Neuronal plasticity and cellular immunity: shared molecular mechanisms

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It is becoming evident that neurons express an unusual number of molecules that were originally thought to be specific to immune functions. One such molecule, class I major histocompatibility complex, is required in the activity-dependent refinement and plasticity of connections in the developing and adult central nervous system, demonstrating that molecules can perform critical roles in both systems. Recent studies reveal striking parallels between cellular signaling mechanisms in the immune and nervous systems that may provide unexpected insights into the development, function, and diseases of both systems.

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Abbreviations

ALS	amyotrophic lateral sclerosis
β2-m	beta 2-microglobulin
CD3ζ	cluster of differentiation 3, zeta chain
CNS	central nervous system
ERK	extracellular signal-regulated kinase
Grb2	growth factor receptor-bound protein-2
IFN-γ	interferon-gamma
IP_3	1,4,5 inositol trisphosphate
JNK	c-Jun NH_2-terminal kinase
LGN	lateral geniculate nucleus
LTD	long-term depression
LTP	long-term potentiation
MHCI	major histocompatibility complex, class I
NF-AT	nuclear factor of activated T cells
NF-κB	nuclear factor-kappa B
NHEJ	non-homologous end joining
NK	natural killer
NMDA	*N*-methyl D-aspartate
RAG-1,2	recombination activating gene -1,-2
TAP1	transporter associated with antigen processing 1
TCR	T-cell antigen receptor
TNFα	tumor necrosis factor-alpha

Introduction

It may prove to be the rule, not the exception, that proteins perform multiple functions within and between systems. Recent studies have uncovered novel functions for a wide range of neuronal molecules (e.g. [1,2]). Given such findings, it is interesting to note the magnitude of the molecular repertoire shared by the nervous and immune systems, which may reflect novel neuronal functions for immune molecules in the brain, and vice versa. Alternatively, the molecular overlap may reflect sites of molecular crosstalk or functional parallels between these seemingly disparate biological systems. Rather than providing an exhaustive review of immune molecules expressed in neurons, we illustrate commonalities between these systems by summarizing the role of one specific immune gene family, the major histocompatibility complex, class I (MHCI), in activity-dependent plasticity of synapses within the mammalian central nervous system (CNS). We then briefly discuss molecules involved in MHCI signaling in the immune system that are also involved in brain development and plasticity, and thus represent compelling candidate mediators of MHCI's function in the CNS.

MHCI in neurons

Identification of MHCI in a blind screen

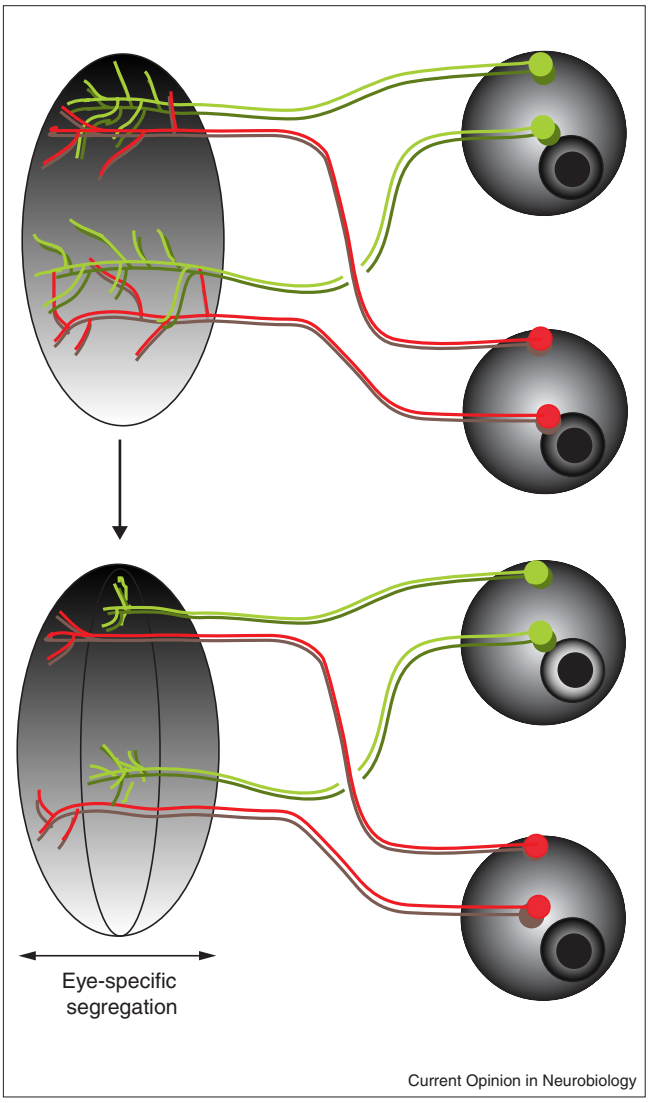
MHCI was initially discovered in the brain through an unbiased differential screen to identify molecules required for activity-dependent refinement of connections during visual system development. Although adult visual projections are strictly organized, this level of anatomical and functional precision is not present initially. Retinal ganglion cell axons send a coarse projection to their primary target in the thalamus, the lateral geniculate nucleus (LGN), which is later refined such that inputs are strictly segregated into eye-specific laminae (reviewed in [3]; Figure 1). Many long-term synaptic changes, such as those thought to underlie activity-dependent synaptic refinement, require new gene expression (e.g. [4]). Because segregation is activity-dependent — it is disrupted by blockade of endogenously-generated action potentials [5] — it was reasoned that genes that control afferent segregation in the LGN should also be regulated by endogenous activity.

Therefore, an unbiased differential screen was conducted to identify genes regulated by the blockade of endogenous action potential activity during eye-specific segregation. The most promising candidate from this screen was found to be expressed at times and places of activity-dependent structural and functional plasticity, including early postnatal LGN and adult hippocampus. Unexpectedly, this candidate was found to be an MHCI gene. Additional experiments revealed that mRNAs encoding beta 2-microglobulin ([β2-m] a cosubunit of MHCI) and CD3ζ (a protein complexed to many receptors for MHCI) were also expressed in neurons ([6]; Figure 2).

Requirement for MHCI in normal activity-dependent plasticity

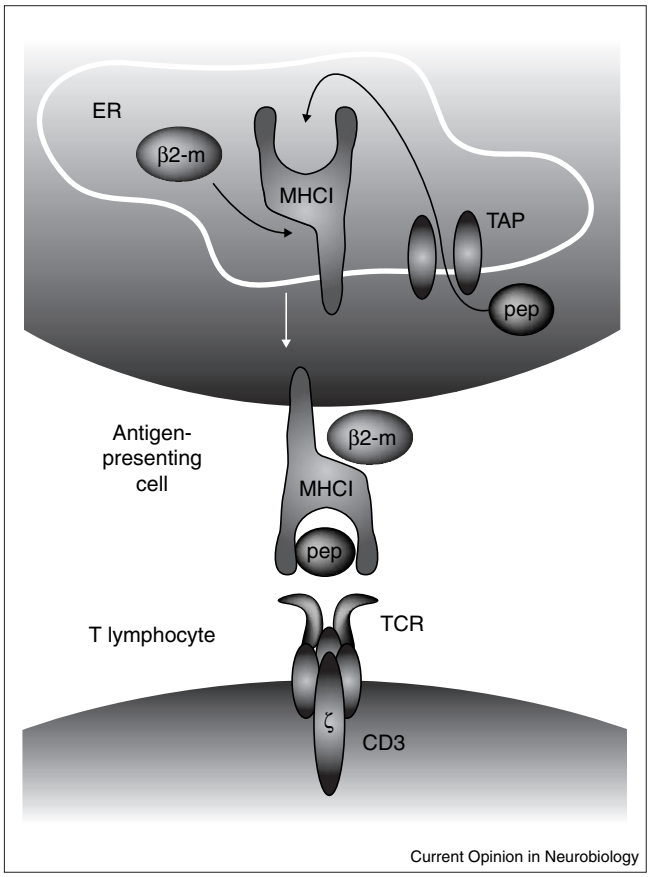
To test the potential role of MHCI in brain plasticity, a subsequent study [7••] examined well-characterized examples of structural and functional activity-dependent plasticity in mice genetically deficient for MHCI signaling, Specifically, mice lacking molecules required for either proper cell-surface MHCI expression (β2-m or the transporter associated with antigen processing 1 [TAP1]) or for

Figure 1



Refinement of mammalian retinal projections driven by spontaneous activity. Initially overlapping retinal ganglion cell projections (top) segregate into eye-specific layers within the LGN (bottom) through a process that requires spontaneous activity arising in the retinas.

Figure 2



MHCI in the immune system. TAP1 in the endoplasmic reticulum (ER) is required for loading of peptide (pep) onto MHCI. Both peptide and the MHCI cosubunit β2-m are required for cell surface expression of most MHCI. One receptor for MHCI, the TCR, is expressed on T cells and interacts with peptide-presenting MHCI on antigen-presenting cells. TCR signaling is initiated via the ζ subunit of the CD3 complex, which associates with the TCR.

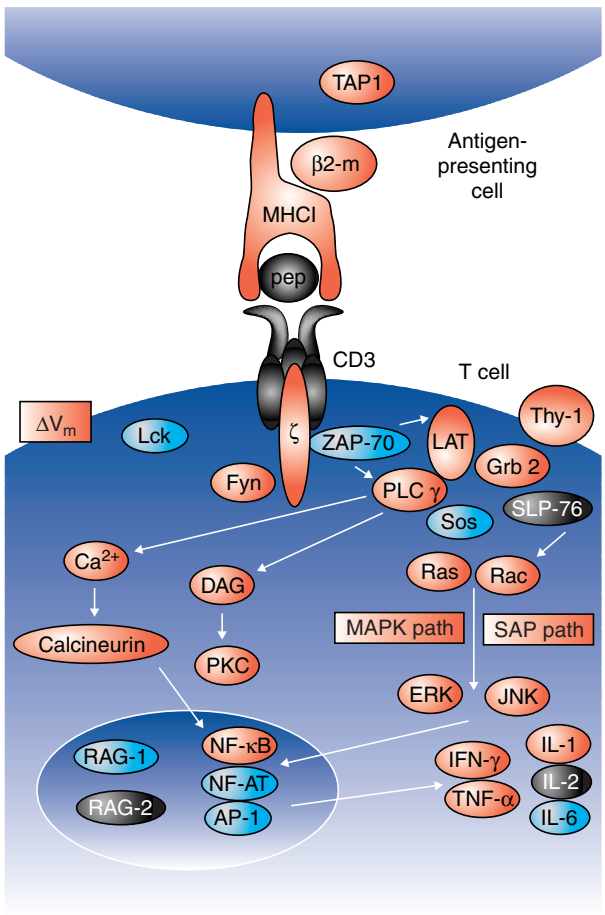
most MHCI receptor-mediated signaling (CD3ζ; Figure 2) were tested. In all these mutant mice, the normal segregation of retinal afferents in the LGN was disrupted, a phenotype consistent with the manner in which MHCI was originally identified in the CNS. Although mutant retinal projections were located approximately normally within the LGN, the area occupied by projections from the ipsilateral eye was significantly expanded, suggesting a specific deficit in the final events of synaptic and structural refinement. This is consistent with the fact that coarse positioning of retinal afferents is established through molecular cues, which are thought to be activity-independent [8].

The fine-tuning of neural connectivity is thought to follow changes in synaptic strength, with long-term depression (LTD) preceding withdrawal of connections, and long-term potentiation (LTP) preceding stabilization of connections (reviewed in [9–11]). Upon examining synaptic plasticity in adult hippocampus, LTP was enhanced and LTD was absent in all mutant mice. Therefore, if MHCI-mediated LTD is necessary for the removal of inappropriate connections in the LGN, the observed disruption of refinement could arise from the lack of synaptic depression in mice deficient for MHCI signaling.

Neural expression of MHCI

MHCI molecules have been best characterized in the immune system, where one of their primary functions is to present antigenic peptides to cytotoxic T lymphocytes (Figure 2). The finding that MHCI is also necessary for some forms of neuronal plasticity is surprising for two reasons: there is no known role for MHCI in the development or function of the brain and even the presence of MHCI in neurons has been hotly debated [12]. The brain has long been considered an ‘immune privileged’ site, a property

Figure 3



Simplified summary of signaling pathways downstream of MHCI–TCR ligation, as well as ligation of most other MHCI receptors, in the immune system. Molecules depicted in black are not known to be expressed in neurons; blue molecules are expressed in neurons; red molecules are expressed in neurons and implicated in activity-dependent synaptic and/or functional plasticity. Only those molecules implicated in neuronal plasticity are discussed in the text. AP-1: activating protein 1; DAG: diacylglycerol; IL-1: interleukin-1; IL-6: interleukin-6; LAT: linker for activation of T cells; Lck: lymphocyte-specific protein tyrosine kinase; PKC: protein kinase C; PLC-γ: Phospholipase C; SAP: stress-activated protein kinase; SLP-76: SH2 domain-containing leukocyte protein of 76kDa; Sos: son of sevenless; V_m: membrane potential; ZAP-70: 70kD zeta-associated protein.

attributed in part to the apparent lack of MHCI on neurons [13]. However, accumulating evidence supports regulated expression of MHCI by subsets of neurons in the CNS [6,7••,14–17]. MHCI mRNA and/or protein have been detected in diverse neuronal populations in rodents, including dorsal root ganglia neurons [16], brainstem motoneurons [14,15], dopaminergic nigral cells [14], developing [17] and adult [6] hippocampal pyramidal cells, and layer 5 pyramidal cells in somatosensory cortex [6]. There are several likely explanations for the apparent lack of neuronal MHCI in many previous studies. MHCI is expressed at relatively low levels and in a developmentally regulated pattern [6,7••], with highest expression in many regions occurring perinatally, but many previous studies assayed whole brain harvested from adult animals. In addition, existing MHCI antibodies were developed primarily for live cell sorting, and many only recognize aldehyde-sensitive epitopes, which are not detectable in the fixed tissue sections often used for brain immunohistochemistry. Furthermore, some antibodies are specific for a single MHCI subtype, and each subtype is expressed in a unique, spatially and temporally restricted, pattern [7••]. Finally, there is evidence that antibody binding to MHCI, similar to T-cell antigen receptor (TCR) binding, is influenced by the peptide being presented by MHCI [18]. Although it is unknown if neuronal MHCI presents peptides, neuron-derived peptides are likely to differ, to some extent, from peptides presented by other, non-neuronal cells.

It is perhaps not so surprising that MHCI is expressed in neurons. In the immune system, T cells must respond appropriately to a nearly unlimited array of foreign antigens. Similarly, in the brain, there are approximately 10^{12} neurons, and each must make thousands of specific synapses. Even though a good deal is known about the laying down of major axon pathways [8], there remains the major issue of how specific connectivity is established and maintained. The brain and immune system therefore face the same basic challenge: to generate enormous complexity, specificity, and flexibility from a limited genome. The role of MHCI in synaptic plasticity and structural refinement raises the intriguing possibility that both systems have addressed similar problems of diversity and specificity in a similar fashion: through MHCI signaling.

Candidate mediators of MHCI signaling in neurons

How is MHCI signaling transduced in neurons? Strikingly, numerous key components of classical MHCI signaling (many once thought of as immune-specific) have been detected in the brain, and some have already been shown to participate in neuronal plasticity (Figure 3, in red), making them likely candidate mediators of MHCI's action in the brain. It is also possible that MHCI signaling in neurons occurs in novel ways, perhaps through atypical, CNS-restricted receptors and pathways. Detailed biochemical studies and neurologic analyses of mice harboring null mutations in specific signaling candidates will be necessary to begin to uncover the precise mechanisms of MHCI signaling in neurons.

Receptors for MHCI

MHCI molecules are recognized by several families of receptors in the immune system, including TCRs, natural killer (NK) receptors, and CD8 dimers [19,20]. Of these, CD3ζ is known to associate with TCRs and some NK receptors (reviewed in [21,22]). The fact that identical phenotypes occur in both MHCI loss-of-function and in CD3ζ

knockout mice implies that MHCI signals in the brain via a CD3ζ-containing receptor [7••]. To date, no complete MHCI-binding receptors have been detected in neurons; therefore, the following discussion will focus on molecules common to multiple MHCI receptor-signaling pathways.

Ig superfamily members

Neuron–neuron interactions mediated by Ig family adhesion molecules are crucial in the establishment of brain architecture, in most cases via their effects on neuronal adhesion and synaptic strength, and MHCI is a founding member of the Ig superfamily. Many additional Ig-containing molecules are central to MHCI signaling in the immune system, including MHCI receptor components, adhesion molecules, and costimulatory receptors and their ligands. These Ig family proteins, like MHCI, may modulate neuronal adhesion and changes in synaptic strength in neurons. Indeed, in fibroblasts, cell–cell adhesion in *in vitro* assays is regulated by MHC haplotype [23].

Cadherins

Cadherins are Ig family members that perform multiple functions in the brain through homophilic cell–cell adhesion. In *Drosophila melanogaster*, *N*-cadherin has been implicated in the targeting of connections made by developing photoreceptor neurons [24]. Cadherin receptors are localized to synapses and associate with Fyn [25], suggesting a potential role for cadherin signaling in synaptic function and/or plasticity. Candidate cadherins are expressed on T lymphocytes, where they may participate in cell recognition and adhesion [26].

Thy-1

Thy-1, another member of the Ig superfamily, regulates T cell signaling, likely via its interaction with other cell surface molecules on antigen-presenting cells [27]. Although it was first described on mouse thymocytes, Thy-1 is one of the most abundant glycoproteins on mammalian neurons [28], where it is enriched at synapses and is involved in adhesion [29]. The developmental appearance of Thy-1 in mouse brain closely parallels the histological and physiological maturation of neurons, with highest expression during the peak of activity-dependent rearrangements, during early postnatal life [28]. Thy-1 is required for LTP, a process thought to underlie learning and memory, in specific regions of mammalian hippocampus [30], and antibodies against Thy-1 abolish long-term memory in chicks [31]. Thy-1 is expressed on almost all neurons after the completion of axonal growth [32], and introduction of Thy-1 into a neuronal cell line inhibits neurite outgrowth *in vitro* [33]. The presence of Thy-1 in retinal projections during retinal afferent segregation [34] raises the possibility that MHCI could restrict retinal axons to eye-specific layers through Thy-1-mediated inhibition of axonal extension.

Specific phosphatases and kinases

Src protein tyrosine kinases

Fyn is a member of the Src family of kinases that is activated by the TCR–CD3ζ complex and transduces early events in T cell signaling [35]. Fyn is also expressed in neural growth cones and axons [36], and Fyn-deficient mice exhibit reduced neurite outgrowth in response to neural cell adhesion molecule *in vitro* [37]. Hippocampal LTP is impaired in Fyn knockout mice [38], and is rescued by restoring Fyn in the hippocampus via a transgene under the CamKII promoter [39].

Calcineurin

Calcineurin is a calcium/calmodulin-dependent serine/threonine phosphatase that is activated by sustained low-level Ca^{2+} signals arising during TCR signaling. Calcineurin is required for the induction of cytokine expression and T cell proliferation [40]. In the brain, calcineurin is important in limiting LTP [41,42•] and may be required for LTD ([43], reviewed in [44], but see also [42•]). These effects may in part be due to calcineurin's ability to induce desensitization of *N*-methyl D-aspartate (NMDA) receptors during synaptic stimulation [45–47]. Inhibiting the function of calcineurin enhances LTP [42•] and may prevent LTD [43], as does the lack of MHCI signaling [7••].

The calcineurin inhibitors cyclosporin A and FK506 are used clinically in the treatment of patients undergoing organ transplantation, where they are effective in preventing host–graft rejection. Because receptors for these drugs (immunophilins) are far more abundant in the nervous system than in the immune system [48], FK506 and cyclosporin A could have serious side-effects in the CNS. Indeed, adverse neuronal effects of immunosuppressive therapies have been reported, including headaches, tremor, neurotoxicity, hallucinations, seizures, and coma [49]. However, lower doses of these calcineurin inhibitors may be effective immunosuppressants without appreciable neurologic effects [50,51], illustrating the clinical importance of further study of conserved signaling mechanisms between the immune and central nervous systems.

ERK and JNK

Extracellular signal-regulated kinase (ERK) and c-Jun NH_2-terminal kinase (JNK) are mitogen-activated protein kinases that are crucial for development, activation, and differentiation of T cells [22]. These kinase cascades mediate cytokine and growth factor signals, affecting the growth and survival of thymocytes as well as neurons [52,53•,54]. ERKs and JNKs have also been implicated in many activity-dependent neuronal events including LTP and LTD ([55], reviewed in [56]).

Adapter proteins

Immune adapter proteins do not have enzymatic or transcriptional activity themselves, but rather participate in complexes that regulate such activity. Adapter proteins couple antigen receptor ligation to functional responses in lymphocytes, and are crucial for the formation of effective signaling complexes in the immune system. The adapter protein growth factor receptor-bound protein-2 (Grb2) links TCR ligation to Ras activation via recruitment of son

of sevenless (Sos), a guanine nucleotide exchange factor for Ras [57]. In neurons, Grb2 binds synapsin I, suggesting a role for Grb2 in synaptic vesicle cycling [57,58], and inhibitors of Grb2 block neurite outgrowth [59]. Similarly, the adapter protein Cbl is associated with the down-regulation of several protein tyrosine kinase signaling pathways, in both the brain and the immune system, including the down-regulation of receptors for growth factors, cytokines, and antigen [60].

Rho GTPases

Upon TCR engagement by MHCI in the immune system, phosphorylation cascades lead to activation of a Rho GTPase family member, Rac [61]. Rho-family GTPases regulate the actin cytoskeleton and subsequent growth in both neuronal and immune cells. Rac has been shown to affect the stability of developing axonal and dendritic processes as well as neuronal pathfinding and target recognition, primarily through control of cytoskeletal rearrangements [62,63•,64,65]. Thus, activation of Rho GTPases downstream of MHCI-receptor interactions could mediate the observed effects of MHCI on structural refinement in the CNS.

Transcription factors

NF-κB

Nuclear factor-kappa B (NF-κB) is a transcription factor that was initially thought to be restricted to immune cells; however, both constitutive and inducible expression of NF-κB have recently been detected in a subset of cultured cortical, hippocampal, and cerebellar neurons [66,67]. In the immune system, NF-κB is activated by cytokines (such as tumor necrosis factor-alpha [TNF-α] and interferon-gamma [IFN-γ]) and initiates the transcription of numerous genes including those encoding additional cytokines, cell adhesion molecules, and many MHCI genes [67]. In the nervous system, expression of NF-κB is developmentally regulated, and its function is modulated by electrical activity. Nuclear translocation of neuronal NF-κB can be induced by stimulation of glutamate receptors in cerebellar cultures [67] as well as by induction of LTP in the hippocampus [68]. Hippocampal slices treated with NF-κB-binding oligonucleotides lack LTD [69••], as do hippocampal slices obtained from mice lacking MHCI signaling [7••].

NF-AT

The nuclear factor of activated T cells (NF-AT) family of transcription factors is activated downstream of calcineurin in lymphocytes. NF-AT was previously thought to be restricted to immune cells, but recently was found to be expressed in neurons in the murine CNS, where it is expressed in the hippocampus and is enriched in the olfactory bulb [70]. In cultured hippocampal neurons, nuclear translocation and transcription by endogenous NF-AT is rapidly activated via calcineurin in response to spontaneous NMDA receptor activation or depolarization-induced L-type calcium channel activation [71], suggesting that NF-AT-mediated gene expression could participate in long-term synaptic plasticity. In addition, NF-AT regulates the expression of 1,4,5 inositol trisphosphate (IP_3) receptor I in hippocampal neurons, an interesting result given that induction of LTD in hippocampus depends on Ca^{2+} release from IP_3-sensitive stores [71], and hippocampal LTD is absent in mice deficient for MHCI signaling [7••]. Thus, MHCI-mediated activation of NF-AT via calcineurin may affect synaptic plasticity by altering the amplitude and cellular distribution of Ca^{2+} signals.

Cytokines

In the immune system, signaling through MHCI receptors leads to expression of multiple cytokine effectors, which in turn regulate TCR signaling and expression of MHCI ([16], reviewed in [72]). In this way, cytokines either stimulate or inhibit immune responses, depending on co-factors such as additional cytokines, co-stimulators, and metabolic activity.

Many cytokines and their receptors are expressed in neurons under normal conditions (reviewed in [73,74]), and IFN-γ receptors have been detected specifically at synapses [75]. In neurons, cytokine expression can be regulated by activity [76]. Cytokines such as IFN upregulate MHCI expression in many central and peripheral neuronal types *in vitro* and *in vivo* (e.g. [13]). Interleukin 1-β, TNF-α, and IFN-α all inhibit hippocampal LTP ([77], reviewed in [78]). In addition, IFN-γ can reduce neurite outgrowth on specific substrates *in vitro* [79], consistent with the possibility that reduced cytokine induction in MHCI-signaling-deficient mice permits exuberant extension of axonal projections as well as imposing limits on LTP.

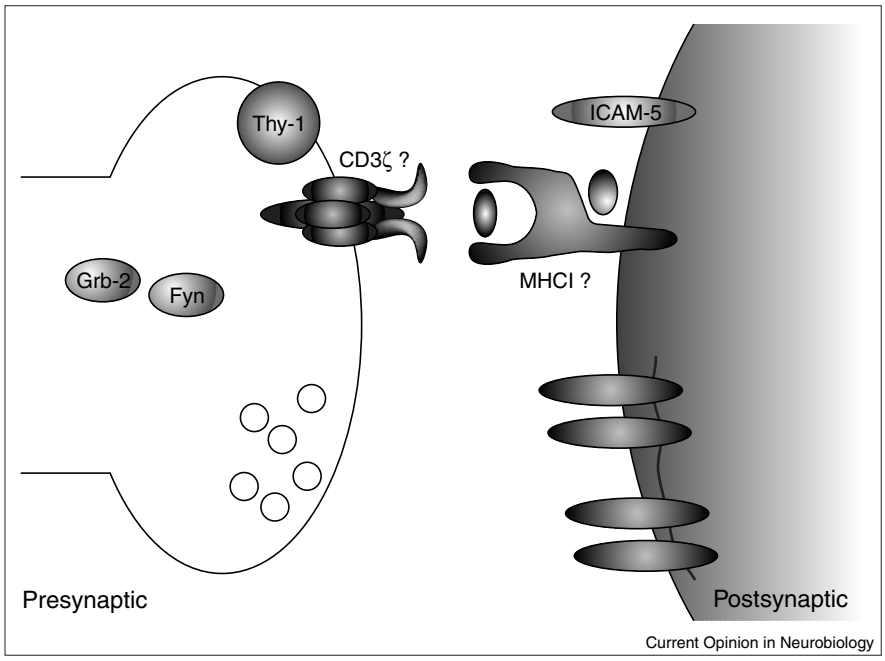
Modulation of MHCI function by activity

Transcriptional regulation

In neurons, electrical activity clearly regulates the expression of MHCI. In dissociated cultures of rat hippocampal neurons, electrically silent neurons express detectable MHCI, either at rest or in response to stimulation with IFN-γ, more frequently than spontaneously active neurons [17]. *In vivo*, conversely, MHCI expression is upregulated by spontaneous activity in the developing cat visual system and by seizures in adult rat hippocampus and neocortex [6]. There are a number of likely explanations for these apparently paradoxical findings. First, the hippocampal cultures described by Neumann *et al.* [17] were made from embryonic (E18) rats, but little MHCI expression can be detected in sections of the prenatal hippocampus ([6], GS Huh, personal communication) although expression increases in adult hippocampus [6,7••]. Second, neuronal MHCI expression *in vitro* can be altered dramatically by the process of dissociation and plating of nerve cells [80]. Finally, other contrasts between *in vitro* and *in vivo* systems, such as differences in the level of neuronal connectivity and the presence of secreted factors, may lead to different MHCI regulatory environments [12]. For these reasons it is conceivable that the rules governing regulation of MHCI expression in a culture environment may be different from those found *in vivo*.

Figure 4

Working model of MHCI signaling at central synapses. MHCI may be expressed postsynaptically, and during activity-dependent plasticity, retrograde signaling via a presynaptic, CD3ζ-containing receptor may lead to selective weakening and retraction of inappropriate synaptic contacts, perhaps via the downstream effects of Fyn [34], Grb2 [36] or Thy-1 [57].



Post-translational regulation

Neuronal activity may also regulate MHCI function post-translationally. In the immune system, depolarization of non-neuronal antigen-presenting cells causes a rapid, reversible conformational change in MHCI that is thought to affect its recognition by receptors [81]. Indeed, changes in the membrane potential of MHCI-expressing non-neuronal target cells can enhance TCR signaling [82]. There is also evidence that depolarization of the T cells themselves inhibits T cell signaling [83]. In these experiments, pharmacologic blockade of voltage-dependent and Ca^{2+}-activated K^+ channels resulted in membrane depolarization and subsequent inhibition of T-cell activation. T cell signaling is also inhibited by activation of endogenous $GABA_A$ receptors, which are likely to be depolarizing, as the resting membrane potential is more negative than the Cl^- equilibrium potential in T cells [84]. Thus, depolarization of neurons expressing either MHCI or MHCI receptors may rapidly regulate the efficiency of MHCI-receptor interactions and downstream signaling.

Specificity of signaling molecules

While many of the molecules outlined above are widely expressed signaling intermediates, some have been detected exclusively in the nervous and immune system. The ability of ubiquitous signaling molecules to induce specific responses is likely the product of a number of factors, including restricted expression of molecular subtypes, level of expression, dynamic features of the triggering signal, and cellular context, to name but a few (reviewed in [50]). Thus, it is likely that these signaling molecules, if they are activated downstream of MHCI-receptor binding in neurons (as they are in the immune system) lead to a distinct, neuron-specific readout in the CNS. Consistent with this possibility, replacement of the TCR with a muscarinic acetylcholine receptor harnesses the downstream machinery of the T cell in response to muscarinic receptor activation [85]. Similarly, the activation of mediators of MHCI function in neurons may lead to the forms of neuronal plasticity with which they are associated in neurons. For example, activation of calcineurin downstream of MHCI in neurons might lead to LTD, as it is known to in neurons, rather than proliferation, as it is known to in T cells.

Towards a model for neuronal MHCI function in synaptic plasticity

In the immune system, MHCI mediates cellular immunity by permitting recognition and removal of cells bearing foreign antigens. In the brain, MHCI may be required for the weakening and elimination of synaptic connections, and these analogous 'regressive' roles may be linked by shared molecular mechanisms. Normal neuronal activity upregulates MHCI (either directly or via cytokine induction) specifically during periods of synaptic remodeling and plasticity. Neuronal MHCI might then selectively weaken less-active synapses from a given MHCI-expressing population, because depolarization can inhibit MHCI signaling post-translationally in the immune system [83,84]. Therefore, more-active neurons may exhibit reduced MHCI-mediated downstream signaling. Less-active neurons, however, would fall prey to unmitigated MHCI-mediated pruning and retraction. As in the immune system, engagement of neuronal MHCI by a

CD3ζ-containing receptor in the brain may activate calcineurin, causing synaptic depression, and in parallel activate Rho-family GTPases, leading to cytoskeletal-mediated structural retraction (Figure 3).

Many important aspects of this model remain to be explored. For example, it is uncertain whether MHCI is expressed in remodeling axon terminals or target dendrites. Whereas MHCI is enriched in synaptosome fractions [7••], the localization of MHCI to the presynaptic or postsynaptic membrane is not yet known: current knowledge of expression patterns of MHCI and CD3ζ are consistent with both configurations [6,7••]. In the developing visual system, however, MHCI and its co-subunit β2-m are expressed in neurons that are postsynaptic to neurons in the final stages of activity-dependent remodeling — for example, LGN neurons early in development and layer IV cortical neurons at later ages [6]. In addition, when MHCI is expressed in layer IV of visual cortex, CD3ζ mRNA is expressed in remodeling presynaptic LGN neurons [6]. This observation implies that CD3ζ-mediated retrograde signaling is required in the remodeling presynaptic axon, and is triggered by contact with an MHCI-expressing postsynaptic target neuron (Figure 4). In support of this suggestion, signaling components downstream of CD3ζ in the immune system have been localized to presynaptic axons and growth cones (i.e. Fyn [34], Grb2 [36] and Thy-1 [57]) whereas cofactors normally expressed on antigen-presenting cells are postsynaptically expressed (i.e. ICAM-5 [86]; Figure 4).

MHCI and chemoaffinity

Which cell–cell interactions trigger MHCI signaling in the CNS? Like many molecules, including neurotrophins, MHCI could be important in the early establishment of neuronal connections, subsequent developmental refinement and plasticity in adulthood. Early in development, MHCI might provide a dedicated receptor-ligand system for axon guidance. The collection of MHCI molecules on a cell's surface normally presents peptides derived from the array of proteins expressed by that cell. This molecular 'signature' could be translated into growth cone target selection, or specific destabilization of new connections that do not display the appropriate receptors. In this way, MHCI could encode considerable diversity and specificity of connections, as proposed by Sperry [87], but, importantly, in a manner that could be regulated by activity. One requirement of such a model is that a multitude of MHCI receptors, each capable of recognizing one or a few specific MHCI-peptide complexes, should be expressed by subsets of neurons.

In the immune system, the problem of generating the repertoire of specific TCRs is solved through somatic recombination, a process that requires the recombination activating genes 1 and 2 (RAG-1 and RAG-2). Somatic V(D)J recombination brings together discontinuously coded V (variable), J (joining), and sometimes D (diversity) regions of the TCR and Ig genes. The multiplicity of possible combinations is a major source of TCR diversity. V(D)J recombination has never been detected outside the immune system, although it was initially proposed that somatic recombination would be well suited to explain the targeting specificity observed in the regeneration of patterned connections to goldfish tectum [88]. Although RAG-1 transcripts have been detected in CNS neurons [89], mice lacking RAG-1 do not have obvious neuronal phenotypes [90,91] and have normal LTP [7••], and RAG-2 has not been detected in neurons to date, suggesting that effects of MHCI in the brain may not require somatic recombination. Alternatively, a novel RAG-independent form of somatic recombination, analogous to Ig heavy chain class switching [92], may exist in neurons. Signaling diversity and specificity may also be conferred by the restricted expression of specific MHCI subtypes [7••]. Finally, the function of MHCI in the brain may not require a multitude of specific receptors and ligands, but rather may rely on cellular context to ensure specificity. To extend the current findings, it will be crucial to determine the role of such factors as MHCI subtypes, allelic diversity, and costimulatory molecules in neuronal development and plasticity.

Implications for disease

The presence of MHCI in neurons suggests new approaches to the study and treatment of a variety of neurological disorders, including (but not limited to) those with a known autoimmune etiology. Expression of MHCI by specific subsets of neurons may be the reason for the selective vulnerability of these neurons in neurodevelopmental and neurodegenerative disorders. For example, rat MHCI and β2-m proteins are expressed most strongly in the dopaminergic and motor neurons that are susceptible to neurodegeneration in Parkinson's disease and amyotrophic lateral sclerosis (ALS) in humans [14]. Furthermore, a number of diseases with a neurological component exhibit genetic linkage to the MHC region, including multiple sclerosis, insulin-dependent diabetes mellitus, ALS, epilepsy, spinocerebellar ataxia, Huntington's disease, Parkinson's disease, narcolepsy, (reviewed in [93]), and dyslexia [94]. Genetic linkage between a given brain disorder and MHCI may be due to a causal defect in other immune or non-immune molecules that map within the MHC (e.g. the $GABA_B$ receptor [95]), or it may reflect the newly discovered requirement for MHCI signaling in normal brain development and plasticity [7••]. Although the correlations at this point are tantalizing, further experiments are necessary to test the significance of neuronal MHCI in each disease.

Conclusions

On the basis of the evidence to date, it appears that the brain and the immune system speak a common biochemical language [96]. Many key immune signaling molecules are expressed in neurons, and subsets of these are now known to perform critical functions in the developing and adult

brain. It is interesting that immunologists have noted the similarities between T cell contacts and neuronal synapses, recently dubbing the MHCI–TCR-assembled complex the 'immunological synapse' [97]. It is becoming clear that the parallels go far beyond a shared semantic of 'synapses' and 'memory' to molecular and perhaps even evolutionary commonalities. As the CNS is more evolutionarily ancient than the adaptive immune system, it reasonable to posit that MHCI arose first in the brain, and was then adopted and elaborated in the immune system during the evolution of an adaptive immune response. The ontogeny of immune cells is consistent with this hypothesis: some thymic components are of neural crest origin [98]. Thus, the characterization of signaling pathways and receptors for MHCI in the nervous system may be of fundamental importance in understanding the evolution of immunity.

The existence of multiple functions for a single molecule is a major emerging theme bridging diverse fields of biology. Clearly, molecules once considered 'immune' also function in the CNS. Conversely, many molecules originally thought to be brain-specific have since been detected in the immune system (e.g. neuropeptides, hormones, neurotransmitters, neurotrophins, and their receptors; reviewed in [73,96]). Fewer examples of molecules thought to be brain-specific but operating in the immune system are known, however, likely reflecting the more recent origins of the field of molecular neuroscience. With the advent of large-scale genomics approaches to studying the brain and immune system, many more 'moonlighting' molecules are sure to be discovered. Neuroscientists are fortunate that many basic questions regarding immune molecules' functions have already been addressed in the immune system, providing a framework for the investigation of their roles in activity-dependent neuronal plasticity.

Update

We state above that RAG-1 but not RAG-2 have been detected in neurons 'to date': since the submission of our review, however, Jessen *et al.* [99••] have reported the first evidence that RAG-2 is expressed in neurons, and furthermore, that it is expressed concurrently with its obligate partner, RAG-1. This study, which is the first demonstration of concurrent RAG expression in any non-lymphoid tissue, reveals RAG-1 and RAG-2 mRNA expression in individual olfactory sensory neurons during embryogenesis, suggesting a potential novel role for RAGs in early brain development [99••].

Agrin, known for its role in inducing synaptic differentiation at the neuromuscular junction, has recently been shown to perform an analogous function at the immunological synapse: agrin is expressed on the surface of T cells and participates in the clustering of TCRs and costimulatory molecules [100••]. Agrin is also expressed at central synapses, although its function in the CNS is unclear. Aggregation of signaling components into rafts or synapses may be a conserved mechanism for regulating the specificity, speed and efficacy of transmembrane signaling, a possibility that will need to be explored in other agrin-expressing tissues.

Chun [101•] has recently published a comparison of immune and nervous system development, written for an immunology readership, in which he describes the theory that developmental programmed cell death, in both the brain and the thymus, is regulated by molecules implicated in nonhomologous end-joining (NHEJ). This theory offers a reinterpretation of previous data suggesting that V(D)J recombination is important in early neuronal survival, since NHEJ is a necessary event in V(D)J recombination. This interpretation is supported by the fact that genetic deletion of genes involved in NHEJ and V(D)J recombination, but not those involved only in V(D)J recombination, leads to early death of embryonic neurons ([91], reviewed in [101•]).

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