New Roles for MHC Class I Immune Molecules in the Healthy and Diseased Nervous System

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Introductory article

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Proteins of the major histocompatibility complex class I (MHC class I) are best known for their central role in the immune response. However, accumulating evidence shows that MHC class I proteins also have nonimmune roles in the healthy nervous system. MHC class I is expressed by developing and adult neurons, and is required for the proper establishment, function and modification of synaptic connections. The newly discovered, critical functions of MHC class I in the healthy nervous system suggest that MHC class I could directly link the immune response to changes in brain structure and function in diverse neurological disorders.

Introduction

Proteins of the major histocompatibility complex class I (MHC class I) are expressed on the surface of most nucleated cells in the vertebrate body. The MHC class I gene family is comprised of dozens of genes, which encode structurally similar proteins, generally consisting of three extracellular alpha domains (α-1, -2 and -3), one transmembrane domain, and a short intracellular domain (Bjorkman and Parham, 1990) (**Figure 1**). The obligatory extracellular MHC class I light chain, β2 microglobulin (β2m), is encoded separately, by the *B2M* gene. **See also**: Major Histocompatibility Complex (MHC); Major Histocompatibility Complex (MHC) Genes: Evolution

The large MHC class I gene family is best known for its role in antigen presentation. Remarkably, however, only a small subset of the many MHC class I proteins present diverse antigenic peptides. These so-called 'classical' MHC class I proteins (encoded by three genes in humans, and three in mice (**Figure 1b**)) are ubiquitously expressed, and present peptides derived primarily from intracellular proteins for immune system surveillance. In contrast, 'nonclassical' MHC class I proteins (encoded by three genes in humans, and more than 40 in mice) generally have more restricted expression patterns, and several have little or no known role in the immune response. Indeed, the functions and expression patterns of some nonclassical MHC class I genes remain completely mysterious.

In addition to being polygenic (containing many genes), MHC class I is polymorphic (each gene has multiple variants). Indeed, the antigen-presenting, classical MHC class I genes are among the most polymorphic genes in the human genome. For example, there are thousands of known variants of the human classical MHC class I gene HLA-A. Each individual expresses two MHC class I variants that can present somewhat different antigenic peptide repertoires. Therefore, this extreme polymorphism at the population level may increase the probability that at least some individuals will be able to develop immunity to emerging infections. **See also**: Major Histocompatibility Complex (MHC); Major Histocompatibility Complex (MHC) Genes: Evolution; Major Histocompatibility Complex (MHC) Genes: Polymorphism; Major Histocompatibility Complex (MHC): Mouse

The brain is considered 'immune-privileged', since immune surveillance mechanisms are blunted or delayed in the central nervous system (CNS) (Carson *et al*., 2006). MHC class I does not mediate full, rapid adaptive immunity in the nervous system. However, a growing number of

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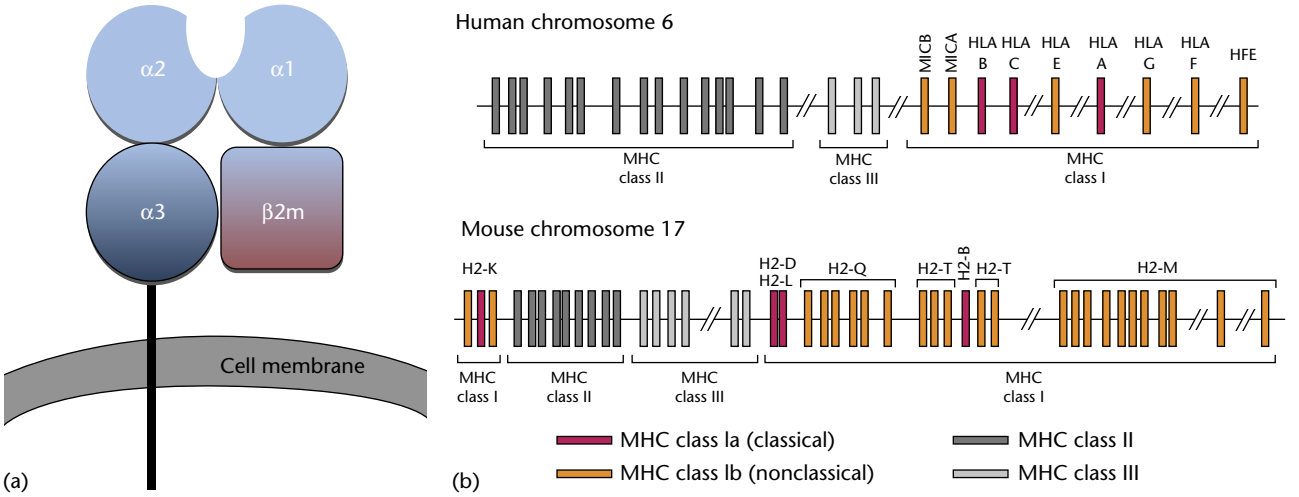


Figure 1 (a) Schematic of a canonical MHC class I protein, showing the three extracellular alpha domains (in complex with the β2M light chain), the single-pass transmembrane domain, and the short intracellular tail. Note that the cytoplasmic domain is not drawn to scale. (b) Human and mouse MHC gene families. MHC class I is comprised of both classical (red) and nonclassical (orange) members in humans and in mice. Reprinted with permission from Elmer and McAllister, 2012. © Elsevier.

studies have identified unexpected, nonimmune roles for MHC class I in the brain (e.g. (Chacon and Boulanger, 2013; Datwani *et al*., 2009; Elmer *et al*., 2013; Fourgeaud *et al*., 2010; Glynn *et al*., 2011; Goddard *et al*., 2007; Huh *et al*., 2000; Lee *et al*., 2014; Leinders-Zufall *et al*., 2014; Loconto *et al*., 2003; McConnell *et al*., 2009; Needleman *et al*., 2010; Nelson *et al*., 2013; Washburn *et al*., 2011; Wu *et al*., 2010; Zohar *et al*., 2008)).

MHC Class I is Expressed by Healthy Neurons in the Developing and Adult Nervous System

MHC class I expression was long thought to be suppressed by neurons, and this lack of MHC class I was considered a potential cause of the immune-privileged status of the CNS. However, MHC class I has since been detected in many brain regions. MHC class I expression was initially detected in the developing mammalian visual system in an unbiased screen for genes that are regulated by synaptic activity (Corriveau *et al*., 1998). During the development of the visual system, spontaneous electrical activity arising in the retinas sculpts developing connections, by driving the strengthening of appropriate synapses, and the elimination of redundant synapses. MHC class I expression in the visual system is driven by the same activity that drives developmental synapse elimination, since pharmacologically blocking this activity decreases MHC class I levels (Corriveau *et al*., 1998). Thus rather than being absent from neurons, MHC class I is present, and is regulated by developmentally-important forms of neural activity. **See also**: Visual System; Synapses

Subsequently, many studies have showed that MHC class I is present in normal, healthy neurons throughout the developing and adult nervous system, including the visual system, hippocampus, cerebral cortex, cerebellum and spinal cord (Goddard *et al*., 2007; Huh *et al*., 2000; McConnell *et al*., 2009; Needleman *et al*., 2010; Oliveira *et al*., 2004; Thams *et al*., 2008). Different members of the MHC class I gene family are expressed in distinct spatial and temporal patterns in the adult brain (**Figure 2**; Huh *et al*., 2000; McConnell *et al*., 2009). For example, some members of the nonclassical MHC class I family *H2-Mv* appear to be exclusively expressed in the olfactory system, where they are required for the proper cell-surface delivery of V2R pheromone receptors (Loconto *et al*., 2003), and may be involved in axon guidance (Ishii and Mombaerts, 2008).

MHC class I protein is found at synapses, sites of electrochemical communication between neurons, and has been detected both pre- and postsynaptically in CNS neurons (Goddard *et al*., 2007; Needleman *et al*., 2010). MHC class I is highly expressed during early brain development, and is upregulated by neural progenitors just as they begin to adopt a neural cell fate (Chacon and Boulanger, 2013). MHC class I is also expressed in the peripheral nervous system (PNS), where it has been detected at the adult neuromuscular junction (Thams *et al*., 2009). The function of MHC class I in many of these parts of the nervous system currently remains unknown. However, studies in specific brain regions, outlined below, have begun to shed light on the effects that MHC class I has on developing, adult and diseased neurons. **See also**: Neuromuscular Junction

MHC Class I Promotes Developmental Axon Remodelling and Synapse Elimination

MHC class I was identified in a screen for molecules that might be involved in developmental axon remodeling in of

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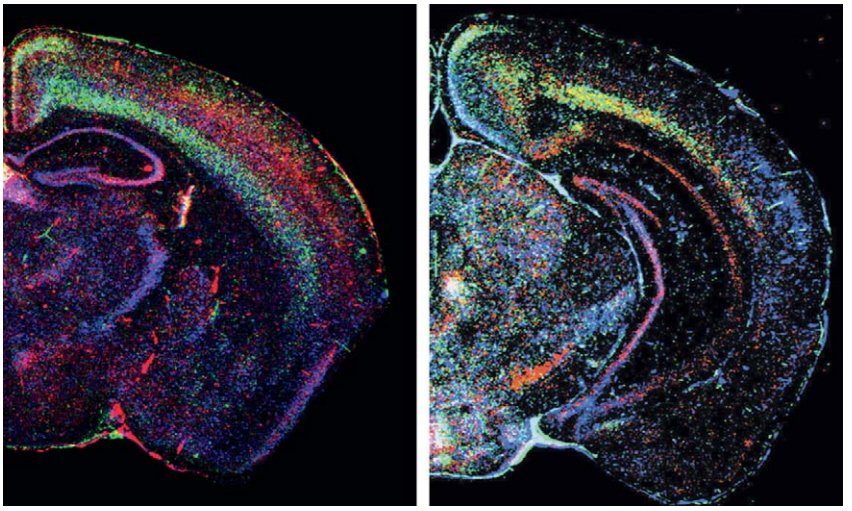


Figure 2 Pseudocolored *in situ* hybridisation shows mRNA encoding three different MHC class I genes in three superimposed, consecutive coronal sections from anterior (left) and (posterior) regions of adult mouse brain. Blue, H2-Db; red, T22; Green, Qa-1. Reprinted with permission from Boulanger and Shatz, 2004 and Boulanger, 2009. © Elsevier.

the mammalian visual system (Corriveau *et al*., 1998). Prior to eye opening, axons from the two eyes project to overlapping territory in the lateral geniculate nucleus (LGN), a relay station in the thalamus. Axons from the two eyes segregate into eye-specific layers over the first two weeks after birth, through selective pruning of inappropriate axonal projections, and stabilisation of appropriate connections (**Figure 3**). Establishment of eye-specific layers in the LGN requires naturally-occurring spontaneous electrical activity in the retina, because blocking this activity prevents eye-specific segregation (Shatz, 1990). Establishing eye-specific layers also requires new gene expression, because blocking gene expression pharmacologically retains an immature, overlapping pattern of inputs, but the specific genes involved were unknown. To identify candidates that might be involved in eye-specific segregation, gene expression was compared in the developing LGN under normal conditions and after activity blockade. MHC class I levels were significantly lower in the LGN following activity blockade, suggesting that MHC class I expression is driven by the normally-occurring activity that causes inputs to form eye-specific layers. This pattern of expression is consistent with a model in which MHC class I is involved in eye-specific segregation.

To directly test if MHC class I is required for developmental axon remodelling and eye-specific segregation in the LGN, retinal axons were examined in mice that have been genetically modified to express lower levels of MHC class I on the cell surface. In these MHC class I-deficient mice, axon remodelling is impaired in the developing LGN, and eye-specific segregation is impaired. Thus reducing the expression of MHC class I immune proteins is sufficient to disrupt eye-specific retinal axon segregation, demonstrating that MHC class I normally plays a surprising and critical role in the developing brain (Datwani *et al*., 2009; Huh *et al*., 2000; Lee *et al*., 2014).

Similar activity-dependent axon remodelling is a critical step in the development of many regions of the central and peripheral nervous systems. However, MHC class I is not required for all activity-dependent remodelling in the developing brain. MHC class I is present in the cerebellum during remodelling of climbing fibre (CF)-Purkinje cell (PC) synapses, but MHC class I is not required for normal developmental remodelling of these connections (Letellier *et al*., 2008; McConnell *et al*., 2009). MHC class I is also not required for the developmental remodelling of projections from LGN to visual cortex to form eye-specific regions (in higher vertebrates, termed ocular dominance columns). However, MHC class I may restrict the ability of these thalamo-cortical projections to remodel in adults in response to chronic visual deprivation (ocular dominance plasticity). Ocular dominance plasticity is normally restricted to an early developmental window, the so-called 'critical period', but in MHC class I-deficient mice, ocular dominance plasticity is enhanced at all ages, and the critical period is effectively prolonged (Datwani *et al*., 2009). Together, these and other results demonstrate that MHC class I promotes activity-dependent axon remodelling in the developing LGN, limits deprivation-induced plasticity in visual cortex, and is dispensable for activity-dependent developmental axon remodelling in the cerebellum and visual cortex. Loss of MHC class I may differently affect axon remodelling in these parts of the nervous system because of the specific MHC class I proteins and/or signalling mediators that are present in each region. Another possibility is that despite similarities in timing and appearance, axon remodelling occurs through distinct molecular mechanisms in different regions of the nervous system. **See also**: Cerebellum: Anatomy and Organisation

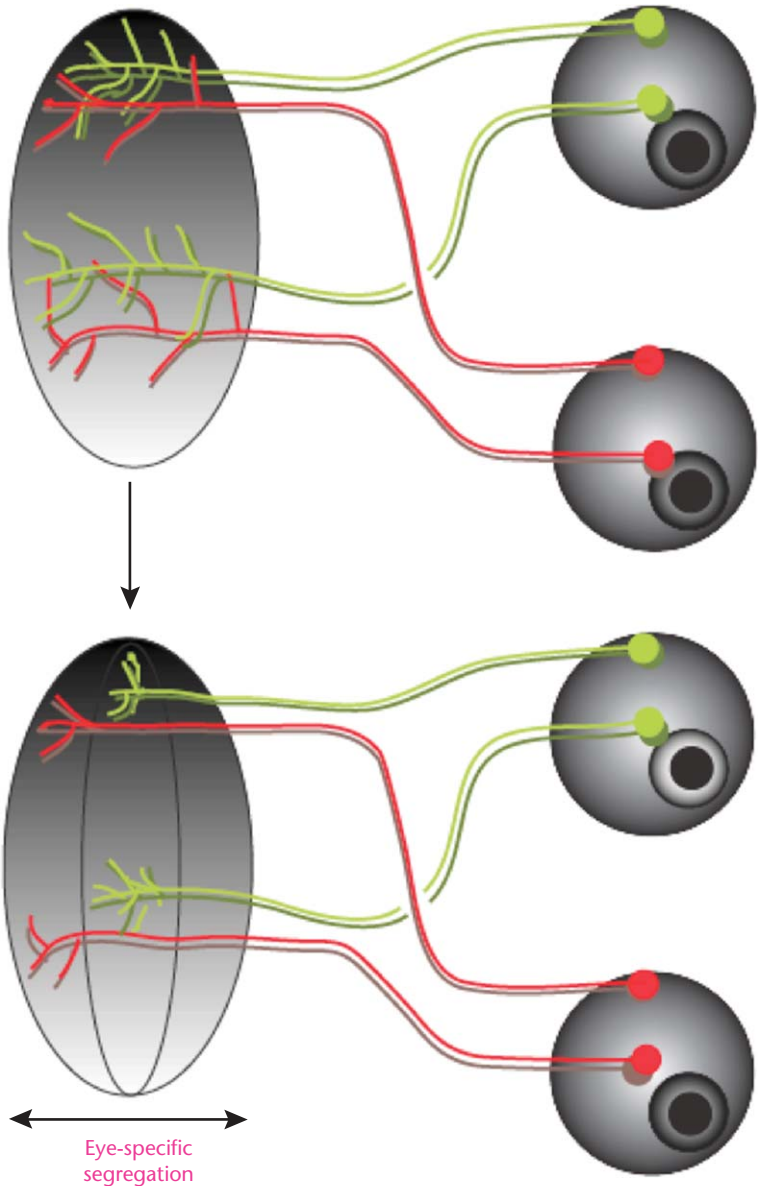


Figure 3 Activity-dependent refinement of RGC projections into the LGN. Initially (top) axon arbours from both eyes are overlapping. RGC inputs from the two eyes resolve into eye-specific layers (bottom) through a process of activity-dependent axon remodelling during development. Reprinted with permission from Boulanger *et al.*, 2001. © Elsevier.

MHC Class I Negatively Regulates Synapse Density

MHC class I negatively regulates synapse density in the LGN, visual cortex, and hippocampus. In cultured cortical neurons, reducing cell-surface expression of MHC class I increases the density of both excitatory and inhibitory synapses. Conversely, increasing MHCI levels above basal levels decreases synapse density in cortical cultures (Glynn *et al.*, 2011). Thus, changing MHC class I levels can bidirectionally regulate cortical synapse density *in vitro*. It is tempting to speculate that MHC class I might limit synapse density in visual cortex by promoting synapse elimination, as it does in the developing LGN (Datwani *et al.*, 2009; Lee *et al.*, 2014). However, unlike the LGN, MHC class I is not required for developmental synapse elimination in visual cortex (Datwani *et al.*, 2009). Thus it is as yet unclear if the effects of MHC class I on synapse density in cortex are due to MHC class I influencing the formation, stability, or removal of synapses. One possibility is that rather than promoting a synapse-eliminating pathway, MHC class I inhibits a synapse-promoting pathway.

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Indeed, this seems to be the case in area CA3 of hippocampus, where loss of MHC class I causes an increase in synapse density in brain slices. Loss of MHC class I also de-represses signaling mediated by the insulin receptor, a known synapse-promoting factor, and inhibiting insulin receptor signaling in MHC class I-deficient mice rescues synapse density in the hippocampus. Thus endogenous MHC class I ensures appropriate synapse density in the hippocampus by inhibiting the synapse-promoting effects of the insulin receptor (Dixon-Salazar *et al*., 2014).

Intriguingly, normal and pathological levels of MHC class I may affect synapse number through distinct molecular pathways. When MHC class I levels are artificially elevated in cortical neurons, synapse number declines. However, overexpressing MHC class I fails to reduce synapse density in the absence of the transcription factor myocyte enhancer factor 2 (MEF2). Decreasing MEF2 alone does not affect synapse density (Elmer *et al*., 2013; Glynn *et al*., 2011), suggesting that MEF2 is not required for the basal inhibition of synapse number by normal, endogenous levels of MHC class I , but rather specifically mediates the decrease in synapse number below normal levels when MHC class I levels are abnormally high. Thus MHC class I can reduce synapse density by inhibiting synapse-promoting pathways or activating synapse-elimination pathways, depending on the brain region and/or level of MHC class I present. Consistently, increases in MHC class I expression are associated with fewer synapses, whereas reducing MHC class I expression increases synapse density.

MHC Class I Inhibits Synapse Elimination Following Nerve Injury

Synapse elimination during development is a normal part of forming healthy functional circuits, but synapse elimination in the aftermath of nerve injury can have devastating consequences. Following motor neuron axotomy (cutting of the axon leading from the motor neuron to muscle), synapses onto the cell body of the damaged motor neuron are lost, a form of pathological synapse elimination known as 'synaptic stripping' (Linda *et al*., 2000). MHC class I regulates this form of harmful synapse elimination, as it does synapse elimination during development. However, its effects on post-injury and developmental synapse elimination are strikingly different. Although MHC class I-deficient transgenic mice show reduced developmental synapse elimination, after injury they show increased elimination of inhibitory synapses, and decreased regeneration (Oliveira *et al*., 2004). Thus MHC class I normally helps maintain synapses following peripheral nerve injury, but promotes synapse loss during development. Interestingly, in both cases, MHC class I is important in promoting the establishment (or re-establishment) of healthy neuronal circuits.

MHC Class I Regulates Axonal and Dendritic Growth

Experiments with MHC class I-deficient or -over-expressing neurons growing *in vitro* suggest that MHC class I limits axon outgrowth in retinal explants and cultured dorsal root ganglion neurons (Bilousova *et al*., 2012; Escande-Beillard *et al*., 2010; Washburn *et al*., 2011; Wu *et al*., 2011). Similarly, anti-MHC class I antibodies promote neurite outgrowth in cultured cortical neurons (Zohar *et al*., 2008). These *in vitro* studies suggest that MHC class I normally restricts neurite outgrowth in many brain regions. Shorter axons may not be able to support as many synapses, and in this way, the negative effects of MHC class I on axon length and synapse number may be related. Given that MHC class I is expressed in the developing brain when initial neurite outgrowth is occurring (Chacon and Boulanger, 2013), MHC class I's effects on the geometry of axons could have profound functional consequences for developing and mature circuits.

MHC Class I Regulates Synaptic Transmission and Synaptic Plasticity

In addition to its effects on the number of synapses, MHC class I regulates the strength of communication at synapses, termed synaptic transmission. In the hippocampus, a part of the brain that is important in some forms of learning and memory, MHC class I normally inhibits synaptic transmission mediated by postsynaptic *N*-Methyl-D-aspartate receptors (NMDARs). Loss of cell-surface expression of most MHC class I proteins nearly doubles the current carried by NMDARs in response to the excitatory neurotransmitter glutamate, but does not affect the response to glutamate mediated by another receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid receptor (AMPAR) (Fourgeaud *et al*., 2010). Thus the change in current is not likely caused by changes in the amount of available glutamate, which might affect both glutamate receptors. Instead, MHC class I seems to selectively inhibit NMDARs. Despite the large increase in current carried by NMDARs, NMDAR levels, localisation, and composition are all normal in MHC class I-deficient mice (Fourgeaud *et al*., 2010). Thus the cellular basis of MHC class I's effect on hippocampal NMDAR function remains unknown. One possibility is that MHC class I inhibits the single-channel function of NMDAR ion channels.

In the LGN, in contrast, loss of just the classical MHC class I proteins increases the current carried by Ca^{2+}-permeable AMPAR, but has no effect on NMDARs (Lee *et al*., 2014). Thus the effects of MHC class I on synaptic transmission, like its effects on axon remodelling, may be specialized in different brain regions, and the specific MHC class I proteins that are present. However, it is also possible that the effects of MHC class I on NMDARs and

AMPARs are related, since NMDAR activation can trigger changes in the trafficking of AMPARs. Signalling mediated by NMDARs is an essential player in the normal outgrowth, pathfinding, synaptogenesis, and remodelling of neurites in the developing brain. Indeed, a key unanswered question is whether MHC class I affects neurite outgrowth and synapse elimination through its effects on NMDAR function. **See also**: AMPA Receptors; Hippocampus; NMDA Receptors

MHC class I's ability to inhibit hippocampal NMDARs is of even broader interest given that NMDARs drive cellular and behavioural changes collectively known as plasticity. Cellular plasticity includes long- and short-term changes in the strength of synapses, whereas behavioural plasticity encompasses most forms of learning. Consistent with the fact that MHC class I regulates hippocampal NMDAR function, MHC class I is also required for NMDAR-dependent forms of hippocampal synaptic plasticity. In MHC class I-deficient mice, NMDAR-dependent long-term potentiation (LTP) is increased, while NMDAR-dependent long-term depression (LTD) is absent (Huh *et al*., 2000; Nelson *et al*., 2013). In contrast, NMDAR-independent forms of hippocampal plasticity, as well as plasticity at other synapses that requires pre- but not postsynaptic NMDARs, are all unaffected (Nelson *et al*., 2013). These results together suggest that MHC class I is specifically required for normal synaptic plasticity mediated by postsynaptic NMDARs. **See also**: Long-term Depression and Depotentiation; Long-term Potentiation

Current models suggest that hippocampal synaptic plasticity, including LTP and LTD, underlie some forms of learning and memory. Consistent with this model, MHC class I-deficient mice demonstrate not only changes in LTP and LTD, but also deficits in hippocampal-dependent memory tasks, including novel objection recognition, contextual fear memory, and social recognition memory (Nelson *et al*., 2013). These memory defects, like the changes in synaptic plasticity, may be a result of enhanced NMDAR function in MHC class I-deficient mice.

MHC class I also regulates synaptic and behavioral plasticity in the cerebellum. In MHC class I-deficient mice, LTD at the parallel fibre (PF)-PC synapse has a lower induction threshold and a larger magnitude (McConnell *et al*., 2009). MHC class I-deficient mice also perform better on the Rotarod task, and show better retention of learned motor skills, behaviours which are thought to require synaptic plasticity in the cerebellum (McConnell *et al*., 2009).

NMDAR-dependent LTP and LTD, both of which require MHC class I, are rapid forms of synaptic plasticity that occur on a timescale of minutes, in response to brief periods of patterned synaptic activity. MHC class I may also be involved in synaptic scaling, a form of plasticity that occurs in response to more chronic changes in activity. Chronic decreases in activity can cause synaptic strength to climb, increasing the sensitivity to small signals, whereas chronic overactivation of synapses causes synaptic strength to drop, potentially protecting the cell from harmful excitotoxicity (Turrigiano, 2008). In this way, synaptic scaling can help maintain appropriate activity levels in dynamic circuits. MHC class I-deficient hippocampal synapses fail to 'scale up' the levels of specific synaptic proteins during long-term activity blockade (Goddard *et al*., 2007), suggesting that MHC class I may be required for synaptic scaling. Intriguingly, synaptic scaling also requires other immune proteins, including the cytokine TNFα (Stellwagen and Malenka, 2006).

Molecular Mechanisms of MHC Class I's Nonimmune Functions in the Nervous System

Several studies, including the ones outlined above, have begun to identify critical, nonimmune functions for MHC class I in the developing and adult brain. MHC class I helps define the shape of axonal and dendritic arbours, determine synapse density, regulate synaptic transmission and plasticity, and influence learning and cognition. A key unanswered question is: what are the molecular mechanisms by which MHC class I influences neuronal structure and function? Although many molecular mediators of MHC class I function in the immune response have been characterised over a period of decades, very little is known about the protein binding partners and downstream signalling cascades that mediate the newly discovered functions of MHC class I in the nervous system.

Several kinds of models are possible. First, neuronal MHC class I might bind to traditional immunoreceptors on immune cells – either resident immune cells, such as microglia, or infiltrating immune cells, such as T cells. Second, MHC class I might bind to traditional immunoreceptors expressed by nonimmune cells, including neurons. Third, MHC class I might bind to proteins with no known immune functions. Importantly, none of these possibilities are mutually exclusive. Indeed, MHC class I employs a similar diversity of binding strategies outside the nervous system (Li and Raghavan, 2010; Salter-Cid *et al*., 2000).

Several immunoreceptors for MHC class I are expressed in the nervous system. T-cell receptor (TCR) subunit β messenger ribonucleic acid (mRNA) is present in both the developing and adult brain, and is found in some areas where MHC class I is expressed (Syken and Shatz, 2003). However, no recombined TCRβ mRNA has been detected in the brain, implying that functional TCRs are not formed, and indeed, TCRβ protein and cognate TCRs have never been observed in the brain. Another TCR component, CD3ζ, is expressed in the brain, and transgenic mice lacking this protein show some parallels to mice deficient in MHC class I (Baudouin *et al*., 2008; Huh *et al*., 2000; Xu *et al*., 2010). However, no MHC class I immunoreceptors containing CD3ζ have yet been detected in neurons, and it remains unknown if the nonimmune functions of CD3ζ are due to interactions with MHC class I, or occur through parallel, independent pathways.

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Paired immunoglobulin-like receptor B (PirB), another MHC class I immunoreceptor, is expressed in neurons, and binds to neurons in a partially MHC class I-dependent manner. Furthermore, mice lacking either PirB or MHC class I have similar defects in ocular dominance plasticity, suggesting that MHC class I-PirB binding could potentially mediate MHC class I's effect on deprivation-induced plasticity in visual cortex (Datwani *et al*., 2009; Syken *et al*., 2006). However, MHC class I-dependent changes in plasticity in LGN and hippocampus are not seen in PirB-deficient mice, suggesting that these effects of MHC class I involve PirB-independent signalling pathways (Atwal *et al*., 2008; Raiker *et al*., 2010; Syken *et al*., 2006).

Other proteins can form a complex with MHC class I family members in nonimmune contexts. The insulin receptor can bind to classical MHC class I proteins in liver (Fehlmann *et al*., 1985a,b), and the transferrin receptor can bind directly to the MHC-like protein HFE to regulate iron homoeostasis (Salter-Cid *et al*., 2000). While the transferrin receptor is expressed in the nervous system, it remains unclear if the transferrin receptor binds to neuronal MHC class I, or mediates any of MHC class I's many neuronal functions. However, recent studies suggest that MHC class I normally limits synapse density in the hippocampus through its effects on insulin receptor signaling (see Section 'MHC Class I Negatively Regulates Synapse Density'). MHC class I forms a complex with the insulin receptor in brain lysates, and unmasks a cytoplasmic epitope of the insulin receptor. In the absence of MHC class I, insulin receptors are constitutively active, and pharmacologically rescuing downstream insulin receptor signaling rescues synapse density in the hippocampus of these mutants (Dixon-Salazar *et al*., 2014). These studies suggest that MHC class I helps ensure proper hippocampal circuit formation through interactions with non-immunoreceptor proteins in the mammalian brain. In the future, it will be important to determine if MHC class I binds directly to the insulin receptor, and identify the sites in each protein which mediate the necessary interactions.

MHC Class I in the Damaged and Diseased Brain

The discovery that MHC class I plays essential roles in the healthy nervous system raises the possibility that MHC class I could play unexpected roles in brain disorders. The results to date show that MHC class I immune proteins help establish appropriate synapse number, excitatory synaptic transmission, and synaptic plasticity in multiple brain regions, and even influence some forms of behaviour. Thus it is concerning that MHC class I levels in neurons can be altered by systemic signals that are produced during the immune response (Elmer *et al*., 2013; Linda *et al*., 1998; Neumann *et al*., 1995). This means that diverse immune stimulants – including infections, toxins, obesity, stress, injury and cancer – could potentially modify the critical functions of MHC class I in the brain, impacting synapse density, synaptic transmission, synaptic plasticity, and even cognition. While these changes may well be reversible, if they occur during a critical period of development – for example, during the brief period when plasticity is sculpting developing neural circuits, or during recovery from brain injury – the effects could be more lasting.

Consistent with this possibility, work in animal models shows that maternal immune activation (MIA) increases MHC class I expression on the surface of cortical neurons (McAllister, 2014). This increase in MHC class I expression in turn causes a decrease in cortical synapse density in mice (Elmer *et al*., 2013). Thus, peripheral immune challenges are sufficient to exaggerate the synapse-limiting function of MHC class I in the developing brain, persistently reducing connectivity in neural circuits.

Several lines of evidence suggest that MHC class I dysfunction could contribute to neurodevelopmental disorders. In humans, MIA has been associated with a small but significant increase in the risk of autism or schizophrenia in the offspring (Brown, 2006; Brown and Derkits, 2010). In rodents, MIA triggers neuropathology that mimics several features of these disorders. Paralleling the effects of changing MHC class I expression, patients with autism or schizophrenia may have changes in synapse number, and schizophrenia may involve reduced NMDAR function (McAllister, 2014). Schizophrenia is a highly heritable disorder, and remarkably, the single strongest and most consistent genetic linkage to schizophrenia maps to the MHC class I region (Jia *et al*., 2012; Shi *et al*., 2009; Stefansson *et al*., 2009). Because there is no clear evidence that schizophrenia is an autoimmune disorder, the mechanistic reason for the genetic association between MHC class I and schizophrenia has remained mysterious. The discovery that MHC class I is involved in normal brain development suggests an unexpected and surprisingly direct mechanism by which altered MHC class I could disrupt synapse density and NMDAR-mediated synaptic transmission. Thus it is possible that changes in MHC class I function, due to genetic variation or immune challenges during developmental critical periods, could contribute to disrupted circuit connectivity and function.

In addition to its potential role in disorders of the developing brain, MHC class I may also inhibit recovery following nerve injury and stroke in adults. MHC class I and the immunoreceptor PirB are both upregulated in the rodent brain following stroke, and mice genetically lacking either MHC class I or PirB show better-than-normal anatomical and functional recovery following stroke. Thus the increase in MHC class I expression following stroke may actively exacerbate post-stroke pathology (Adelson *et al*., 2012). These results are exciting because they suggest that inhibiting this apparently harmful effect of MHC class I in the damaged brain might improve stroke outcomes. However, these studies were performed in transgenic mice that genetically lacked MHC class I or PirB proteins throughout the body, from birth. Therefore it is uncertain

if the effects on stroke recovery are mediated by MHC class I acting at or after the time of injury in neurons, or are due to more indirect effects of MHC class I on brain development or the immune system. Conditional knockouts, which lack MHC class I only in specific tissues and/or at specific ages, will be an important step to help resolve these questions. It will also be important to identify the molecular mechanisms by which MHC class I impairs post-stroke recovery, with the ultimate goal of finding ways to suppress this harmful function of MHC class I in stroke patients, while leaving their immune response intact.

Summary

MHC class I, once thought to be exclusively a component of the adaptive immune response, also has essential, non-immune functions in the vertebrate nervous system. Over the past decade, a growing body of literature has identified roles for MHC class I proteins in the development and function of the healthy CNS and PNS. MHC class I regulates axon outgrowth and activity-dependent axon remodelling, synapse density, synaptic plasticity and cognition. The discovery that MHC class I is so important in the healthy brain has raised the possibility that changes in MHC class I signalling could be an unexpected contributor to diverse neurological disorders. To explore the therapeutic potential of manipulating the nonimmune functions of MHC class I, there is an urgent need to identify the binding partners and signalling pathways through which MHC class I contributes to generating and maintaining normal neuronal structure and function.

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