IMMUNE SIGNALLING IN NEURAL DEVELOPMENT, SYNAPTIC PLASTICITY AND DISEASE

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Research has long supported the view that the brain is immunologically privileged, in part because normal, uninfected neurons were not thought to express major histocompatibility complex (MHC) class I molecules. Recently, however, it has been shown that neurons normally express MHC class I molecules *in vivo*. Furthermore, accumulating evidence indicates that neuronal MHC class I does not simply function in an immune capacity, but is also crucial for normal brain development, neuronal differentiation, synaptic plasticity and even behaviour. These findings point to new directions for research, and imply that immune proteins could be involved in the origin and expression of neurological disorders.

HISTOCOMPATIBILITY
The ability of tissues to be successfully grafted. Also refers to the genetic systems that determine tissue rejection through immune responses of histocompatibility antigens.

ADAPTIVE IMMUNE SYSTEM
The system that coordinates the response of antigen-specific T cells to an antigen. The process is mediated by clonal selection of lymphocytes.

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The major HISTOCOMPATIBILITY complex (MHC) (BOX 1) was originally identified as a region that encodes a family of molecules that are responsible for the rejection of transplanted organs. However, these so-called 'transplantation antigens' were soon found to perform a much broader recognition function in the context of the ADAPTIVE IMMUNE SYSTEM. MHC class I molecules bind peptides derived from proteolysis of intracellular proteins. They present these peptides on the cell surface, where they are monitored by CYTOTOXIC T LYMPHOCYTES (CTLs) and are identified as self or non-self. This discrimination is at the core of our ability to rid ourselves of bacterial and viral infections, and to curb the development of some cancers.

There is increasing evidence that MHC class I molecules have additional functions in the developing and adult CNS. These findings have revived a long-standing debate about the ability of neurons to express MHC class I proteins, and have broad implications for both normal and abnormal brain development and function. In this review, we discuss evidence from various systems regarding MHC class I expression, signalling and function in neurons, as well as the potential roles of this class of molecules in neurological disorders.

Neuronal expression of MHC class I

Members of the MHC class I family are expressed on the surface of most nucleated cells. For many years, however, CNS immune privilege (the relative slowness or failure of the immune response in the CNS) was considered strong evidence that normal neurons do not express MHC class I genes[1,2]. In addition, numerous studies failed to detect MHC class I protein in normal untreated brain slices[3], cultured neurons[4] or neuron-like immortalized cell lines[2,5–8] (reviewed in REF. 9). By contrast, neurons do express high levels of MHC class I protein after various treatments, including axotomy[10,11], ventral-horn root avulsion[12], viral or parasitic infection[13–15], exposure to cytokines[4,8,16–18] and pharmacological manipulation of electrical activity[4,19,20].

Recent results, however, indicate that even normal, uninjured neurons express both classical and non-classical MHC class I genes *in vivo* (FIG. 1). MHC class I mRNA and/or protein has been detected in diverse neuronal populations, including motor nuclei, substantia nigra pars compacta[12,21], dorsal root ganglia neurons[22], dopaminergic nigral cells[23], developing and adult hippocampal pyramidal cells[17,20], sensory neurons of the vomeronasal organ (VNO)[24,25], brainstem[12,23] and spinal[12,19] motor neurons, and cortical pyramidal cells[20,21] (FIG. 1). Some of these studies also confirm that MHC

Box 1 | The MHC gene family: members, nomenclature and functions

The major histocompatibility complex (MHC) is a tightly linked cluster of genes that has been found in every vertebrate genome to date[120]. The mouse MHC, also called the H-2 (for histocompatibility-2) region, is analogous to RT in the rat and HLA (human leukocyte antigen) in humans, but there are interspecies differences in the number and identity of individual MHC genes. The mouse MHC, on chromosome 17, contains over 200 genes, most of which are divided into three broad categories: class I (equivalent to HLA A, B and C in humans); class II (HLA DP, DQ, and DR in humans); and class III, which includes components of the complement system. The class I genes are further distinguished as encoding classical (Ia) or non-classical (Ib) MHC class I genes[121].

MHC class I genes encode heavy chains (~45 kDa), most of which non-covalently bind the 12 kDa light chain β2-microglobulin (β2m), which is encoded on chromosome 2. There are also an increasing number of MHC-like molecules, many of which are encoded outside the MHC locus. These molecules can share striking sequence, structural and functional features with MHC molecules, including the ability to present molecular cargo at the cell surface, and to bind β2m and immunoreceptors[51].

MHC genes are highly POLYMORPHIC, and they display some of the highest allelic diversity in the genome — more than 50 alleles of the MHC class Ia gene H-2D alone have been characterized. MHC class Ia molecules are key players in the adaptive immune system, and their extraordinary polymorphism enables them to present a diverse array of antigenic peptides. MHC alleles are co-dominantly expressed, increasing the diversity of MHC proteins that can be expressed by a given individual. MHC class Ib products are homologous to the class Ia molecules, but are usually less polymorphic. In many cases, their roles and expression patterns are unknown[122,123].

Individuals who express certain MHC class I haplotypes might have an increased probability of developing certain neurological diseases, including autism[93] and narcolepsy[124]. The source of genetic linkage between the MHC region and these and other neurological disorders remains a mystery (see main text).

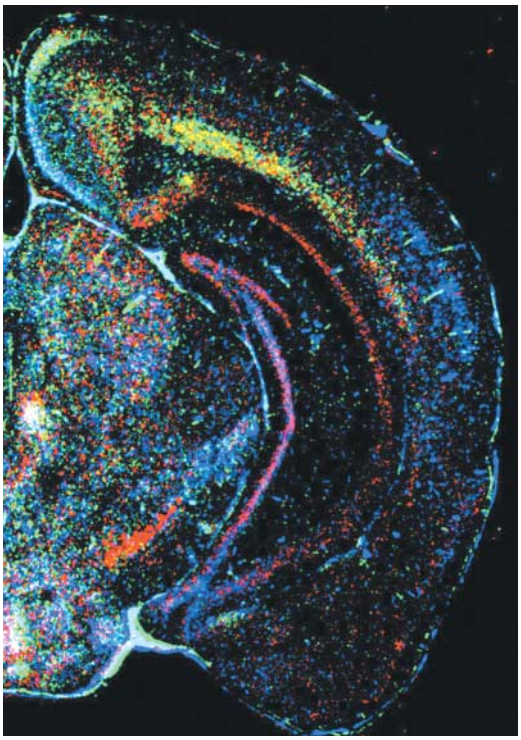


Figure 1 | **Expression of mRNA for three different major histocompatibility complex (MHC) class I molecules in a coronal section of adult mouse brain.** Blue, H-2D; red, T22; green, Qa-1. Image courtesy of G. S. Huh and C.J.S.

CYTOTOXIC T LYMPHOCYTE (CTL). An effector cell of the adaptive immune system that binds MHC class I and induces cytolysis of cells bearing non-self peptides derived from cytosolic pathogens. Most CTL express the co-receptor CD8.

T CELLS
A subset of lymphocytes that are defined by their development in the thymus and by the expression of receptors associated with CD3 proteins. T cells mediate cellular adaptive immunity, whereas B lymphocytes (B cells) mediate humoral adaptive immunity.

FLUORESCENCE-ACTIVATED CELL SORTING
A method that allows the separation of cells that express a specific protein by tagging them with a fluorescent antibody against the molecule of interest. A laser beam excites the fluorescent tag, and the emission of light triggers the cell sorting.

EPITOPE
A site on an antigen that is recognized by an antibody or antigen receptor.

class I expression in neurons can be further increased by treatments such as axotomy, exposure to cytokines[19] and changes in electrical activity[20,21].

It is becoming clear that brain immune privilege is not absolute — most viral and bacterial infections of neurons are cleared through an active immune response (albeit with different kinetics than in other tissues[26–28]), and foreign brain tissue can induce MHC class I-mediated transplantation immunity[29–31]. Also, several lines of evidence indicate that the partial CNS immune privilege that is observed under some conditions cannot be attributed simply to a lack of MHC molecules on the neuronal cell surface. Even neurons that overexpress MHC class I genes are resistant to CTL-mediated lysis following viral infection, despite increased CTL infiltration of the brain and enhanced viral clearance from MHC-overexpressing infected neurons[1].

So, immune privilege probably reflects the regulation of the immune response at other levels. For example, the entry of immune effector cells (including T CELLS) into the brain is regulated by the blood–brain barrier (BBB). Although this barrier is permeable to activated T cells (FIG. 2), and overall permeability increases with systemic infection, the BBB excludes most T cells from the brain, under normal conditions[32]. Additionally, factors released from neurons or glia might interfere with CTL–neuronal interactions, neuronal lysis or T-cell viability, contributing to an immunosuppressive microenvironment in the brain. For example, MHC class I-overexpressing neurons that resist T-cell lysis *in vivo* can be efficiently lysed if they are dissociated and grown *in vitro*[1]. So, both the entry and activity of immune effectors seem to be tightly regulated in the CNS. Our current understanding of CNS immune responses indicates that CTL-mediated lysis, which is commonly used to detect MHC class I protein function, would yield false negative results in neurons. However, it does not explain why so many studies have failed to detect MHC class I expression in neurons using more direct measures.

There are several possible explanations. First, many of the studies relied on immunostaining of aldehyde-fixed brain, using antibodies that were developed for FLUORESCENCE-ACTIVATED CELL SORTING of live immune cells. The EPITOPES that are detected by these antibodies are often exquisitely sensitive to fixation[1]. Indeed, even in mice that overexpress functionally measurable MHC class I protein under a neuron-specific promoter, MHC protein was not detected by immunocytochemical methods in fixed tissue slices, reflecting the challenges of the technique and the lack of suitable antibodies[1]. In addition, each antibody might detect only a fraction of the hundreds of MHC class I gene and allelic variants (BOX 1). So-called non-classical MHC class I proteins were most strongly detected in one study of the rat brain[12], but most of the antibodies that were used in previous CNS studies do not crossreact with this population. Furthermore, outside the nervous system, antibody binding to MHC class I molecules is known to be influenced by the peptide being presented by the MHC class I gene[33], a feature that might be different for neurons.

Biological factors probably also contributed to the divergent findings. MHC class I expression in neurons and some other non-neuronal CNS cell types is low compared with the levels that are seen in tissues such as the spleen[20] and the endothelial cells that line CNS blood vessels. More sensitive techniques, such as *in situ* hybridization and RNASE PROTECTION assays, might improve the detection of MHC class I molecules in neurons, as PCR-based analysis consistently reveals neuronal MHC class I mRNA expression, both *in vitro* and *in vivo*[14,21,24,25,34].

The age and identity of the neurons also affect the ability to detect MHC class I protein. MHC class I protein is expressed by only a subset of neurons at any given time, and it is developmentally regulated in the brain, the highest levels being seen in the perinatal period[20,21]. Another probable source of discrepancy in expression data is the wide variety of systems used. Many studies tested for MHC class I expression on acutely dissociated neurons *in vitro*, whereas immortalized neuron-like cell lines, such as OBL-21, CHP-126, RN33B and HEK293 cells, were used in others[2,5–8]. So, MHC class I protein diversity and expression patterns, as well as problems with detection methods and systems, probably all contribute to difficulties in detecting MHC class I molecules in neurons.

The role of neural activity in regulating MHC class I expression is also a contentious issue. In one set of experiments, blockade of sodium-based action potentials with tetrodotoxin (TTX) led to upregulation of MHC class I gene expression[17], whereas in another set, TTX treatment led to an equally dramatic downregulation[20]. However, these studies differ fundamentally. The first study examined TTX-treated (action potential blocked) hippocampal pyramidal neurons that had been dissociated from embryonic day 18 (E18) rats *in vitro*[17], and electrical silencing itself did not upregulate MHC class I expression unless it was paired with interferon (IFN) treatment. The second study showed that blocking spontaneously generated, endogenous electrical activity in the fetal cat brain decreased MHC class I expression in the dorsal lateral geniculate nucleus (dLGN) *in vivo*[20]. Subsequent *in vivo* experiments showed that MHC class I expression is increased in the rat hippocampus after seizures[20]. Therefore, in both *in vivo* experiments, activity is associated with elevated levels of neuronal MHC class I protein. It might therefore be expected that the relatively low connectivity (and subsequent low levels of activity) *in vitro* might result in lower basal levels of MHC class I expression in various culture systems. Regulation of MHC class I expression is also known to change with development: adult dorsal root ganglion (DRG) sensory neurons are refractory to IFNγ[35], whereas the same neurons from rats at E15 respond with robust upregulation of MHC class I expression[18].

Although MHC class I genes are best known for their 'classical' products, which are crucial for the adaptive immune response mediated by T cells, most class I genes actually code for 'non-classical' MHC class I products (FIG. 3), many of which have no known function in the immune system. Some non-classical class I proteins associate with the MHC class I light chain β2 microglobulin (β2m), bind and present peptides (TABLE 1), and have high sequence and structural homology with members of the classical MHC class I proteins, although they display more restricted expression patterns and little or no polymorphism. Interestingly, recent studies located one family of these 'orphan' molecules exclusively within the VNO, a small pit in the anterior nasal cavity of some mammals that is specialized to detect pheromones (see below)[24,25].



Figure 2 | **T cells can enter the CNS.** Pseudocoloured transmission electron micrograph shows adoptively transferred myelin-basic-protein-restricted CD4$^+$ T cells (green) entering the CNS through the tight endothelial layer of the blood–brain barrier (BBB) during induction of experimental autoimmune encephalomyelitis. Image courtesy of Hartmut Wekerle, Max-Planck Institute for Neurobiology.

In situ hybridization with specific probes for individual classical and non-classical MHC class I genes reveals a complex pattern of MHC class I mRNA expression in the healthy adult brain[20,21,24,25] (FIG. 1). MHC class I genes display overlapping but distinct neuronal expression patterns, and these patterns are particularly dynamic during normal development[20,21]. Along with the fact that MHC class I expression can be regulated by naturally occurring electrical activity, these results indicate that the precise timing and level of MHC class I expression might be crucial for its function in the brain. An important step towards understanding the role of MHC class I molecules in the brain is to determine which of the many MHC class I proteins are expressed in neurons, and to characterize the specific expression profile of each MHC class I product in the developing and adult brain.

Physiological functions of neuronal MHC class I

Investigations into the function of MHC class I genes in the brain were prompted by the identification of MHC class I family members in genomic screens of specific neuronal populations. The first hint of a non-immune function for MHC class I molecules in neurons came from an unbiased functional screen for genes that are involved in activity-dependent plasticity in the developing visual system[20]. MHC class I gene expression was found to decrease after activity blockade

POLYMORPHIC
Having multiple alleles at a single locus.

RNASE PROTECTION
A technique that is used to measure the quantity of mRNA that corresponds to a given gene in an RNA sample. A labelled RNA probe that is complementary to the relevant sequence is hybridized with the RNA sample; any RNA that does not hybridize with the probe is then digested away using ribonuclease. The undigested mRNA can then be quantified on an electrophoresis gel.

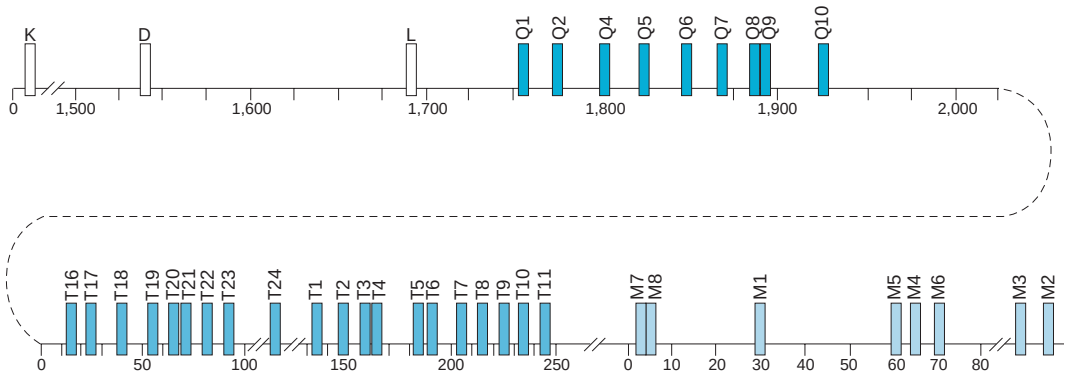


Figure 3 | **The mouse major histocompatibility complex (MHC) class I region.** Mouse chromosome 17 showing classical (MHC class Ia; white) and non-classical (MHC class Ib; blue shades) genes.

with TTX, specifically during the period when spontaneous retinal activity is needed for synaptic refinement of overlapping eye-specific inputs to LGN neurons to form a mature, segregated pattern of connections[20]. Subsequent examination revealed that MHC class I expression closely parallels the spatiotemporal pattern of activity-dependent plasticity in the developing and adult mammalian brain, including the early postnatal retina and LGN, and the adult cerebellum and hippocampus[20,21,36]. Together, these observations indicated that MHC class I molecules might be involved in activity-dependent structural and functional plasticity[20,21,36].

These tantalizing correlations were tested directly by examining two forms of activity-dependent plasticity in mice that were genetically deficient for MHC class I proteins[21]. Rather than knocking out the class I genes themselves, the authors used mice that lacked two crucial players in the MHC class I protein expression pathway — β2m, the obligatory light chain of most MHC class I (REF. 37), and TAP1, a transporter that is required to load peptides onto MHC class I molecules for delivery to the cell surface[38]. In the absence of these two proteins, there is little stable expression of MHC class I molecules at the cell surface[37,38] (FIG. 4).

In these MHC class I-mutant mice, retinal afferents fail to segregate into eye-specific layers (FIG. 4) despite the presence of normal retinal activity[21], indicating that MHC class I might be involved in translating neural activity into developmental changes in connectivity[21,36]. These and other activity-dependent changes in the pattern of connections are thought to involve functional weakening and strengthening of synapses — phenomena that have been best-studied in the mammalian hippocampus. In MHC-deficient mice, adult hippocampal long-term potentiation is enhanced, whereas long-term depression is absent[21] (FIG. 4). These results indicate a crucial role for MHC class I in functional weakening and structural retraction of synaptic connections[21,36]. Remarkably, the same specific defects were found in mice that were mutant for CD3ζ, a component of many receptors for MHC class I proteins in the immune system. However, more severely immunocompromised RAG1-deficient mice did not share these defects. Therefore, brain phenotypes in MHC-deficient mice are not the nonspecific result of general immune abnormalities, but rather reflect a novel non-immune function for MHC class I molecules in the CNS[21,36]. In addition, they are not likely to be the result of iron overload, a known phenotype in β2m-deficient mice[39], for the following reasons. First, *CD3ζ*$^{-/-}$ mice, which share the specific neuroanatomical and synaptic defects of *β2m*$^{-/-}$;*TAP1*$^{-/-}$ mice, do not share their defects in iron trafficking (see below). Second, β2m-deficient mice do not exhibit a significant increase in cerebral iron levels, despite striking increases in hepatic iron, perhaps owing to the ability of the BBB to restrict plasma iron entry[40]. Third, iron overload in these mice is cumulative, with pathology emerging as the mice age. These experiments were conducted on very young mice (1 week–2 months of age), before iron accumulations are detectable[41].

A second screen identified several members of the non-classical MHC class I family of genes that are expressed specifically in the mammalian VNO[25]. This cluster of MHC class I genes (encoded in the M10 region, FIG. 3) is selectively expressed in subpopulations of sensory neurons in the VNO, such that each VNO neuron expresses only one or a few of these MHC class I molecules[24,25], and specific MHC class I molecules are co-expressed with specific receptors of the pheromone system, the V2Rs. In heterologous cells, co-expression of the pheromone receptor EC1-V2R, the MHC class I light chain β2m and the MHC class I heavy chain M10.5 led to surface expression of the pheromone receptor *in vitro*, whereas in the absence of β2m, surface expression of the VN4/V2R pheromone receptor in the lumen of the VNO was compromised *in vivo*[24]. β2m-deficient mice do not display normal male–male aggression[24], indicating that MHC class I is important in social interactions (recently reviewed in REF. 42).

These studies are important in that they provide unexpected insights into the role of MHC class I in normal neuronal function, both centrally and in the periphery. They also provide a valuable starting point for further studies. One caveat of both studies is that they make use of mice that are deficient in β2m, which reduces cell-surface expression of most MHC class I genes. In addition, these mutations are systemic and present from birth. β2m is expressed throughout the body

Table 1 | MHC class 1 proteins expressed by neurons in the mouse CNS

Genes or gene families	Presents	Binds β2m?	Function	Receptor(s)	Refs
Classical class I (class Ia)					
D and K	Antigenic peptides	Yes	Antigen presentation, activation/inhibition of $CD8^+$ T cells, NK cells;dysfunction implicated in autoimmune disease, cancer	αβTCR, Ly49, CD8	4,8, 10,11, 13–17, 20,21
Non-classical class I (class 1b)*					
M1, M10	?	Yes	Pheromone receptor targeting, social interactions?	?	24,25
Qa-1	Signal peptide of class Ia molecules, TCRα chain, bacterial heat-shock peptide, other hydrophobic peptides?	Yes	Recognized by T cells,used for control of NK (and presumably NKT) activity	CD94/NKG2A, CD94/NKG2C	21
T22	Empty?	Yes	Cell activation marker; immunoregulation?	γδ-T cells?	21

*see REF. 12. MHC, major histocompatibility complex; NKT, natural killer T cell.

and at many stages of development, so interpretation of the origins of functional and behavioural phenotypes in full knockouts must be made with caution. Nevertheless, this approach is useful as a first-pass to demonstrate functional requirements for MHC class I molecules in the nervous system.

It will be important to clarify the location, identity and timing of MHC class I protein expression that is relevant for its functional and structural effects in neurons, perhaps using conditional knockouts or reagents that acutely and/or locally manipulate MHC class I expression. Possible interactions between MHC class I and other proteins, including pheromone receptors, should be verified using methods that permit discrimination of direct interactions from participation in large, multi-protein complexes. It will also be important to attempt acute rescue of MHC class I-deficient activity-dependent plasticity and behavioural phenotypes to determine whether they are the result of ongoing MHC class I signalling or the product of MHC class I function in a developmental cascade.

MHC class I binding partners

How do MHC class I proteins generate and transduce signals in neurons at the molecular level? Almost all MHC class I mRNAs encode transmembrane proteins (the exception being a handful of secreted MHC class I proteins), but the cytoplasmic domains of MHC class I molecules are small, indicating that a binding partner might be required for intracellular as well as intercellular MHC class I signalling. Several candidate partners have been identified on the basis of the known functions of MHC class I molecules outside the CNS (FIG. 5).

Immunoreceptors. In the immune system, MHC class I signalling largely involves interactions with other transmembrane immune proteins. Known binding partners for MHC class I proteins in the immune system include T-cell antigen receptors (TCRs), NKG2/CD94 receptors, human KIR and LIR proteins, CD8 dimers and mouse Ly49 proteins[43–45]. These receptors include players in both the INNATE and adaptive immune systems.

A crucial aspect of studies into the function of MHC class I molecules in neurons is the identification of MHC class I receptors that are expressed endogenously in the CNS, either on neurons or on non-neural cells. One clue to the possible identity of a neuronal MHC class I receptor came from the finding that CD3ζ — a required signalling component of TCRs and also some natural killer cell receptors[46,47] — is expressed in a restricted set of neurons and is regulated during development[21]. Outside the brain, cells do not express CD3ζ stably on their cell surface unless they also express TCR[48], indicating that TCR or a related receptor might be present in the developing and adult CNS[21]. CD3ζ-deficient mice exhibit defects in developmental and adult activity-dependent plasticity that are indistinguishable from those that are seen in MHC class I-deficient mice, indicating that at least some of the neuronal functions of MHC class I molecules might involve a CD3ζ-containing receptor[21]. In addition, much of the signalling machinery that lies downstream of MHC class I receptors in the immune system is also present in neurons, and some components are already known to have a role in activity-dependent plasticity (reviewed in REF. 36).

Despite evidence for a neuronal role for CD3ζ, so far no complete MHC class I-binding receptors have been identified in neurons. However, recent studies have detected mRNA that encodes a component of the TCR — TCRβ — in adult and developing brain tissue[49,50]. TCRβ mRNA is dynamically regulated during mouse brain development: in neonates, expression is highest in thalamic nuclei, including the LGN, at postnatal days 4 and 7, which corresponds to the period when visual inputs are undergoing activity-dependent refinement[49]. However, mice that are genetically deficient for TCRβ undergo normal visual refinement, unlike those lacking CD3ζ, indicating that TCRβ-containing receptors are not required for this process[49]. In adults, TCRβ

INNATE IMMUNE SYSTEM
The system that mediates the early phases of the host response to a group of related pathogens. Innate immune responses, unlike adaptive immune responses, do not increase with repeated exposure to a given pathogen.

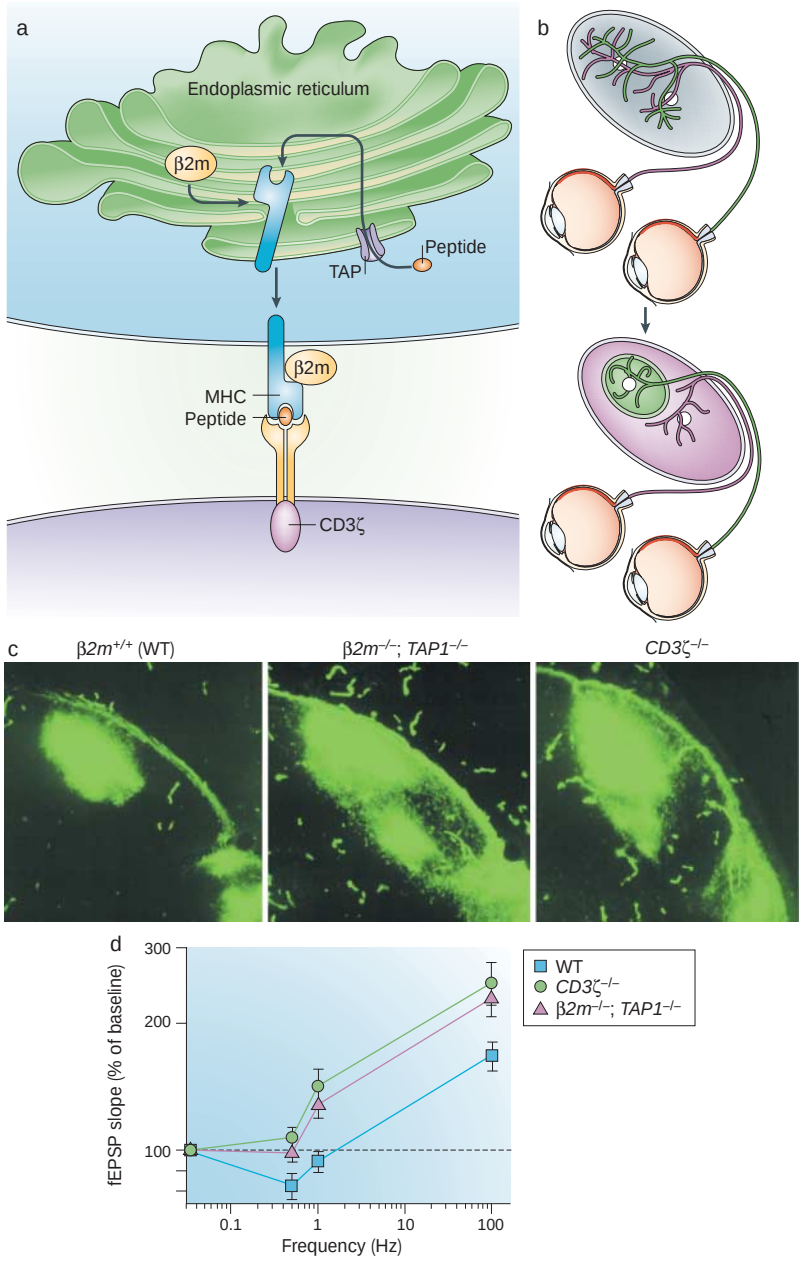


Figure 4 | **Major histocompatibility complex (MHC)-deficient mice have specific defects in activity-dependent plasticity. a** | Mice that are genetically deficient for β2m and TAP1 lack stable cell surface expression of most MHC class I, owing to lack of the required light chain and peptide[36]. **b** | Endogenous activity arising in the eyes drives refinement of an initially overlapping projection from the retina to the lateral geniculate nucleus (top) into the mature, laminar, segregated pattern (bottom)[36]. **c**,**d** | Mice that are deficient for MHC class I genes or CD3ζ fail to undergo normal activity-dependent refinement of the developing visual projection (**c**) and display systematic shifts in hippocampal synaptic plasticity (**d**). fEPSP, field excitatory postsynaptic potential; WT, wild type. Parts **c** and **d** modified, with permission, from REF. 21 © (2000) American Association for the Advancement of Science.

SOMATIC RECOMBINATION
Gene segment rearrangements during lymphocyte development that lead to the production of a wide variety of complete, variable regions for T-cell antigen receptors and immunoglobulins.

transcripts are strongly expressed in layers 5 and 6 of the neocortex, whereas expression in the thalamus declines[49,50].

In the immune system, functional TCRβ transcripts are encoded by loci that have undergone SOMATIC RECOMBINATION, whereas all TCRβ transcripts that are detected in the brain are the product of direct splicing of non-rearranged genomic loci[49,50]. One of these brain TCRβ transcripts encodes a hypothetical 23 kDa protein, but immunoprecipitation and Western blotting of brain tissue with antibodies specific for the TCRβ constant region failed to detect proteins of any size[49,50]. Furthermore, another obligatory component of the functional immune TCR, TCRα, was not detected in neurons[49]. It is possible that TCR subunit proteins are expressed only transiently or at low levels in neurons, or they might not be recognized by reagents that were developed for use in the immune system. It is also possible that other CD3ζ-containing receptors are involved in the actions of MHC class I molecules in the brain. In support of this suggestion, DIgR1, a putative activating immunoreceptor that might bind CD3ζ-like proteins, and DIgR2, its inhibitory partner, are expressed in neurons in several regions of the brain, including the hippocampus, striatum, cortex and cerebellum (J. Syken and C.J.S., unpublished data).

It is possible that CD3ζ might also influence neuronal development and plasticity through a distinct, convergent mechanism that is independent of MHC class I. Alternatively, CD3ζ-containing receptors on neurons or other cells might compete for MHC class I interactions with other functionally relevant cell surface proteins (FIG. 5).

Non-immunoreceptor transmembrane proteins. MHC class I-like molecules are encoded outside the MHC class I region, and they share sequence, structural and functional features with the MHC class I products (BOX 1). There is evidence that several of these molecules function outside the immune system by binding non-immunoreceptor transmembrane proteins[51] (FIG. 5). Indeed, disruption of one such interaction is the probable cause of a common heritable disease, hereditary haemochromatosis (HH) (FIG. 6). HH is a disorder of dietary iron homeostasis, and it is usually caused by a point mutation in a gene that encodes an MHC class I-like molecule, HFE[52]. HFE forms a complex with the transferrin receptor (TFR)[53,54], which binds iron-loaded transferrin. The HFE–TFR interaction regulates iron homeostasis, and the point mutation that is found in ~83% of HH patients[52] probably interferes with HFE surface expression[55], leading to toxic accumulation of iron in many tissues[54].

Another MHC class I-like molecule, the neonatal Fc receptor (FcRn), is involved in transport of maternal immunoglobulin across the fetal intestinal epithelium. FcRn shares the distinctive MHC class I fold, a structure on the extracellular domain that is specialized to bind peptide antigens in MHC class Ia and some Ib proteins. In class Ia molecules, the fold is open and forms a groove that holds the peptide, whereas in FcRn, the fold is closed and cannot bind peptides[56]. Instead, the molecule uses parts of this domain to bind the Fc portion of maternal immunoglobulin[57].

These results demonstrate that some MHC class I-like proteins can bind non-immunoreceptor macromolecules[58] and affect their transport between different cellular compartments. Consistent with this role, recent results indicate that the M10 non-classical MHC class I

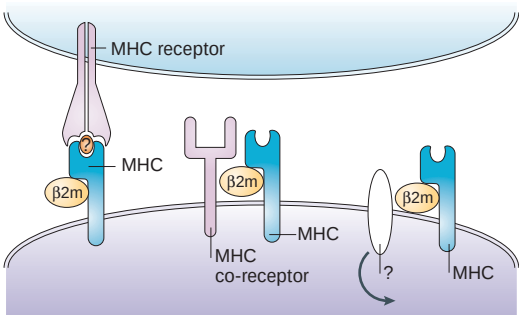


Figure 5 | **Modes of major histocompatibility complex (MHC) class I protein–protein interactions.** In the immune system, MHC class I proteins can interact with other immune proteins (yellow) on the same cell or on other cells, including T cells and natural killer cells. Outside the immune system, MHC class I-like proteins are known to interact with non-immune proteins (white) on the same cell, and in some cases might modulate their surface expression.

proteins might be required for proper cell-surface expression of members of the V2R family of pheromone receptors in the VNO[24], raising the possibility that there are other such examples.

Implications for neuronal disorders

Products of the MHC class I region have been linked to a wide variety of disorders with neurological symptoms, including spinocerebellar ataxia, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, narcolepsy, dyslexia, schizophrenia and autism (reviewed in REFS 59–62). This diversity of associations is a product of the role of MHC class I in adaptive immunity, as well as its extraordinary genetic diversity. In addition, disruptions of MHC class I function in either direction — too weak (permitting rampant infections and tumour expansion) or too strong (causing transplant rejection and AUTOIMMUNITY) — can lead to clinical disturbances. It is becoming clear, however, that this long list of disorders implicating MHC class I molecules also reflects the crucial functions of MHC class I proteins beyond the immune system.

Targeted immune attack of neurons. As some neurons express MHC class I, they could be susceptible to targeted attack by the body's own immune system[63,64]. Such an attack could be triggered by many stimuli, including neurotropic viral or bacterial infection, or cancer. For example, neurons and other cell types upregulate the expression of MHC class I proteins after spinal cord infection[13]. It is unclear whether increases in MHC protein in these and other cases are a symptom or a cause of neuronal damage. Interestingly, in an animal model of virus-induced demyelination (Theiler's murine encephalomyelitis), MHC class I-deficient mice are protected against degeneration following demyelination[65], indicating a causal role for MHC class I in some aspects of neuronal damage. Cytotoxic T cells can enter the CNS when they are activated, as well as during periods of systemic stress, so they could potentially participate in MHC class I-mediated neuronal damage[32,66].

In some cases, the immune surveillance that holds cancers at bay can go awry, leading to neuron-directed autoimmunity. Paraneoplastic neurological degenerations (PNDs) are a group of neurodegenerative disorders that develop in some patients with non-neuronal cancers[67]. PNDs are triggered by a T-cell-mediated immune response against cancer antigens that are also expressed in neurons (onconeural antigens), leading to autoimmunity with neurological symptoms. In addition, humoral immunity (in the form of antibodies against specific neuronal antigens) has an important role. Several PNDs have been identified, each with distinct neurological symptoms and each linked to characteristic tumour types[68]. It is unknown why different neurons are targeted in each PND, as the identified target antigens are often much more widely expressed. One possibility is that the affected neurons must express both the target antigen and the appropriate MHC class I molecule to present it. In support of this idea, PNDs primarily affect the limbic areas and cerebellum, which are sites of high MHC class I protein expression in the adult brain[20,21].

Neuroprotection. Counter-intuitively, neuronal MHC class I protein might also be neuroprotective. Although MHC class I-restricted T cells are thought to contribute to clinical demyelination in multiple sclerosis and other disorders, new evidence indicates that innate and adaptive immune responses can facilitate CNS repair at a later stage by restricting a prominent secondary wave of damage (reviewed in REF. 69). For example, anti-myelin basic protein T cells arrest the progression of this secondary degeneration through an unknown mechanism[70].

Developmental and behavioural disorders

Because MHC class I is involved in normal brain development and plasticity[21,36], it is conceivable that altered MHC class I function could contribute to the disruption of these processes. This possibility is consistent with reports that several neurological disorders also have associated immune symptoms. This complex of symptoms might reflect crosstalk between the immune and nervous systems, or alternatively, might result from a disruption of shared molecular machinery. In addition to MHC class I, key players in the CELLULAR IMMUNE RESPONSE include adhesion molecules, pro-inflammatory cytokines, chemokines and proteases, many of which also have important roles in neuronal development and function. So, an immune response might have direct neuronal consequences, because both systems use the same molecular machinery, albeit with different cellular readouts.

In this section, we will discuss the evidence that MHC class I is involved in three common neurological disorders: schizophrenia, autism and dyslexia (a full discussion of the symptoms and aetiology of these disorders is beyond the scope of this review).

Schizophrenia. Schizophrenia affects about 1% of the population worldwide, and it is thought to be a neurodevelopmental disorder[71]. Schizophrenia has a strong

AUTOIMMUNITY
Immune responses directed at self antigens.

CELLULAR IMMUNE RESPONSE
An adaptive immune response that is dominated by antigen-specific T cells, as opposed to humoral immunity, which is primarily mediated by antibodies.

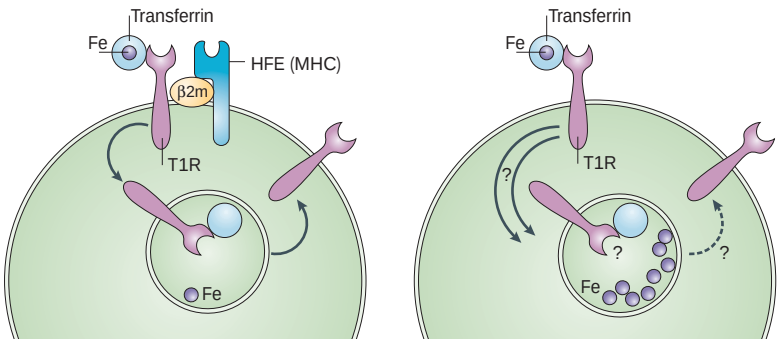


Figure 6 | ***HFE* point mutation causes hereditary hemochromatosis.** HFE interacts with the transferrin receptor, which is involved in internalization and unloading of iron-loaded transferrin. A point mutation in the *HFE* gene prevents interactions between HFE and its obligatory light chain β2m, preventing stable cell surface expression of HFE, and leading to enhanced dietary iron absorption.

genetic component[72], and over 60 studies to date have noted a genetic correlation between schizophrenia and MHC class I, although these results remain controversial (REFS 73,74; reviewed in REF. 75). Environmental factors probably also have a crucial role, because identical twin concordance rates are only ~50% (REFS 76,77).

One possible environmental risk factor for schizophrenia might be an infectious insult. Reports have correlated maternal viral infection with an increased chance of schizophrenia in the child[78]. Furthermore, an animal model of respiratory infection of pregnant mice induces a syndrome with many parallels to schizophrenia in the offspring, including abnormal social interactions, increased anxiety in novel or stressful situations, defects in prepulse inhibition, thinning of the neocortex and hippocampus, and pyramidal cell atrophy[79]. Therefore, changes in maternal or fetal immune signalling might influence the development of aberrant neuronal connectivity and function in schizophrenia. Genetic immune abnormalities could contribute to the relative vulnerability to infection, as well as the ability to mount an appropriate immune response.

There is widespread but contentious evidence of immune abnormalities in people with schizophrenia, including increased serum autoantibodies[80], interleukin-6 (IL-6)[81] and soluble IL-2 receptor[82], but decreased expression of IL-2 and IFNγ[83]. These features, along with adolescent onset, stress triggers and variability of course, are shared with known autoimmune disorders[84]. Patients who have a first degree relative with schizophrenia are significantly more likely to also have a parent or sibling with an autoimmune disease[85]. Conversely, there is a strong negative correlation between schizophrenia and two specific autoimmune disorders — insulin-dependent diabetes mellitus[86] and rheumatoid arthritis[87]. Psychotic episodes have been shown to be preceded by raised levels of immune cytokines in the cerebrospinal fluid[88], and treatment with cytokines can provoke psychiatric symptoms[83]. CYTOKINES are known to affect brain development and adult synaptic transmission and plasticity, although the mechanisms are unknown.

In neurons, cytokines markedly upregulate expression of MHC class I proteins *in vitro*[4,8,16–19]. Therefore, it is possible that cytokine-induced changes in neuronal MHC class I expression, at a time when MHC class I is involved in sculpting developing neuronal circuits, might cause neurodevelopmental abnormalities that lead to schizophrenia. In addition, cytokine-induced changes in MHC class I expression in the adult might acutely affect synaptic function during psychotic episodes. It will be important to determine whether cytokines induce similar changes in MHC class I expression *in vivo*.

Schizophrenia is typified by a baffling array of neurological symptoms, including enlarged lateral ventricles[89] — a phenotype that is occasionally seen in MHC class I-deficient mice[21]. Furthermore, anatomical studies of post-mortem brain tissue from people with schizophrenia show an apparent defect in normal developmental pruning of synaptic connections[90], also one of the main phenotypes of MHC class I-deficient mice[21]. Although schizophrenia is thought to be a neurodevelopmental disorder, symptoms are not typically observed until late adolescence or early adulthood, so the bulk of the reported syndrome of symptoms could be the result, not the cause, of aberrant synaptic organization or loss of connections.

Autism. Several studies have indicated a genetic link between autism and genes within the MHC class I region[91–93] (but see also REF. 94). In particular, an unusual number of children with autism share all or part of the extended MHC HAPLOTYPE B44-SC30-DR4 (REFS 91,92,95). Although this linkage is not statistically significant, recent studies on hundreds of multiplex families have consistently failed to identify any genes that are significantly linked, despite a clear genetic component to the disorder on the basis of inheritance patterns[96]. This implies that autism is a POLYGENIC disorder and/or that interactions with environmental factors are required. Consistent with a role for environmental factors, identical twin concordance rates are less than 100% (REF. 96). As with schizophrenia, there is evidence that maternal viral infection can increase the risk of the child developing autism[97–99].

There are also reports of elevated incidence of immune disorders in patients with autism and their first-order relatives. These include abnormal T-cell populations and cell-mediated immunity[100–102], reduced natural killer cell activity[103], and abnormal humoral and autoantibody responses[104–109]. These abnormalities are not sufficient to cause autism, however, as first-order relatives that do not have autism often share immune system dysfunction[110]. Rather, an environmental factor (such as an immune challenge) might interact with these and other — possibly genetic — factors to cause autism.

Although autism is usually diagnosed in children around age three or four, pathology probably precedes diagnosis. For example, recent studies reveal abnormal brain development by the early postnatal period, which is manifested in increased head circumference[111]. Larger brain volumes could be the result of a failure to remove inappropriate connections during the course of normal

CYTOKINES
Proteins that affect the behaviour of other cells through specific cytokine receptors. Cytokines that are made by lymphocytes are often called lymphokines or interleukins.

HAPLOTYPE
The combination of alleles that is expressed by a given individual. The MHC genes are usually inherited as a haplotype from each parent.

POLYGENIC
A term that refers to several loci that encodes proteins of similar function.

development, a phenotype that has been identified in specific regions of the MHC-deficient mouse brain[21]. It is also of interest that populations of neurons that are known to be specifically affected in autism, including cerebellar Purkinje cells, normally express high levels of MHC class I proteins[20,21].

Dyslexia. Developmental dyslexia is the most common childhood learning disorder. Children with dyslexia have difficulties in reading, despite sufficient intelligence, education and social environment. There is clearly a strong genetic component to dyslexia, although MONOZYGOTIC twin concordance is less than 100%, indicating a role for environmental contributions[112]. Linkage and association studies have identified at least six loci that correlate with dyslexia. The second locus to be identified — DXY2 — maps to the MHC complex[113], a finding that has been confirmed by several independent studies (reviewed in REF. 112). Linkage of reading-related phenotypes to this region is currently one of the most consistent findings in the genetics of human cognition[112].

There are also controversial reports of co-morbidity in patients with dyslexia and their immediate relatives for immune disorders, including Hashimoto's thyroiditis, ulcerative colitis, rheumatoid arthritis, Crohn's disease and systematic lupus erythematosus[114,115]. In addition, unusual autoantibodies have been detected in the serum of mothers whose children have dyslexia[116,117].

Notably, people with dyslexia exhibit specific difficulties in visual and auditory discrimination[118] — tasks that involve pathways that express high levels of MHC class I during mouse development[21,59,119]. Furthermore, development of primary visual projections is abnormal in mice that are deficient for cell surface MHC class I proteins[21], indicating that changes in MHC class I expression are sufficient to disrupt the mature form of important visual pathways. Therefore, it would be of great interest to determine whether MHC class I is also expressed in primate and human visual structures, including the LGN, and whether this expression is disrupted in post-mortem brains from people with dyslexia.

Critique. Clearly, further experiments are necessary to test the possible significance of MHC class I in each of the above neurological disorders, as the genetic links to MHC class I (or any other gene) remain contentious. Many tantalizing human studies rely on small pools of patient data, which are in some cases poorly controlled. In addition, methodological and aetiological heterogeneity are likely to contribute to the conflicting results. All three disorders discussed here are complex and probably involve multiple predisposing genes, as well as environmental influences. An infectious event is a tantalizing candidate environmental factor, because it could account for two puzzling aspects of these disorders: the fact that immune abnormalities are merely predisposing, and the maddening heterogeneity of these syndromes in terms of symptoms. Infection could provide the mandatory 'second hit' that produces disease in a predisposed individual, and the identity, time, duration and intensity of infection could all potentially affect the range, timing and severity of symptoms on a continuum.

The potential involvement of MHC class I genes in these and other neurological disorders might also provide a clue to the puzzle of the specificity of neuronal destruction. Neurodevelopmental and neurodegenerative disorders usually produce distinctive patterns of neuronal loss, disruption or damage. Why are some neurons targeted and others spared? One possibility is that expression of specific MHC class I molecules might render subsets of neurons temporarily and selectively vulnerable to autoimmune attack or MHC class I-mediated disruption of development or function. Additional specificity could be conferred by the timing of MHC class I expression relative to distinct developmental events, as well as the co-expression of crucial cofactors or target proteins. A key first test of this hypothesis will be to compare the spatial and temporal expression patterns of individual MHC class I proteins with the populations of neurons involved in these disorders. Intriguingly, rat MHC class I and β2m proteins are expressed most strongly by the dopaminergic and motor neurons that are most susceptible to neurodegeneration in Parkinson's disease (FIG. 1) and amyotrophic lateral sclerosis in humans[21,23].

Owing to the probable multiplicity of disease aetiologies, it will be important to develop objective — perhaps molecular or biochemical — diagnostic criteria that discriminate subsets of patients with different pathophysiology and disease course. This must be accompanied by the development of appropriate animal models, in which MHC class I protein expression and function are monitored along with behavioural and pharmacological abnormalities. It would also be of interest to determine MHC class I protein expression, function and dysfunction in patients with these disorders. Subsequent studies could examine the value of immunodiagnostics and immunotherapy specifically in the pool of patients that is most likely to be responsive; that is, those with a probable immune aetiology.

Concluding remarks

Determining the extent to which neuronal and immune system MHC class I functions share similar mechanisms is of vital importance. Many MHC class I receptors[49] and downstream signal transduction components[36] are expressed in neurons. Which of these, if any, are required for the neuronal functions of MHC class I? Are other aspects of MHC class I function in the immune system — for instance, peptide loading — instructive or permissive in the neuronal capacity of MHC class I? What is the role of the genetic diversity in neuronal functions of MHC class I?

Considerations raised in this review indicate new approaches to the study of brain development and plasticity. Understanding the role of MHC class I in the brain might also provide unexpected new avenues for the diagnosis, treatment and prevention of neurological disorders.

MONOZYGOTIC
A term that refers to identical twins, which develop from a single egg.

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Competing interests statement

The authors declare that they have no competing financial interests.

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