal week and become glutamatergic during the second postnatal week (Fig. 1B) [reviewed in Torborg & Feller (2005)]. How is patterned retinal activity translated into anatomical changes in retinal axons in the LGN? The prevailing model is that LGN synapses are eliminated or stabilized via Hebbian-like forms of synaptic plasticity. In this model, presynaptic and postsynaptic cells that fire together undergo a long-term potentiation (LTP)-like increase in synaptic strength that leads to anatomical stabilization, whereas inappropriate inputs fail to drive the postsynaptic cell to threshold, and the resulting asynchronous presynaptic and postsynaptic activation causes a long-term depression (LTD)-like decrease in synaptic strength that leads to anatomical withdrawal (Katz & Shatz, 1996). Consistent with this model, electrophysiological recordings demonstrate that, over the course of the remodeling process, retained RGC–LGN synapses are strengthened ~50-fold (Chen & Regehr, 2000). Despite the fact that $C1q^{-/-}$ LGN neurons remain functionally multi-innervated, one input is far stronger than the others, and is similar in strength to the single 'winning' input in wild-type (WT) animals. Thus, the selective strengthening and weakening of synaptic transmission at subsets of retinogeniculate synapses occurs normally in the absence of C1q, suggesting that C1q is important for later events in the remodeling process, such as the physical removal of weak synapses, perhaps analogously to their role in the immune system (Stevens *et al.*, 2007).

Although it is clear that neuronal activity is essential to RGC remodeling, at present the importance of specific characteristics of spontaneous retinal activity (e.g. wave frequency, wave duration, burst rate, and wave orientation) in instructing remodeling are the subject of active debate (Chalupa, 2009; Feller, 2009). The delay in eye-specific segregation and persistent impairment of eye-specific patterning in NP1/2-deficient animals closely mimics the phenotype seen in animals in which early retinal activity was blocked specifically during eye-specific segregation. This manipulation of early activity was accomplished either by infusion of TTX during the period of RGC remodeling (Huberman *et al.*, 2003) or application of the acetylcholine receptor agonist (+)-epibatidine, which leads to receptor desensitization and completely blocks spiking activity in the RGCs (Penn *et al.*, 1998). Despite the similarities between the wiring of activity-blocked and NP1/2-deficient LGNs, multi-electrode extracellular recordings showed that spontaneous waves of correlated retinal activity are present, and, in fact, the level of spontaneous activity is increased, in NP1/2-deficient retinas (Bjartmar *et al.*, 2006). Similarly, although RGC remodeling is impaired in mice lacking the β_2 subunit of the nicotinic acetylcholine receptor (β_2KO mice), cholinergic retinal waves are not entirely lost in these mutants, but rather the temporal characteristics of the waves in β_2KO mice differ significantly from those in the wild type (Sun *et al.*, 2008; Stafford *et al.*, 2009). Thus, it is likely that the altered temporal features of retinal waves seen in NP1/2-KO and β_2KO mice give rise to the impairment of retinogeniculate remodeling. Grossly normal retinal waves were observed in both MHCI-deficient and C1q-deficient animals (Huh *et al.*, 2000; Stevens *et al.*, 2007). Given the above results, however, it is possible that a closer look could reveal more subtle changes in the precise spatiotemporal properties of retinal waves that are sufficient to underlie the observed defects in eye-specific segregation in MHCI-deficient or C1q-deficient mutants. A recent study by Xu *et al.* (2010) showed that loss of the immunoreceptor component CD3ζ, which disrupts retinogeniculate remodeling (Fig. 1) (Huh *et al.*, 2000), is associated with normal retinal waves at P3, when they are primarily cholinergic, but a lower frequency of retinal waves at P10, when they are primarily glutamatergic (Fig. 1). These results suggest that some or all of the effects of CD3ζ on retinogeniculate remodeling could result from presynaptic changes in retinal activity, although they do not rule out the possibility that CD3ζ expressed in postsynaptic LGN cells affects remodeling. Importantly, however, these results do not provide any information regarding the source of the remodeling phenotype in MHCI-deficient animals. No CD3ζ-containing receptor for MHCI has

been identified in the brain to date, suggesting that the retinal changes in CD3ζ-deficient mice could reflect novel neuronal functions of CD3ζ that are MHCI-independent. It remains unknown whether similar or distinct changes in retinal activity are present or play any part in the remodeling phenotype in MHCI-deficient animals. One important step in answering this question will be to perform a detailed analysis of the spatiotemporal properties of retinal activity in MHCI-deficient animals at multiple time points during the first two postnatal weeks. In addition, electrophysiological recordings at RGC synapses in MHCI-deficient or NP1/2-deficient animals, akin to those performed in C1q-deficient animals, would help identify the precise step at which the remodeling process is impaired: during initial functional synapse strengthening and weakening, or during later anatomical expansion and retraction.

In building a model of how immune molecules act in synapse elimination, it may also be informative to consider the roles of these proteins outside of the CNS. The non-neuronal homologs of NP1/2, the short pentraxins (acute-phase and C-reactive proteins), mark cells for phagocytosis and degradation by binding to C1q and thereby activating the classical complement cascade (Garlanda *et al.*, 2005; Manfredi *et al.*, 2008). Given the data above, one possibility is that a similar pathway is engaged during the final stages of retinogeniculate remodeling. In this model, NP1/2 might mark extraneous axons, allowing the recruitment of C1q and activation of the complement pathway, and leading to the eventual removal of those axons by phagocytosis. In order to reconcile this model of structural remodeling with the Hebbian model of functional remodeling above, however, NP1/2 expression and/or C1q binding would need to be restricted to those axons that are targeted for elimination by a failure of concordant presynaptic and postsynaptic activation. The expression of NP2, like that of MHCI, is regulated by the level of activity (Tsui *et al.*, 1996; Huh *et al.*, 2000), but it is as yet unknown whether the expression of these molecules is differentially regulated by specific patterns of activity or presynaptic and postsynaptic synchrony. Ongoing studies to identify the precise features of retinal activity that instruct retinogeniculate remodeling will pave the way for subsequent experiments on whether these relevant features of activity locally regulate the expression of MHCI, NP1/2 or C1q/C3 in the developing retina or LGN.

Remodeling in the developing cerebellum

As in the RGC–LGN projections, synapse elimination is a key step in the development of a subset of excitatory synapses formed onto cerebellar Purkinje cells (PCs). Each PC is initially innervated by multiple climbing fiber (CF) axons of roughly equal synaptic weight, and during the course of development, one input strengthens while other inputs are weakened and eliminated, such that, by the end of the third postnatal week in mice, each PC receives inputs from only a single CF (Kano & Hashimoto, 2009). MHCI molecules are expressed in cerebellar PCs during remodeling, but experiments in both $\beta 2m^{-/-}TAP^{-/-}$ and $K^{b-/-}D^{b-/-}$ mice have shown that MHCI molecules are not required for normal CF–PC synapse elimination (Letellier *et al.*, 2008; McConnell *et al.*, 2009). Members of the CD3 family of molecules are also expressed in the cerebellum, and mice deficient for CD3ε display PCs with reduced dendritic arbor size and branching, although the elimination of CF axons occurs normally (Nakamura *et al.*, 2007). It is as yet unknown whether C1q or NP1/2 participate in cerebellar development. However, a brain-specific protein structurally related to both the C1q and tumor necrosis factor (TNF)-α families, Cbln1, is required for normal developmental elimination of excess CF synapses onto PCs (Hirai *et al.*, 2005 and Yuzaki, this issue). Thus, although immune or immune-related proteins are involved in axon pruning and synapse elimination during both visual system and cerebellar development, the particular molecular players differ between the two structures.

Establishment of synapse density among visual cortical neurons

Additional studies have explored the possible role of immune molecules in glutamatergic synaptogenesis. In mixed cultures of acutely dissociated visual cortical cells, the level of MHCI is inversely correlated with excitatory synapse density; applying RNA interference against *β2m*, which decreases cell surface MHCI expression, increases the number of glutamatergic synapses in this *in vitro* system. Conversely, overexpression of one particular MHCI in these cultures decreases the number of excitatory synapses (Wampler & McAllister, 2005; Glynn & McAllister, 2006; McAllister, 2007). The inverse correlation between synapse number and MHCI levels suggests that endogenous MHCI may limit synapse formation between cortical neurons *in vitro*, although it is also possible that MHCI promotes synapse elimination in this system, as it does in the developing LGN. In contrast to these results in cortical neurons, excitatory synapse density is similar in WT and MHCI-deficient ($\beta 2m^{-/-}TAP^{-/-}$) hippocampal neurons *in vitro* (Goddard *et al.*, 2007), indicating that, regardless of whether they reflect changes in synapse formation, stabilization, or elimination, the effects of MHCI on synapse number are specific for certain brain regions and/or cell types.

Immune molecules in the functional plasticity of mature glutamatergic synapses

Hippocampal synaptic plasticity and synaptic scaling

In addition to their role during development, several immune molecules have been implicated in short-term and/or long-term functional plasticity of glutamatergic synapses in different regions of the brain, including the hippocampus, cerebral cortex, and cerebellum (Table 2). Synaptic plasticity is fundamental property of CNS synapses that contributes to changes in brain circuitry over multiple time scales and is thought to underlie some forms of learning and memory. In the hippocampus, the cellular and molecular mechanisms of synaptic plasticity have been most extensively studied at the glutamatergic synapses formed between CA3/Schaeffer collateral axons and CA1 pyramidal cell dendrites (Shepherd & Huganir, 2007; Citri & Malenka, 2008). Synaptic plasticity at CA3–CA1 synapses is bidirectional, in that synaptic efficacy can be either strengthened (LTP) or weakened (LTD), depending on the patterns of synaptic activity. At this synapse, postsynaptic ionotropic glutamate receptors (GluRs)–primarily AMPA receptors (AMPARs) and NMDA receptors (NMDARs) – are central players in the induction and expression of functional synaptic plasticity. In current models, the magnitude and/or kinetics of the integrated NMDAR response determines the sign of the resulting plasticity: owing to the temporal summation of NMDAR activation, high-frequency stimulation (HFS) protocols induce large increases in intracellular Ca^{2+}, insertion of AMPARs into the synapse, activation of kinases, and LTP, whereas low-frequency stimulation (LFS) protocols induce more modest increases in intracellular Ca^{2+}, activation of phosphatases, removal of AMPARs from the synapse, and LTD (Fig. 3A and B) (for details, see reviews by Kennedy & Ehlers, 2006; Shepherd & Huganir, 2007; Citri & Malenka, 2008; Choquet, 2010).

TABLE 2. Activity-dependent synaptic plasticity phenotypes

	Mouse model studied	Long-term synaptic plasticity	Homeostatic plasticity
Innate immune system			
Cbln1	Cbln1$^{-/-}$	Abolished cerebellar LTD[1]	ND
Neuronal pentraxins	NP1/2$^{-/-}$	Normal hippocampal LTP Normal hippocampal LTD[2]	ND
TNF-α	TNF-α$^{-/-}$	Normal hippocampal LTP Normal hippocampal LTD[3]	Impaired[3]
	TNFR$^{-/-}$	Normal hippocampal LTP Normal hippocampal LTD[3] *but* impaired hippocampal LTD[4]	ND
Adaptive immune system			
MHCI	β2m$^{-/-}$TAP$^{-/-}$	Enhanced hippocampal LTP Abolished hippocampal LTD[5]	Impaired[6]
	K^{b}D$^{b-/-}$	Enhanced cerebellar LTD[7]	ND
CD3ζ	CD3ζ$^{-/-}$	Enhanced hippocampal LTP Abolished hippocampal LTD[5,8]	ND
DAP12/KARAP	DAP12^{KI}	Enhanced hippocampal LTP[9]	ND

[1]Hirai *et al.* (2005); [2]Bjartmar *et al.* (2006); [3]Stellwagen & Malenka (2006); [4]Albensi & Mattson (2000); [5]Huh *et al.* (2000); [6]Goddard *et al.* (2007); [7]McConnell *et al.* (2009); [8]Barco *et al.* (2005); [9]Roumier *et al.* (2004). ND, not determined.

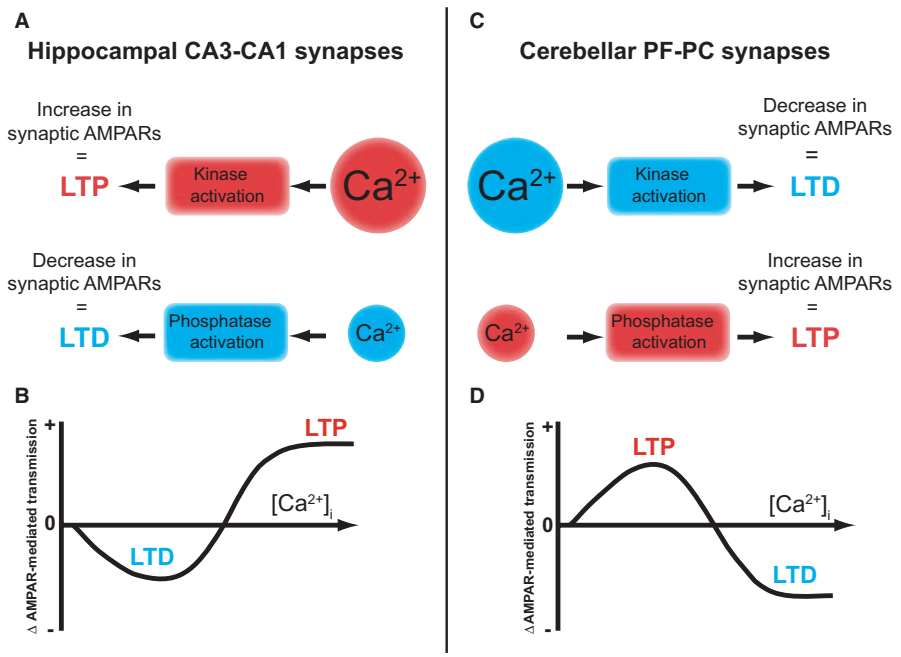

FIG. 3. Comparison of cellular mechanisms of synaptic plasticity at hippocampal CA3–CA1 synapses (left) and cerebellar PF–PC synapses (right). LTP pathways are shown in red and LTD pathways are shown in blue. (A) At hippocampal synapses (left), a large increase in intracellular calcium concentration ($[Ca^{2+}]_i$) induces activation of kinases, an increase in synaptic AMPARs, and LTP, whereas a more modest increase in $[Ca^{2+}]_i$ induces activation of phosphatases, a decrease in synaptic AMPARs, and LTD. (B) Schematic representation of the Bienenstock, Cooper, and Munro (BCM) model (Bear *et al.*, 1987) of synaptic plasticity at CA3–CA1 hippocampal synapses. At these synapses, the calcium threshold is higher for LTP than for LTD. (C) At cerebellar PF–PC synapses (right), in contrast, a large increase in $[Ca^{2+}]_i$ induces activation of kinases, a decrease in synaptic AMPARs, and LTD, whereas a more modest increase in $[Ca^{2+}]_i$ induces activation of phosphatases, an increase in synaptic AMPARs, and LTP. (D) Schematic representation of a model of the calcium-dependent threshold for synaptic plasticity at PF–PC cerebellar synapses. At these synapses, in contrast to hippocampal CA3–CA1 synapses, the calcium threshold amplitude is higher for LTD than for LTP (adapted with permission from Jorntell & Hansel, 2006).

MHCI mRNAs are expressed in hippocampal neurons, and MHCI proteins colocalize with a postsynaptic marker of excitatory synapses (PSD95) in hippocampal neurons in culture (Corriveau *et al.*, 1998; Huh *et al.*, 2000; Goddard *et al.*, 2007), indicating that MHCI is expressed in a pattern consistent with a role in regulating the function or plasticity of hippocampal glutamatergic synapses. Indeed, studies in MHCI-deficient (β2m$^{-/-}$TAP$^{-/-}$) hippocampus show that although the amplitude of glutamatergic excitatory postsynaptic currents (EPSCs) is normal, MHCI is required for the normal expression of NMDAR-dependent bidirectional synaptic plasticity in this system. At CA3–CA1 synapses, HFS induces LTP in β2m$^{-/-}$TAP$^{-/-}$ animals that is roughly twice as large as that seen in WT animals. In contrast, LFS fails to produce the expected LTD in β2m$^{-/-}$TAP$^{-/-}$ animals (Fig. 2A–C) (Huh *et al.*, 2000). Thus, endogenous MHCI molecules may limit the extent of LTP and either promote or permit LTD in WT animals.

At CA3–CA1 synapses, LTP can be broadly divided into two mechanistically distinct periods: an early phase [early LTP (E-LTP)], which does not require protein synthesis and lasts from minutes to a few hours, and a late phase [late LTP (L-LTP)], beginning approximately 3 h after stimulation, which requires protein synthesis and lasts from hours to days (Huang *et al.*, 1996). Although the above

studies demonstrate that MHCI is required for normal E-LTP, no studies to date have directly tested whether MHCI is required for L-LTP. However, indirect evidence suggests that MHCI may play a role in L-LTP. In mice expressing a constitutively active form of the transcription factor cAMP response element-binding protein (CREB) (VP16-CREB mice) in CA1 cells, L-LTP induction is facilitated, such that a stimulus that only elicits E-LTP in wild-type animals induces L-LTP in VP16-CREB mice (Barco *et al.*, 2002). The interpretation is that in VP16-CREB mice, genes that are normally required for the expression of L-LTP are constitutively upregulated. A subtractive gene expression-profiling screen conducted in the hippocampus of VP16-CREB mice revealed a significant and specific increase in only a handful of genes, including several MHCI genes, consistent with a role for MHCI genes in the induction or expression of L-LTP (Barco *et al.*, 2005). In the future, it will be important to determine how, on a cellular and molecular level, MHCI molecules affect hippocampal synaptic plasticity on a given time scale.

Similar hippocampal synaptic plasticity phenotypes are present in animals deficient for three different proteins that are immunoreceptors or components of immunoreceptors known to bind MHCI outside of the CNS, namely CD3ζ, DAP12/KARAP, and PirB (Tomasello *et al.*, 1998; Call & Wucherpfennig, 2004; Takai, 2005). CD3ζ is expressed in hippocampal neurons, and in animals lacking CD3ζ ($CD3\zeta^{-/-}$), CA3–CA1 LTP is enhanced and LTD is absent (Fig. 2B and C) (Huh *et al.*, 2000; Barco *et al.*, 2005). In animals lacking DAP12, pairing-induced LTP is enhanced at CA3–CA1 synapses, although HFS-induced LTP and LFS-induced LTD have not yet been examined in these mutants (Roumier *et al.*, 2004). However, pharmacological experiments have shown that the enhanced LTP in DAP12-deficient mice is, in part, attributable to the recruitment of an NMDAR-independent form of LTP. This is in contrast to the enhancement of LTP in MHCI-deficient mice, which is completely blocked in the presence of the NMDAR antagonist APV (2-amino-5-phosphonovaleric acid) (Huh *et al.*, 2000). Like MHCI-deficient animals, PirB-deficient mice show enhanced HFS-induced LTP, raising the possibility that the LTP-limiting effects of MHCI might be mediated by binding to PirB in hippocampal neurons (Djurisic *et al.*, 2007). Ly49 and KIR-like immunoreceptors are also known to bind MHCI outside of the CNS, and are expressed in hippocampal neurons (Bryceson *et al.*, 2005; Zohar *et al.*, 2008), but the role of these receptors in CA3–CA1 synaptic plasticity has not yet been evaluated. Further experiments will be needed to unequivocally determine which immunoreceptors (or other, non-immune, molecules) mediate the effects of MHCI on hippocampal synaptic plasticity. Outside of the CNS, immunoreceptors can bind to MHCI either in *cis*, that is, on the same cell, or in *trans*, that is, on another cell (Back *et al.*, 2009), and it is as yet unknown whether MHCI engages immunoreceptors in either configuration in the hippocampus or other brain regions. Given the diversity of cell types in the brain, it will be of particular interest to determine whether MHCI and immunoreceptors affect synaptic plasticity through cell-autonomous, neuron–neuron or neuron–glial signaling events. For example, DAP12 is expressed exclusively in microglia perinatally, and is required in microglia, but not neurons, for normal synaptic plasticity (Roumier *et al.*, 2004), indicating that the effects of this particular immunoreceptor involve some form of direct or indirect glial–neuronal interaction.

Cytokines are small, secreted molecules involved in innate immunity that can act as either pro-inflammatory or anti-inflammatory immunomodulators. In the CNS, cytokines are mainly produced by microglia, but can also be produced by astrocytes and neurons (Bailey *et al.*, 2006). Several pro-inflammatory cytokines have been implicated as mediators or modulators of hippocampal synaptic plasticity (Jankowsky & Patterson, 1999; Deverman & Patterson, 2009). Bath application of either of the pro-inflammatory cytokines interleukin (IL)-6 or IL-1β inhibits hippocampal LTP, and induction of LTP increases the levels of IL-6 and IL-1β in the hippocampus (Jankowsky & Patterson, 1999), suggesting that these cytokines could contribute to a negative feedback loop that prevents runaway potentiation. Conflicting results have been published regarding the role of the pro-inflammatory cytokine TNF-α in LTP. Initial studies found that bath application of TNF-α inhibits LTP, and that LFS-induced LTD is absent in TNF-α receptor (TNFR)-deficient animals (Albensi & Mattson, 2000). However, more recent studies challenged those findings by showing that bath application of TNF-α does not affect either LTP or LTD, and that CA3–CA1 LTP and LTD are normal in both TNF-α-deficient and TNFR-deficient animals (Stellwagen & Malenka, 2006). This apparent discrepancy may result, in part, from differences in the amount of TNF-α used as well as differences in the way in which LTP and LTD were induced and measured. Further studies are needed to reconcile these findings.

Independent of its debated role in long-term synaptic plasticity, TNF-α has been shown to modulate the intracellular trafficking of AMPA-type GluRs in mammalian neurons (Beattie *et al.*, 2002; Stellwagen *et al.*, 2005; Stellwagen & Malenka, 2006). Acute application of TNF-α to hippocampal neurons in culture induces a dose-dependent increase in cell surface expression of synaptic AMPARs lacking the GluR2 subunit. Acute TNF-α application also induces a concurrent increase in the frequency and amplitude of miniature EPSCs (mEPSCs), indicating that the newly inserted AMPARs are probably functional. Conversely, application of a recombinant soluble form of TNFR1 (sTNFR), which acts as a dominant negative for TNF-α signaling, decreases the level of cell surface AMPARs. Consistent results were obtained in hippocampal slices, where brief bath application of TNF-α increased the AMPA/NMDA ratio, and bath application of sTNFR decreased the AMPA/NMDA ratio. The effects of TNF-α on GluR trafficking are specific for AMPARs, as acute application of TNF-α does not affect the synaptic levels of NMDARs in hippocampal neurons in culture (Beattie *et al.*, 2002). The effects of TNF-α on AMPAR trafficking are not common to all pro-inflammatory cytokines, as acute treatment of hippocampal neurons in culture with the pro-inflammatory cytokines IL-6 and IL-10 does not affect surface levels of AMPARs (Stellwagen *et al.*, 2005).

Whereas acute forms of long-term synaptic plasticity such as LTP and LTD involve changes in synaptic efficacy over several hours in response to brief, local patterned activity, synaptic scaling (or homeostatic plasticity) involves changes in synaptic efficacy in response to prolonged, global changes in the overall level of synaptic activity. Initially identified and studied in cortical neurons, synaptic scaling has also been studied at hippocampal synapses (Turrigiano, 2008). In hippocampal neurons in culture, chronic activity blockade (48 h of TTX treatment) induces an increase in cell surface AMPARs that is accompanied by an increase in mEPSC frequency and amplitude (i.e. a scaling up of synaptic responses). A key observation is that acute application of conditioned media from chronically TTX-treated cultures is sufficient to transmit a similar increase in AMPAR cell surface expression and mEPSC frequency in hippocampal neurons, indicating that a soluble factor is responsible. Chronic activity blockade increases TNF-α production by glia cells, and acute application of TNF-α enhances cell surface AMPARs and increases mEPSC frequency and amplitude, suggesting that TNF-α is a candidate soluble mediator of synaptic scaling (Beattie *et al.*, 2002; Stellwagen & Malenka, 2006). Indeed, addition of sTNFR to the conditioned media from TTX-treated cultures prevents its effects on AMPAR trafficking and enhancement of mEPSC amplitude. Together, these results suggest a model in which chronic activity blockade leads

to the release of TNF-α, which increases the levels of synaptic AMPARs and thereby induces synaptic scaling (Stellwagen & Malenka, 2006).

How does TNF-α mediate its effects on glutamatergic synapses at the cellular and molecular levels? Recently, a family of cell adhesion molecules, the β_3 integrins, has been shown to also be involved in hippocampal synaptic scaling. Chronic TTX treatment induces an increase in cell surface expression of β_3 integrins in wild-type hippocampal neurons in culture, and synaptic scaling in response to activity blockade is absent in β_3 integrin-deficient hippocampal neurons. Moreover, acute (20 min) TNF-α application induces an increase in β_3 integrin cell surface expression, suggesting that TNF-α could affect synaptic scaling, in part, by regulating the expression of β_3 integrins (Cingolani *et al.*, 2008). In future experiments, it will be important to attempt to block TNF-α effects on scaling by blocking β_3 integrins, and the converse.

In addition to TFN-α, another family of immune molecules, members of the MHCI family, have been implicated in synaptic scaling. Chronic activity blockade in WT hippocampal neurons causes synaptic scaling that is reflected in an increase in mEPSC amplitude and frequency, as well as an increase in the expression of specific presynaptic and postsynaptic markers (synapsin and PSD95, respectively). However, in MHCI-deficient neurons, chronic activity blockade fails to induce scaling-up of mEPSC amplitude or frequency or expression of these markers (Goddard *et al.*, 2007). It is important to note that in these MHCI-deficient neurons, presynaptic parameters (mEPSC frequency and size of synapsin-immunoreactive or VGluT1/2-immunoreactive puncta) are already scaled up in the basal state, so it is not clear whether the failure of presynaptic scaling is a consequence of saturation of presynaptic scaling or impairment of presynaptic scaling mechanisms. However, the failure of postsynaptic scaling mEPSC amplitude and PSD95 immunoreactivity more clearly reflects a requirement for MHCI in the postsynaptic scaling response to chronic activity blockade, as these parameters are unchanged in the basal state in MHCI-deficient neurons. Chronic activity blockade reduces MHCI expression in the developing cat LGN and in mouse hippocampal neurons in culture (Corriveau *et al.*, 1998; Goddard *et al.*, 2007). This suggests a model in which activity-dependent changes in MHCI expression translate changes in global activity into functional and biochemical hallmarks of synaptic scaling.

It is also possible that the data implicating both TNF-α and MHCI in synaptic scaling reveal separate steps in a single pathway. Chronic activity blockade increases the amount of TNF-α produced by glia cells (Stellwagen & Malenka, 2006), and TNF-α can decrease the expression of MHCI and CD3ζ in the developing hippocampus (Sourial-Bassillious *et al.*, 2006). Therefore, it is possible that TNF-α released in response to activity blockade reduces neuronal MHCI levels, which in turn leads to scaling up of excitatory synaptic transmission. Further experiments will be needed to determine whether TNF-α regulates MHCI expression during synaptic scaling at hippocampal synapses, and whether changes in MHCI levels are required for the effects of TNF-α on synaptic transmission. Regardless of the presence or absence of these direct mechanistic links, it is intriguing that, among the very small number of candidate molecules that have been implicated in cellular mechanisms of synaptic scaling at glutamatergic synapes, two are immune molecules.

Cerebellar synaptic plasticity

In addition to their role in hippocampal synaptic plasticity, immune molecules have been implicated in synaptic plasticity in the cerebellum. In the adult cerebellum, PCs receive numerous weak glutamatergic inputs from granule cell axons [the parallel fibers (PFs)] and a single strong glutamatergic input from axons arising from the inferior olive (CFs). As in the hippocampus, bidirectional long-term synaptic plasticity in the form of LTP and LTD can be induced at PF–PC synapses. Although cerebellar PF–PC LTP, like hippocampal CA3–CA1 LTP, is associated with an increase in synaptic AMPAR levels, and PF–PC LTD, like hippocampal LTD, is associated with a decrease in AMPAR levels, the cellular and molecular events leading to these changes in AMPARs in the cerebellum are, in many ways, opposite to those occurring during plasticity at hippocampal CA3–CA1 synapses (Fig. 3) (Jorntell & Hansel, 2006). Simultaneous stimulation (pairing) of PFs and CFs causes a massive heterosynaptic Ca^{2+} transient in the PCs, followed by the activation of kinases and the subsequent removal of postsynaptic AMPARs and LTD of the PF–PC synapse. This is in contrast to the situation in the hippocampus, where stimulation patterns that cause a large Ca^{2+} transient in CA1 cells and activation of kinases lead instead to insertion of AMPARs and LTP. In the cerebellum, stimulation of PFs alone leads to a smaller Ca^{2+} transient in the PCs, the activation of phosphatases, the insertion of postsynaptic AMPARs, and LTP. In the hippocampus, stimulation patterns that produce small Ca^{2+} transients lead to activation of phosphatases and LTD [see Jorntell & Hansel (2006) for a detailed review].

One common feature that unites functional plasticity of glutamatergic synapses in the hippocampus and in the cerebellum is a role for postsynaptically expressed MHCI molecules. Classical MHCI (K^b and D^b) mRNAs and proteins are expressed in adult PCs, and in mice lacking classical MHCI molecules ($K^{b-/-}D^{b-/-}$ mice), PF–PC LTD induced by co-stimulation of PFs and CFs is altered. In $K^{b-/-}D^{b-/-}$ mice, PF–PC synapses show a lower threshold for the induction of LTD by this protocol (Fig. 2D and E), and a second induction protocol that normally leads to modest LTD at WT PF–PC synapses induces a larger LTD in $K^{b-/-}D^{b-/-}$ PF–PC synapses (McConnell *et al.*, 2009). Although the threshold for depression of PF–PC synapses is reduced in the absence of classical MHCI proteins, potentiation of PF–PC synapses has not been studied in these animals. Thus, in $K^{b-/-}D^{b-/-}$ mice, long-term synaptic plasticity at PF–PC synapses is shifted in favor of depression. This is in contrast to the shift in favor of potentiation seen at hippocampal synapses of MHCI-deficient $\beta 2m^{-/-}TAP^{-/-}$ mice. However, both shifts are in favor of the form of plasticity that is normally associated with a larger postsynaptic Ca^{2+} transient and activation of kinases: in the hippocampus, potentiation, and in the cerebellum, depression (Fig. 3). Thus, it is possible that, despite the fact that loss of MHCI promotes LTP in one system but LTD in the other, MHCI could play a similar mechanistic role in both hippocampal and cerebellar long-term plasticity.

LTD at PF–PC synapses is thought to underlie some forms of motor learning, and impairment in PF LTD has been correlated with poor motor performance (Ito, 2000; Jorntell & Hansel, 2006). Lending further support to this model, the reduced threshold for PF–PC LTD in $K^{b-/-}D^{b-/-}$ mice is associated with improved motor learning: in the Rotarod behavioral test, $K^{b-/-}D^{b-/-}$ animals performed better than WT animals, and retained the acquired skills longer (McConnell *et al.*, 2009).

How do MHCI molecules affect PF–PC LTD and motor learning? Several immunoreceptors (PirB and KIR-like) and immunoreceptor components (CD3ζ and CD3ε) have been detected in the adult cerebellum (Corriveau *et al.*, 1998; Bryceson *et al.*, 2005; Syken *et al.*, 2006; Nakamura *et al.*, 2007). However, PirB-deficient and CD3ζ-deficient animals both display normal motor learning in the

Rotarod test (McConnell *et al.*, 2009), indicating that MHCI probably does not affect motor learning through these receptors. CD3ε-deficient animals show an increase in paired-pulse facilitation at PF–PC synapses, and a similar increase is seen in $K^{b-/-}D^{b-/-}$ mice (Nakamura *et al.*, 2007; McConnell *et al.*, 2009). However, CD3ε-deficient animals show poor learning performance on the Rotarod, at least at high rotational speeds (Nakamura *et al.*, 2007), suggesting that endogenous MHCI does not limit motor learning through interaction with a CD3ε-containing receptor. Thus, the identities of the proteins that mediate MHCI signaling in the cerebellum remain unknown.

Ocular dominance plasticity in the visual cortex

The postnatal development and modification of the mammalian visual cortex is a classic model in which to investigate the cellular and molecular mechanisms underlying experience-dependent plasticity *in vivo* (Smith *et al.*, 2009; Tropea *et al.*, 2009). Following the establishment of mature vision, monocular deprivation (MD) during a critical period can shift the relative contribution of inputs from the two eyes to visual cortical neuron responses [ocular dominance (OD)] in favor of the non-deprived eye. OD plasticity in response to changes in visual experience is a feature of early postnatal development in many mammals with binocular vision. In the mouse, deprivation-induced OD plasticity has been shown to result from rapid weakening of cortical responses to the deprived eye, followed by delayed strengthening of responses to the open eye (Frenkel & Bear, 2004). At the cellular and molecular level, OD plasticity is thought to be driven by a combination of synaptic plasticity and synaptic scaling at glutamatergic synapses between layer 2/3 and layer 4 cortical neurons. In particular, the rapid weakening of the deprived-eye responses is thought to be driven by LTD-like mechanisms, whereas the delayed strengthening of the open-eye responses is thought to be driven by a combination of LTP-like mechanisms and synaptic scaling (Smith *et al.*, 2009; Tropea *et al.*, 2009).

Among the few molecules identified to date that play a role in OD plasticity, several are immune molecules, and loss of these molecules is generally associated with enhancement of OD plasticity or prolongation of the developmental window in which plasticity can be induced. Mice lacking the MHCI immunoreceptor PirB have enhanced OD plasticity in response to MD, both at the structural level – as measured by the expansion of territory occupied by LGN axons from the open eye – and at the functional level – as measured by the expansion of Arc mRNA expression within layer 4 following monocular visual experience (Table 1). Loss of PirB also extends the time window within which significant OD plasticity may be induced (Syken *et al.*, 2006). A recent study found that loss of MHCI (in either $K^{b-/-}D^{b-/-}$ or $\beta2m^{-/-}TAP^{-/-}$ animals), like loss of PirB, enhances OD plasticity after MD at both the structural and functional levels (Datwani *et al.*, 2009). Thus, it is possible that endogenous MHCI, through direct or indirect interactions with PirB, normally limits the extent of OD plasticity and restricts it to specific developmental time periods. In contrast, TNF-α-deficient animals show reduced OD plasticity in response to MD during the critical period (Table 1). In TNF-α-deficient animals, the drop in OD plasticity is associated with selective impairment in the strengthening of the open-eye responses, but no change in the weakening of the deprived-eye responses (Kaneko *et al.*, 2008). Thus, TNF-α signaling may be specifically involved in the scaling that drives strengthening of the open-eye responses during OD plasticity in WT animals.

Conclusions

Many studies of neural–immune interactions have focused on elucidating the role of immune molecules in autoimmunity and other pathological events contributing to neurological dysfunction. However, recent results have shown that some molecules that were originally identified in the immune system also have novel, non-immune functions in the CNS. Specific molecules with roles in either the innate or adaptive immune responses also participate in the formation and plasticity of glutamatergic circuitry during development and adulthood. A number of outstanding questions remain to be explored regarding the expression and function of immune proteins in neurons. Although, in many cases, the regulation of their expression has been well characterized in non-neuronal cell types, almost nothing is known about the factors that regulate their levels or distribution during brain development, in the healthy adult brain, or in neuronal disease states. For example, expression of many immune molecules in the periphery is strongly influenced by pathogens as part of the inflammatory response. However, the regulation of neuronal immune molecules by brain inflammation or inflammation of non-neuronal tissues is less well understood. This is of particular interest given the evidence, some of which is reviewed here, that specific immune molecules can regulate the establishment and function of glutamatergic synapses. Inflammatory events have been associated with many CNS disorders that involve disruption of glutamatergic transmission, including major depression, epilepsy, schizophrenia, and autism spectrum disorder (Vezzani *et al.*, 2008; Miller *et al.*, 2009; Patterson, 2009). Changes in the expression of immune molecules could be a mechanistic link between immune signaling and abnormal development, transmission, and plasticity of glutamatergic synapses. Although more work needs to be done to fully describe the cellular and molecular pathways involved, the studies reviewed here identify immune molecules as novel regulators of glutamatergic synapses, and add a new dimension to our understanding of neural–immune interactions in the healthy and diseased brain.

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Abbreviations

AMPAR, AMPA receptor; APV, 2-amino-5-phosphonovaleric acid; CF, climbing fiber; CNS, central nervous system; CREB, cAMP response element-binding protein; E-LTP, early long-term potentiation; EPSC, excitatory postsynaptic current; GluR, glutamate receptor; HFS, high-frequency stimulation; IL, interleukin; KO, knockout; LFS, low-frequency stimulation; LGN, lateral geniculate nucleus; L-LTP, late long-term potentiation; LTD, long-term depression; LTP, long-term potentiation; MD, monocular deprivation; mEPSC, miniature excitatory postsynaptic current; MHCI, major histocompatibility complex class I; NMDAR, NMDA receptor; NP, neuronal pentraxin; OD, ocular dominance; P, postnatal day; PC, Purkinje cell; PF, parallel fiber; PirB, paired immunoglobulin-like receptor B; RGC, retinal ganglion cell; sTNFR, soluble tumor necrosis factor-α receptor; TAP1, transporter associated with antigen processing; TCR, T cell receptor; TCRβ, T cell receptor β-subunit; TNF, tumor necrosis factor; TNFR, tumor necrosis factor-α receptor; TTX, tetrodotoxin; WT, wild-type; β2M, β_2-microglobulin.

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