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### Immune Privilege Revisited: The Roles of Neuronal MHC Class I Molecules in Brain Development and Plasticity

Adema Ribic Yale University Department of Molecular Biophysics and Biochemistry, New Haven, CT USA

#### 1. Introduction

#### 1.1 MHC class I molecules: Molecular hallmarks of individuality

Ever since its initial discovery in 1948 by George Snell, major histocompatibility (MHC) complex became the focus of intense research that, due to its diverse roles, gradually extended far beyond transplantation biology. MHC class I molecules are found on virtually all nucleated cells of jawed vertebrates and are the most polymorphic molecules described to date (Cresswell et al. 2005, Solheim 1999). Their polymorphism is so high that, with the exception of identical twins, two individuals with the exact same set of MHC molecules (both class I and II) do not exist.

#### 1.2 Structure, function and properties of MHC class I molecules

MHC class I molecules are normally composed of three subunits: transmembrane heavy chain, small  $\beta$ -2-microglobulin subunit and the presenting antigenic peptide [Figure 1; (Cresswell et al. 2005, Solheim 1999)]. MHC class I molecules are assembled in the endoplasmatic reticulum and are generally dependent on the presence of all three subunits for proper cell surface expression. The MHC class I heavy chain is a glycoprotein with reported molecular weight of 42-48 kDa. It consists of three extracellular domains ( $\alpha$ 1-3), and short transmembrane and cytoplasmic regions (Figure 1).  $\alpha$ 1 and  $\alpha$ 2 domains form the peptide binding groove and are the regions responsible for the high polymorphism of MHC class I molecules.  $\alpha$ 3 domain carries the signature of the immunoglobulin superfamily, the immunoglobulin fold.

 $\beta$ -2-microglobulin is the smaller, 11-13 kDa subunit, without a transmembrane domain. It is non-covalently attached to the MHC class I heavy chain on the cell surface.  $\beta$ -2microglobulin is encoded by a gene settled outside of the MHC cluster and it is structurally also immunoglobulin-like (Figure 1). MHC class I molecules are divided in two groups: classical and non-classical MHC class I. Classical MHC class I molecules are highly polymorphic, usually form trimers on the cell surface and are mainly associated with antigen presentation. Non-classical MHC class I molecules are still somewhat of an enigma.

They are not as polymorphic as the classical MHC class I and some of them do not require  $\beta$ -2-microglobulin or the binding of peptide in order to reach the cell surface (Arosa et al. 2007). Non-classical MHC class I are also implicated in a wide range of immune and non-immune processes, from presentation of glycolipids to regulation of pheromone signalling (Arosa et al. 2007, Fishman et al. 2004).



Fig. 1. Structure of MHC class I molecules. Ribbon structure of MHC class I molecule: MHC class I molecule (HLA-A2, in this case) is

composed of heavy chain (red),  $\beta$ -2-microglobulin (violet blue) and the presenting peptide (dark blue). Immunoglobulin fold structure of the  $\alpha$ 3 domain of the heavy chain and the  $\beta$ -2-microglubulin is visible. Image courtesy of Wikimedia Commons.

#### 1.3 MHC class I signaling in immune and non-immune systems

The main function of classical MHC class I molecules is the presentation of foreign, "nonself" peptides to cytotoxic T-cells. This process initiates the canonical MHC class I/T-cell receptor signaling pathway (Figure 2). Cytotoxic T-cells become activated through this pathway after they recognize the MHC class I-presented peptide as foreign and potentially hazardous. The signalling cascade brought about by MHC class I/TCR interaction induces cytoskeletal rearrangements and cytokine production in T-cells activated by it (for more details, the reader should refer to general immunology textbooks). Although this is the canonical MHC class I signalling pathway, the TCR complex is not the only receptor for the MHC class I molecules. MHC class I proteins are able to interact with a large number of receptors within the immune system, both in *cis* and in *trans*, such as killer-cell immunoglobulin-like receptors (KIRs), leukocyte immunoglobulin-like receptors (LILRs), etc., causing a wide range of responses (Parham 2005).



#### Fig. 2. Canonical MHC class I/T-cell receptor pathway.

TCR receptor complex is depicted with its main components: T-cell receptor (TCR) and accessory CD3 molecules ( $\epsilon$ , $\gamma$ , $\zeta$  and  $\delta$ ). CD8 is a co-receptor specific for MHC class I molecules. After T-cell receptor (TCR) complex recognizes the peptide presented by MHC class I as foreign, TCR receptor complex subunits rearrange within the membrane in a more spatially constricted configuration. CD3 subunits become phosphorylated (orange circles) by lymphocyte-specific protein kinase (Lck) and zeta-chain associated protein kinase 70 (ZAP70). ZAP70 also phosphorylates linker of activated T-cell kinase (LAT) before T-cell activation.

Outside of the immune system, MHC class I molecules have been implicated mainly in regulation of trafficking and internalization of hormone receptors. Interactions with insulin receptor (IR),  $\gamma$ -endorphin receptor, luteinizing hormone receptor and many others have been reported (Arosa et al. 2007). The best characterized non-immune interaction of MHC class I is with the IR. It has been suggested that MHC class I molecules are involved in glycosylation of IR and its proper transport to the cell surface, but most evidence has been provided for the role of MHC class I in insulin-induced IR internalization (Olsson et al. 1994, Ramalingam et al. 1997, Stagsted 1998, Stagsted et al. 1993a, Stagsted et al. 1990, Stagsted et al. 1993b). A number of studies have suggested that MHC class I associates with IR after insulin binding thereby causing its internalization and removal from the cell surface. Functional significance of these findings is still debated; however, certain MHC class I genes have been implicated in the aetiology of type I diabetes (Fernando et al. 2008).

#### 1.4 Immune privilege and neuronal expression of MHC class I molecules

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The concept of immune privilege refers to the ability of certain organs (eyes, brain, testicles and the uterus while harbouring a foetus) to evade inflammatory responses during antigen presentation (Hong and Van Kaer 1999). Tissues transplanted to the central nervous system (CNS) show prolonged survival compared to tissues grafted to other locations in the body, such as skin (Carson et al. 2006, Galea et al. 2007). Furthermore, a number of pathogens are able to evade the immune responses by "hiding" in the CNS structures (Carson et al. 2006, Galea et al. 2007). This immune privilege of the CNS is thought to be a consequence of the blood-brain barrier (BBB), considered impermeable to the cells of the immune system (Carson et al. 2006, Galea et al. 2007). A classical inflammatory response would be devastating for immune privileged structures due to their special properties and it is believed that immune privilege is an active process that has developed throughout the evolution (Hong and Van Kaer 1999). However, the concept of CNS immune privilege has been extensively challenged in the last few decades. Increasing evidence suggests not only that immune cells are able to cross the blood-brain barrier under normal conditions, but that they might be indispensable to normal functioning of the CNS (Kipnis et al. 2004). Furthermore, the notion of the CNS being completely devoid of neuronal MHC class I expression due its immune privileged status has been questioned with strong experimental evidence over the past decade. The new line of research on the interactions between the immune and the nervous system is slowly debunking the myth of classical CNS immune privilege. Strong experimental evidence is pointing to a novel concept: CNS functions highly depend on its proper interactions with the immune system.

#### 2. Neuronal MHC class I molecules in brain development and plasticity

Based on the immune privileged status of the CNS, expression of MHC class I by neurons has always been considered either low or non-existent. Based on experimental evidence, it was believed that neurons were able to express MHC class I only after induction by cytokines (Neumann et al. 1995). However, a study by Corriveau et al. in 1998 demonstrated high neuronal MHC class I expression in normal, developing and adult brains. Since then, a number of studies confirmed that neurons do express MHC class I molecules in normal, non-pathological conditions (Datwani et al. 2009, Goddard et al. 2007, Huh et al. 2000, McConnell et al. 2009, Ribic et al. 2010, Rolleke et al. 2006). Furthermore, MHC class I have been implicated in proper development and maintenance of neuronal circuitry in various brain regions, especially in the development of the visual system (Huh et al. 2000, Ribic et al. 2011), and in modulation of synaptic plasticity in hippocampus and the cerebellum (Goddard et al. 2007, Huh et al. 2000, McConnell et al. 2007, Huh et al. 2000, McConnell et al. 2007, Huh et al. 2000, McConnell et al. 2007, Huh et al. 2000, Ribic et al. 2000).

#### 2.1 MHC class I molecules and the mammalian visual system development

#### 2.1.1 Mammalian visual system

Synaptic plasticity is the ability of neurons to change the strength of their synaptic connections in response to various stimuli. Plasticity is one of the fundamental properties of CNS. This process occurs in various forms with distinct properties and is thought to be essential for development and maintenance of brain circuits. The developing visual system is one of the main models of two forms of plasticity: visual activity-independent and visual

input-driven or activity-dependent plasticity. There are two main stages of visual system development. The early stage encompasses the development of the eyes and the brain and the initial development of the neuronal connections between them. It is believed that at this early stage, both growth of neuronal processes and pathfinding are independent of retinal activity, as opposed to the later stage. The second stage involves proper development of connections in and between the thalamus and the visual cortex, regions responsible for the processing of the visual input. The thalamic dorsal lateral geniculate nucleus (LGN) is the first relay structure of visual input and is organized into segregated, eye-specific, neuronal layers that form upon early spontaneous activity from retinal ganglion cells in the eye [Figure 3, (Shatz 1996)].



Fig. 3. Schematic structure of the mammalian visual system.

Retinal ganglion cells from both eyes project to the thalamic dorsal lateral geniculate nucleus (dLGN). Partial crossing of the two pathways occurs in the optic chiasm. Neurons of the lateral geniculate nucleus project to the visual cortex in the occipital lobes where neurons form eye-specific patches, ocular dominance columns (ODCs).

Neurons of the LGN send their projections to the primary visual cortex (V1), where their activity is required for the development of eye-specific patches of neurons in layer IV, i.e., the ocular dominance columns (ODCs) (Sur and Rubenstein 2005).

Although the development of both LGN and V1 is dependent on spontaneous retinal activity, visual activity is also required for their proper maturation. Blocking retinal activity of one eye during the development of the visual circuits while leaving the other one intact leads to the perturbation of the segregation of LGN neurons into eye-specific layers (Shatz 1996). In the visual cortex, ODCs do not form properly if one eye is deprived of input. As a consequence of visual deprivation, the ODCs increase the fraction of neurons responsive to the intact eye at the expense of neurons receiving afferents from the deprived eye (Berardi et

al. 2003, Sur and Rubenstein 2005). Furthermore, neurons receiving afferents from the intact eye tend to expand their synaptic space and occupy more territory within the visual cortex. On the other hand, neurons receiving afferents from the deprived eye shrink their territory [Figure 4; (Berardi et al. 2003)].



Fig. 4. Effects of monocular deprivation on visual cortex development.

Normal development of the visual cortex is based on the competition between the two eyes which confers balanced development of LGN neurons and their connections with the visual cortex neurons in ODCs (upper panel). If one eye is deprived of visual input throughout the development of the visual system, LGN neurons receiving afferents from the deprived eye shrink and prune their connections in the visual cortex (lower panel). This also causes shrinkage of ODCs in the visual cortex that receive input from the deprived eye (in the figure: left eye). On the other hand, ODCs receiving input from the intact eye, expand their territory within the visual cortex (in the figure: right eye).

#### 2.1.2 The roles of MHC class I molecules in visual system development

In the mouse dLGN and visual cortex, MHC class I molecules are associated with mainly excitatory, glutamate-activated synapses (Datwani et al. 2009, Glynn et al. 2011, Needleman et al. 2010). Immunoelectron microscopy of mouse visual cortex has demonstrated that MHC class I molecules may be situated on both sides of the synapse (Needleman et al. 2010). Expression levels of MHC class I proteins decrease with development of mouse cortex, being very prominent in the early stages of cortical development (Needleman et al. 2010). First studies dealing with neuronal expression of MHC class I revealed an essential role for MHC class I genes in the segregation of retinal inputs and proper formation of neuronal layers within the LGN (Corriveau et al. 1998, Huh et al. 2000). MHC class Ideficient mice display an aberrant development of retinal projections and impairments in the formation of eye-specific regions in the LGN, caused by an excess of inappropriate synapses that are normally removed during LGN development in wild-type mice (Huh et al. 2000). These studies implicated MHC class I in weakening, removal and pruning of synapses, and it is believed that MHC class I molecules limit plasticity in the developing visual system (Syken et al. 2006).  $\beta$ -2-microglobulin deficient mice show an increased density of synapses in the visual cortex, consistent with the role of MHC class I in synapse pruning (Glynn et al. 2011). A recent study has shown that classical MHC class I molecules are mediating these effects (Datwani et al. 2009). Mutant mice lacking two classical MHC class I genes (H2-K<sup>b</sup> and H2-D<sup>b</sup>) replicate the phenotype observed in the visual system of β-2-microglubulin/TAP-deficient mice used in previous studies (Datwani et al. 2009). Interestingly, mice that lack the expression of TCR complex subunit CD3- $\zeta$  also display similar defects in visual system development (Corriveau et al. 1998, Huh et al. 2000, Xu et al. 2010). Furthermore, a study that investigated the retinal phenotype of CD3- $\zeta$  knock-out mice revealed an important observation-the phenotype observed in the dLGN and visual cortex of both CD3- $\zeta$  and MHC class I-deficient mice may be just a consequence of retinal defects observed in these mice (Xu et al. 2010).MHC class I genes are also expressed in the retina (Huh et al. 2000) and time will show if this assumption holds true.

Majority of the above mentioned studies have been performed in mice and cats (Corriveau et al. 1998, Huh et al. 2000). The number of class I genes is highly variable between species; moreover, orthologous relationships are found only within same order of mammals such as within primates, but never between primates and rodents (Kumanovics et al. 2003, Gunther and Walter 2001). Mouse and rat MHC clusters are comprised of over 30 functional classical and non-classical genes (Gunther and Walter 2001, Kumanovics et al. 2003). Despite the orthologous relationship, MHC class I genes are still very variable between primates. Strict orthologues of classical human MHC class I genes are present only in the great apes, whereas orthologues of the non-classical genes are found in Old World (baboons, macaques) and New World monkeys. This, coupled with known differences in CNS anatomy and function between rodents and primates, poses a question of possible interspecies differences in the function of neuronal MHC class I genes. It is known that MHC class I genes are highly expressed in the visual cortex of the marmoset monkey (a New World primate) and that their expression closely follows the synapse development in the visual cortex, increasing with postnatal age (Ribic et al. 2011). Neuronal MHC class I gene expression appears activitydependent in all species examined (Corriveau et al. 1998, Huh et al. 2000, Ribic et al. 2011), but the expression profile seems to be highly dependent on both the experimental paradigm and the model organism used (Corriveau et al. 1998, Ribic et al. 2011).



Fig. 5. Expression of MHC class I proteins in the visual cortex of the common marmoset. MHC class I proteins (green) colocalize with the neuronal marker MAP2 (red) in layer IV neuronal cell bodies of the common marmoset primary visual. Image adapted from Ribic et al., 2011.

Unavailability of transgenic non-human primate models has hindered the answers to the question of potential interspecies variability in neuronal MHC class I function. However, having in mind the high evolution rate of these molecules, differential interspecies function seems highly plausible.

#### 2.2 MHC class I molecules and hippocampal plasticity

#### 2.2.1 The hippocampus

Hippocampus is a part of the brain situated in the medial temporal lobe and implicated in learning and memory processes. It is organized as a series of connected cell layers: the dentate gyrus, hilus, and cornu ammonis 1, 2 and 3 (CA1-3, Figure 6), which form the so called "trisynaptic circuit". Due to its relatively simple structure, hippocampus is one of the best studied circuits within the brain. The dentate gyrus is composed of granule cells that receive input from the entorhinal cortex and send projections to the hilus and the CA3 pyramidal neurons region. The dentate gyrus to hilus and CA3 projections are known as the mossy fiber pathway (Figure 6). The CA3 pyramidal neurons innervate the CA1 cell layer, and the CA1 pyramidal neurons in turn send their axons to the entorhinal cortex. The CA3 to CA1 connections are also called Schaffer collaterals. Both mossy fiber pathway and Schaffer collaterals have received a great deal of attention over the past decades due to neuronal long-term plasticity properties within these two hippocampal regions. Prolonged correlated presynaptic (neurotransmitter release) and postsynaptic (activation of neurotransmitter receptors) activity is thought to underlie one form of long-term plasticity, long-term potentiation [LTP; (Cooke and Bliss 2006, Malenka and Bear 2004)]. LTP results in increased synapse strength between participating neurons (Cooke and Bliss 2006, Malenka and Bear 2004). In contrast to LTP, prolonged uncorrelated presynaptic and postsynaptic activity results in long-term depression (LTD), a form of plasticity thought to precede the weakening of synapses and their pruning (Collingridge et al. 2010, Malenka and Bear 2004). Although both LTP and LTD are experimental phenomena, they are considered cellular mechanisms of memory formation and storage and both have been extensively studied using hippocampus as a model system (Collingridge et al. 2010, Malenka and Bear 2004).

LTP and LTD in Schaffer collaterals are considered the classical examples of long term plasticity (Malenka and Bear 2004). Both LTP and LTD have various forms of induction and

maintenance, but the most investigated forms are dependent on the activation of NMDAR (N-methyl D-aspartate receptors), as well as changes in Ca<sup>2+</sup> concentrations (Malenka and Bear 2004). Both LTP and LTD occur in the visual cortex during developmental activity-dependent plasticity, where they regulate the strengthening of appropriate and removal of inappropriate synapses (Berardi et al. 2003, Heynen et al. 2003, Katz and Crowley 2002, Thompson 2000).



Fig. 6. Schematic structure of the hippocampus.

Granule cells in the dentate gyrus receive input from the entorhinal cortex (EC, orange) and send their projections to the CA3 pyramidal neurons [mossy fiber pathway (mf), red]. CA3 neurons innervate CA1 pyramidal neurons [Schaffer collaterals (sc), green], which in turn send their projections back to the entorhinal cortex (blue).

#### 2.2.2 The roles of MHC class I proteins in hippocampal plasticity

MHC class I proteins in mice have been shown to localize postsynaptically on the somata and dendrites of the dentate gyrus granule neurons and the CA1-CA3 pyramidal neurons (Corriveau et al. 1998, Goddard et al. 2007). Both LTP and LTD at the Schaffer collaterals are aberrant in mice lacking MHC class I molecules (Huh et al., 2000). Schaffer collateral LTP in these mice is significantly enhanced, while LTD is completely absent (Huh et al. 2000). These findings parallel the effects of MHC class I in the visual system: LTP reflects strengthening of the neuronal connections and the absence of MHC class I causes strengthening of synapses that would otherwise be weakened by LTD. However, the enhancement of LTP in MHC class I deficient mice is not dependent on NMDAR receptors (Huh et al. 2000). In primates, at least a subset of neuronal MHC class I molecules is presynaptic and expressed exclusively in the mossy fibers within the hippocampal formation (Ribic et al. 2010). Blocking their function in vitro interferes with normal synaptic transmission (Ribic et al. 2010).

So far, presynaptic localization of neuronal MHC class I molecules in mice has only been detected in the spinal cord and at the neuromuscular junction (Oliveira et al. 2004, Thams et al. 2009). Future studies will no doubt reveal if there are any functional differences stemming from different localization of neuronal MHC class I molecules in different species.

#### Histocompatibility



Fig. 7. MHC class I (MHCI) protein is localized to the presynaptic side of the mossy fiber-CA3 synapse in the common marmoset monkey hippocampus.

MHC class I signal (A, green) significantly overlaps with that of piccolo (B, red), a marker of the presynaptic active zone (C and G, white arrowheads). Almost no overlap is detected between MHC class I (D) and the postsynaptic marker PSD95 (E, F and H).

#### 2.3 Molecular mechanisms of neuronal MHC class I action

The main unanswered question is how are neuronal MHC class I molecules mediating all these effects? A few studies have shown that MHC class I may recruit receptors other than TCR in the CNS. Mice lacking PirB, known interaction partner of MHC class I molecules in the immune system, also show similar defects in developmental synapse removal (Syken et al).

It has been hypothesized that MHC class I may engage in trans-synaptic interactions and hence exert presynaptic effects that have been observed (Goddard et al. 2007, Syken et al. 2006). As the phenotype of CD3 $\zeta$  knock-out mice resembles the phenotype of MHC class I deficient mice, it is safe to assume that they may be involved in the same signaling pathway (Xu et al. 2010, Huh et al. 2000). Furthermore, MHC class I molecules may affect the function of synapses through their effects on neurotransmitter receptors, such as glutamate receptors (Fourgeaud et al. 2010). A recent study indicated that MHC class I proteins may regulate trafficking of NMDAR receptors, which parallels their previously described roles in insulin receptor signaling (Arosa et al. 2007, Fishman et al. 2004, Fourgeaud et al. 2010). Interestingly enough, insulin is mediating a non-NMDAR dependent form of LTD in the hippocampus (Ahmadian et al. 2004, Collingridge et al. 2010, Ge et al. 2010, Wang and Linden 2000). Receptor internalization seems to be the main role of MHC class I in the vomeronasal organ of mice, where non-classical MHC class I molecules appear to be involved in internalization of vomeronasal receptors (Olson et al. 2006, Dulac and Torello 2003, Loconto et al. 2003). In the primate hippocampus, blockade of neuronal MHC class I in vitro slows down basal synaptic transmission at the mossy fiber-CA3 synapses (Ribic et al. 2010). The mossy fiber-CA3 synapse displays a number of peculiarities in comparison to the majority of CNS synapses. It is e.g. characterized by a low basal transmission which is

maintained by activation of a number of receptors that have inhibitory effects on synaptic transmission (Nicoll and Schmitz 2005). As previously mentioned, given that the best characterized non-immune function of MHC class I is regulation of trafficking and internalization of various receptors (Olsson et al. 1994, Stagsted 1998, Stagsted et al. 1990, Ramalingam et al. 1997), it is likely that neuronal MHC class I molecules in the marmoset hippocampus are needed for proper internalization of one or several of those receptors (Figure 8). One may speculate that blocking the interaction of MHC class I with such



Fig. 8. Schematic representation of potential mode of action of MHC class I at the mossy fiber-CA3 synapse.

Mossy fiber-CA3 synapse normally displays lower levels of basal activity compared to other synapses in the central nervous system (representative electrophysiological trace of recorded spontaneous excitatory postsynaptic currents (EPSCs) of a marmoset CA3 neuron is shown in the lower part of the image). This is mainly due to large number of receptors (magenta) that have inhibitory effect on synaptic transmission (Nicoll and Schmitz, 2005). It is possible that MHC class I is needed for proper internalization and removal of one of these receptors from the cell surface. MHC class I would presumably bind to the receptor with its a1 and a2 domains. (D) If anti-MHC class I antibodies that bind to a1 and a2 domains are applied in the vicinity of the cell while the cell's activity is recorded using patch clamp technique, frequency of spontaneous EPSCs is decreased (trace in the lower part of the image). It is possible that antibodies block interaction of MHC class I with putative inhibitory receptor, which prolongs inhibitory signaling thereby decreasing the frequency of spontaneous EPSCs.

receptors by application of anti-MHC class I antibodies would prolong inhibitory signaling and exert the inhibitory effects on synaptic transmission. Future studies need to elucidate the exact molecular pathways that neuronal MHC class I molecules are involve in, as well as their potential involvement in insulin-induced hippocampal LTD.

#### 3. Nervous and immune systems-shared molecules and mechanisms

A vast number of studies in the past decades have shown that the immune and the nervous system are interconnected more than previously thought. Recent discoveries have highlighted a number of roles performed by immune molecules in the CNS-molecules and pathways previously thought to be exclusively acting within the immune system. From MHC class I molecules in synapse development (Corriveau et al. 1998, Huh et al. 2000, Ribic et al. 2010), CD3ζ in retinal function and dendrite development (Baudouin et al. 2008, Xu et al. 2010), to DAP12 in astrocyte-neuron signaling (Roumier et al. 2004), a new picture of immune privilege emerges-a picture in which the immune system is actively involved in proper brain development and maintenance of neuronal circuitry. This concept has important implications for a number of diseases associated with MHC cluster, such as schizophrenia and autism (Torres et al. 2006, Kipnis et al. 2004, Needleman et al. 2010). Current research efforts are focused on elucidating the consequences of prenatal immune insult on the brain development, so called "maternal immune activation". Both schizophrenia and autism have been genetically linked to MHC cluster and to prenatal immune insult (Soumiya et al. 2011, Buehler 2011, Escobar et al. 2011, Patterson 2011, Fatemi et al. 2011, Parker-Athill and Tan 2010, Boksa 2010, Currenti 2010, Li et al. 2009, Patterson 2009, Smith et al. 2007, Cohly and Panja 2005, Patterson 2002, Stubbs and Magenis 1980). Future studies will no doubt elucidate the interactions between the nervous and immune systems in more detail, as well as shed more light on the vast polymorphism of MHC class I molecules, especially in the light of their neuronal functions.

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