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Major histocompatibility complex I in brain development and schizophrenia

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Abstract

Although the etiology of schizophrenia (SZ) remains unknown, it is increasingly clear that immune dysregulation plays a central role. Genome-wide association studies reproducibly indicate an association of SZ with immune genes within the major histocompatibility complex (MHC). Moreover, environmental factors that increase risk for SZ, such as maternal infection, alter peripheral immune responses as well as the expression of immune molecules in the brain. MHCI molecules may mediate both genetic and environmental contributions to SZ through direct effects on brain development, in addition to mediating immunity. MHCI molecules are expressed on neurons in the central nervous system (CNS) throughout development and into adulthood, where they regulate many aspects of brain development including neurite outgrowth, synapse formation and function, long-term and homeostatic plasticity, and activity-dependent synaptic refinement. This review summarizes our current understanding of MHCI expression and function in the developing brain, as well as its involvement in maternal immune activation, from the perspective of how these roles for MHCI molecules might contribute to the pathogenesis of SZ.

Keywords

Maternal immune activation; infection; cytokines; neuroimmunology; synapse formation; synaptic plasticity

In the past decade, there has been a paradigm shift in our understanding of the interactions between the immune and nervous systems, leading researchers to explore neural-immune based mechanisms for complex brain disorders that have thus far eluded explanation. Indeed, increasing evidence points to a central role for immune dysregulation in schizophrenia (SZ). SZ is a chronic and disabling brain disorder that affects approximately 1% of the population worldwide and appears to be caused by interactions between genetic mutations and environmental insults during early development (1, 2).

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Many of the genetic associations linked to SZ converge on immune dysregulation through alterations in immune-related genes and/or immune responses (3, 4). SZ is linked to aberrations on chromosome 6, which is densely packed with immune genes (5–7), and specific haplotypes of immune genes—especially those within the major histocompatibility complex (MHC)—correlate with SZ. In fact, the MHC region is one of the few highly replicable sites associated with SZ in large-scale genome-wide association studies (5, 6, 8–12), thoroughly reviewed in this Special Issue (Corvin and Morris 2013). Moreover, individuals with SZ and their relatives also have an increased incidence of immune disorders, suggesting a heritable immune dysregulation associated with SZ (13–15).

Signs of active immune dysregulation are also present in individuals with SZ. Inflammation in the CNS is present in postmortem brains and cytokine levels are altered in the blood, brain, and cerebrospinal fluid (CSF) in SZ (4, 16, 17); specific cytokines may be correlated with periods of active psychosis (18). The expression of many immune-related genes in the brain, including MHC genes, is also altered in SZ (Horvath and Mirnics review, this issue) (19–21). Reports showing a relationship between SZ endophenotypes and MHC class I (MHCI) expression support this association (8). For example, MHCI variants are associated with defects in eye movements in individuals with SZ (22) and a specific MHC SZ risk allele is associated with enlarged ventricles characteristic of SZ (23). Thus, immune dysregulation is associated with, and may underlie, the etiology and pathogenesis of SZ.

In addition to genetic associations, many of the environmental exposures linked to SZ involve immune dysregulation in the maternal-fetal environment (24). Maternal infection, in particular, increases the risk for SZ in offspring (4, 25, 26). It has been estimated that over a third of SZ cases could be avoided if infection in pregnant women was prevented (25). These correlations from epidemiological studies are supported by work from rodent models of maternal immune activation (MIA; reviewed by Meyer in this Special Issue). Offspring of pregnant mice given intra-nasal influenza virus, or injected with the viral mimic, poly(I:C), exhibit behavioral abnormalities and changes in gene expression, neuroanatomy, and neurochemistry consistent with SZ (27). Similar outcomes occur in a non-human primate MIA model (Bauman and Amaral manuscript, this issue). Although little is known about how MIA leads to SZ-like neuropathology and behaviors in offspring, recent work suggests that chronic changes in immune molecules in the brain, including MHCI, may be critical for these outcomes (28, 29).

Together, the genetic associations, epidemiology, and results from animal models are providing increasing support for the hypothesis that immune dysregulation, resulting from either immune-related genetic associations or from environmental exposures, may underlie the pathogenesis of SZ. Because of their strong genetic association with SZ, their dysregulation in the brains of individuals with SZ, and their role in mediating the effects of MIA, MHCI molecules appear to be one of the most important immune gene families in the etiology and pathogenesis of SZ. This review focuses on MHCI molecules in CNS development and plasticity and their potential involvement in mediating the effects of MIA on cortical connectivity. Roles for other immune molecules that are linked to SZ, including specific cytokines and molecules that mediate microglial-dependent synapse elimination, have been reviewed elsewhere (8, 30–32).

MHCI in the immune system

The MHC locus comprises several distinct genes, some of which are the most polymorphic genes known (33). This locus is divided into three classes (MHC I, II, and III). The composition of the MHC locus in humans and rodents has been recently described (34). Although genes throughout the MHC have been implicated in SZ, this review focuses specifically on MHCI. Classical MHCI heavy chains are encoded by three genes in humans—*HLA-A*, *-B* and *-C* and three genes in mice—*H2-K*, *-D* and *-L* (35). Insertions and deletions in the MHCI locus have created many non-classical MHCI genes, especially in rodents (33), but the function of most of these is unknown (36).

MHCI molecules are expressed on all nucleated cells in the body, where they mediate both the adaptive and innate immune responses (36). Classical MHCI molecules are trimeric proteins, comprised of a transmembrane heavy chain, a light chain called β 2-microglobulin (β 2m), and a peptide (36). The peptide, which is derived from proteolysis of intracellular proteins, binds to a polymorphic groove in the heavy chain (36). These peptides are usually derived from self-proteins and do not initiate an immune response. However, MHCI will present non-self peptides following infection or internalization of antigen through phagocytosis. These MHCI complexes will bind to T-cell receptors (TCR) on cytotoxic T cells. Signaling molecules called cytokines are then released, initiating a series of events that lead to enhanced MHCI expression and eventual lysis of the MHCI/non-self-presenting cell (37). MHCI molecules also bind to receptors on natural killer (NK) cells, including paired immunoglobulin receptor B (PirB) and the Ly-49 family of receptors (38, 39).

MHCI in the CNS

MHCI and MHCI receptor expression

The CNS was considered immune-privileged for many years, in large part due to the assumption that classical immune molecules, like MHCI, were not expressed in the brain (40). That assumption was disproved about 15 years ago when the Shatz laboratory made the surprising discovery that MHCI molecules are expressed in the CNS throughout development (41). mRNA encoding MHCI is expressed in neurons and glia from multiple brain regions in many species including mice, rats, cats, marmosets, and humans (19–21, 41–45). MHCI protein levels in the rodent cerebral cortex are highest during neonatal development and decrease to lower levels late in development and into adulthood (45, 46), followed by an increase again with aging, at least in glial cells (47). Although MHCI protein was originally believed to be absent from the neuronal surface (40, 48), recent publications show that MHCI molecules are, in fact, present in the plasma membrane of both axons and dendrites of cultured neurons (called surface MHCI or sMHCI) (49, 50). MHCI protein is also present both pre- and postsynaptically at glutamatergic synapses in vivo in rodent cortex (46, 49–51). Finally, MHCI is found on astrocytes and on activated microglia (52–54).

Classical MHCI receptors are also expressed in the CNS. Although obligate components of the TCR complex are non-functional or missing in the brain (55), TCR co-receptors, including CD3 ζ and CD3 ϵ , are present in the rodent and feline CNS (56–58). It remains

unknown whether or how MHCI interacts with these co-receptors. The NK receptors, PirB and Ly49, are also expressed throughout the rodent brain where they are especially prominent on developing neurons. (59, 60). Another NK receptor, PirA, has not been detected in brain (59). Finally, the mouse killer cell immunoglobulin-like receptor-like 1 (KIRL) genes are expressed in the brain (61), although their function remains unknown. Together, these results indicate that MHCI molecules and their receptors are present in the CNS throughout development and could, therefore, directly alter many aspects of neural development to contribute to SZ.

MHCI and neuronal differentiation

The role for MHCI in development has been studied primarily in mouse and rat model organisms. MHCI is expressed on neurons both during gestation and in the early postnatal period—times of neurogenesis, neuronal migration, and neuronal differentiation. Although MHCI is expressed in progenitor cells (41, 45), it's role in neurogenesis and migration is yet to be determined. MHCI does regulate the earliest steps of neuronal differentiation—neuronal polarization and neurite outgrowth. MHCI controls the extension and differentiation of neurites from very young hippocampal neurons in vitro (62). Target-derived, secreted or recombinant MHCI protein also negatively regulates axon extension from retinal explants (63, 64) or cultured dorsal root ganglia (65). In addition, knockout of an MHCI co-receptor, *CD3ζ*, increases dendritic branching of retinal ganglion cells in vivo (66). Likewise, decreasing *CD3ζ* levels in young cortical neurons increases dendritic complexity while enhancing *CD3ζ* levels decreases it (57). Finally, the LY49 family may also regulate axon extension and expression of presynaptic proteins in cultured cortical neurons (60).

Although these results suggest that MHCI plays an important role in neuronal differentiation, the relevance of this function for SZ in humans remains unexplored. It is unknown if specific variants of MHCI that are associated with, or altered during, SZ regulate neurogenesis or neurite outgrowth. Moreover, although defects in axon guidance have been implicated in SZ (67), the contribution of this phenotype to the pathogenesis of SZ remains unclear. Nevertheless, changes in dendritic morphology have been reported to accompany SZ (67) and this role for MHCI could explain how changes in MHCI in the brain in SZ might contribute to this aspect of the disease.

MHCI and synapse formation

In addition to negatively regulating axon outgrowth and dendritic branching, MHCI also limits the initial establishment of connections in the brain. This conclusion relies on manipulations in rodent models that decrease, or prevent, expression of sMHCI on the plasma membrane of cells through knockdown or knockout of $\beta 2m$, the MHCI light chain, and *TAP1*, which mediates peptide loading. Both proteins are required for MHCI be expressed on the cell surface (36, 46, 49). MHCI does not appear to alter synapse density in mature, cultured hippocampal neurons from $\beta 2m^{-/-}TAP1^{-/-}$ mice (50), but it does limit glutamatergic synapse density between neurons from the visual cortex, both in vivo and in vitro, in $\beta 2m^{-/-}$ mice (49). Synapse density is elevated in $\beta 2m^{-/-}$ cortex throughout development in vivo (49). Similarly, lowering sMHCI levels on young cultured cortical

neurons using siRNAs to $\beta 2m$ increases both glutamatergic and GABAergic synapse density, while overexpressing a specific form of MHCI, H2-Kb, decreases them (49). The effect of MHCI in limiting glutamatergic synapse density requires synaptic activity and activation of calcineurin and MEF2 transcription factors (29).

Together, these results indicate that the effects of MHCI in negatively regulating synapse density in the developing brain are region- and age-specific. If MHCI levels are altered by genetic variants, changes in gene expression, or in response to immune dysregulation, as in SZ in humans, then synapse density should be altered. Indeed, impaired synaptic connectivity has been proposed to be a central pathological finding in SZ (67). Synapse density and markers for dendritic spines, the sites of glutamatergic synapses on pyramidal neurons, are decreased in postmortem tissue from individuals with SZ (68, 69). In addition, ventricles are larger and cortical volume and thickness, but not neuronal density, are decreased in SZ postmortem tissue (70, 71), suggesting that these changes result from decreased neuropil including dendrites, axons, synapses, and glial cells (72). Neuroimaging studies in humans support these observations (73–75). Interestingly, mice deficient in MHCI also have enlarged ventricles (56). The ability of MHCI to bidirectionally control glutamatergic and GABAergic synapse density places it in a prime position to contribute to changes in brain circuitry during development that could account for prodromal symptoms, and increase susceptibility to a second hit, in SZ (76).

MHCI and synaptic function

MHCI molecules also regulate the function of synapses in CNS neurons, in a region- and age-specific manner. In mature hippocampal neurons cultured from $\beta 2m^{-/-}$ $TAPI^{-/-}$ mice, miniature excitatory postsynaptic current (mEPSC) frequency is increased with no change in mEPSC amplitude or synapse density (50). These results indicate that MHCI selectively regulates presynaptic release properties, a conclusion further supported by increased synaptic vesicle number at synapses in $\beta 2m^{-/-}$ $TAPI^{-/-}$ mice (50). The lack of change in mEPSC amplitude suggests that MHCI does not alter AMPA receptor (AMPA) trafficking in mature hippocampal neurons.

In contrast, MHCI clearly alters synaptic strength, as well as synapse density, in rodent visual cortical neurons. mEPSC frequency is doubled in cortical slices from three-week-old $\beta 2m^{-/-}$ $TAPI^{-/-}$ mice, with no change in mEPSC amplitude (50). Similarly, mEPSC frequency is also increased in young cortical neurons following $\beta 2m$ knockdown, while MHCI overexpression decreases mEPSC frequency (49). However, MHCI also negatively regulates mEPSC amplitude in these cortical cultures, suggesting that MHCI may alter AMPAR trafficking in young, but not mature, visual cortical neurons (49, 50). MHCI also limits inhibitory synaptic transmission in young cortical neurons as demonstrated by increases in mIPSC frequency, but not amplitude, in neurons deficient in sMHCI, and decreases in MHCI-overexpressing neurons (49). Because MHCI differentially affects glutamatergic versus GABAergic synapses, it controls the balance of excitation to inhibition (E/I balance) on cortical neurons (49). This role for MHCI may mediate part of its contribution to SZ since altered E/I balance is a hallmark of this disease (77, 78).

Perhaps the most interesting effect of MHCI on synaptic transmission in terms of its relevance to SZ is its role in regulating NMDA receptor (NMDAR) function (79). MHCI controls the development of structural and function asymmetries in NMDAR expression in hippocampal circuitry in rodents (80). In addition, the AMPAR/NMDAR ratio is lower in hippocampal slices from $\beta 2m^{-/-}TAP1^{-/-}$ mice. Because NMDAR-mediated EPSPs and fEPSPs are larger in the absence of sMHCI, while AMPAR-mediated responses are normal, MHCI appears to alter this ratio through specifically repressing NMDAR function. MHCI likely inhibits the channel properties of NMDARs since their expression, composition, and distribution are not changed in $\beta 2m^{-/-}TAP1^{-/-}$ mice (79). This MHCI-induced repression of NMDARs also limits NMDA-mediated AMPAR trafficking and therefore, activity-dependent changes in synaptic strength (79). Thus, the decrease in NMDAR function and resulting deficits in synaptic plasticity thought to underlie SZ (81, 82) may be caused, at least in part, by changes in MHCI expression in neurons in some individuals.

MHCI and synaptic plasticity

MHCI expression in the CNS is potently regulated by synaptic activity. In fact, MHCI was first discovered to be present in the CNS as a result of its presence in a differential display screen designed to identify activity-dependent genes in the visual system (41). Blocking action potentials in either the cortex or in one eye decreases MHCI mRNA levels in the lateral geniculate nucleus (LGN). Conversely, increasing cortical activity increases MHCI expression in the hippocampus and cortex (41). Levels of sMHCI protein on neurons are also regulated by activity in rodent cultured neurons, but the magnitude and direction of these effects are region- and age-dependent (48–50). Additional research is needed to determine the role of physiological activity, and especially SZ-related aberrant activity patterns (78, 82), in regulating MHCI levels in vivo.

The ability of neural activity to regulate the composition and strength of connections within the CNS depends on synaptic plasticity. Two forms of synaptic plasticity—Hebbian and homeostatic plasticity—act together to control the initial formation and activity-dependent dynamics of connections in the brain (83). MHCI molecules are important for both forms of plasticity. The threshold for long-term plasticity (LTP) is lowered and long-term depression (LTD) is absent in the hippocampus of $\beta 2m^{-/-}TAP1^{-/-}$ mice (56), indicating that MHCI inhibits Hebbian strengthening and is required for Hebbian weakening of hippocampal connections. Although MHCI does not regulate Hebbian plasticity through its PirB receptor (59, 84), it may require CD3 ζ , since $CD3\zeta^{-/-}$ mice phenocopy the defects in LTP and LTD found in $\beta 2m^{-/-}TAP1^{-/-}$ mice (56). Homeostatic changes in synaptic strength, reflected as increased mEPSC frequency and amplitude in response to activity-blockade for 3–6 days, are also impaired in mature rodent hippocampal neurons in the absence of sMHCI (50). Similarly, increases in glutamatergic synapse density caused by shorter periods of activity blockade in young cortical neurons are also prevented by MHCI overexpression (49). Because both Hebbian and homeostatic plasticity often require NMDAR-dependent changes in AMPAR trafficking (85), MHCI may regulate synaptic strength through their effects in repressing NMDAR function (79) and/or in altering AMPAR trafficking (49, 79). Together, these effects of MHCI on NMDAR-mediated synaptic plasticity may be central to their involvement in the widespread deficits in plasticity postulated to occur in SZ (81, 82).

MHCI and activity-dependent refinement of connections

As expected from their role in synaptic plasticity, MHCI molecules also mediate activity-dependent refinement of connections (86). The original manuscript describing a non-immune role for MHCI in CNS development reported aberrant activity-dependent refinement of projections from the retina to the LGN in $\beta 2m^{-/-}$ and $\beta 2m^{-/-}TAP1^{-/-}$ mice (56). Mice deficient in *H2-Kb* and *H2-Db* (*KbDb*^{-/-}), or *CD3 ζ* , phenocopy these deficits (56, 87). Because transgenic mice that express inactive PirB receptor (*PirBTM* mice) show no changes in this phenotype (59), MHCI does not appear to work through PirB to mediate retinogeniculate refinement. Transgenic mice that overexpress H2-Db in neurons, *NSE-Db* mice, also exhibit altered retinogeniculate refinement, generally in the direction opposite to MHCI deficient mice (65). Finally, MHCI appears to restrict ocular dominance (OD) plasticity, but not OD formation, through PirB (59, 87).

It is important to note that most of the transgenic mice used to study MHCI and its receptors are non-conditional mice, meaning that these genes are knocked out in all cells at all times during development. This could be important for interpretation of results in this field. For example, mice deficient in *CD3 ζ* also exhibit aberrant dendritic arborization of retinal ganglion cells, suggesting the possibility that the changes in retinogeniculate refinement in these mice could result from abnormal retinal development rather than a direct effect on refinement (66). In addition, although much of the in vitro data published so far indicates that neuronal MHCI plays a direct role in development and plasticity, it is not known if MHCI in the periphery or MHCI expressed on glia modulate these effects in vivo. One intriguing possibility is that MHCI might be involved in complement-mediated synaptic pruning by microglia (88). Indeed, the effects of MHCI on synapse formation and refinement are remarkably similar to those reported for the complement system (89, 90) and MHCI and complement have been reported to interact in the immune system (91). Interestingly, there is evidence for microglial activation in individuals with SZ (92), suggesting a possible role for neural inflammation and synapse elimination in the active disease process.

Together, all of these experiments converge on the conclusion that MHCI mediates the activity-dependent elimination of inappropriate connections in the developing visual system (93). This role for MHCI in synaptic pruning may contribute to the proposed defect in synaptic pruning that could underlie the positive symptoms of SZ and their emergence in adolescence, a period of rapid synaptic pruning (94). Future experiments using inducible, conditional transgenic mice will refine our understanding of the role for MHCI in specific cell types and at specific times during development and facilitate comparison to results obtained from postmortem SZ tissue.

MHCI and environmental risk factors for SZ

In addition to its role in the establishment and refinement of connections, MHCI may also mediate the effects of environmental risk factors in altering brain development and causing the symptoms of SZ. Although there is a wide range of environmental risk factors linked to SZ, the most compelling risk factor to date is maternal infection (4, 26, 95, 96), which has been estimated to account for up to one-third of cases (25). This correlation between

maternal infection and SZ is strongly supported by work from rodent models of maternal immune activation (MIA), especially the poly(I:C) MIA model. As described in more detail in the Meyer review in this issue, this model has both construct validity (similar etiology) and face validity (similar pathophysiology) for SZ. Offspring born to pregnant mice injected with poly(I:C) in mid-gestation display behaviors that are consistent with SZ, including deficits in social interaction, deficits in prepulse inhibition, latent inhibition and working memory, as well as elevated anxiety (97–99). Some of these SZ-like behaviors can be alleviated by anti-psychotic drugs (100). Adult MIA offspring also exhibit abnormalities in gene expression, neurochemistry, and neuropathology similar to those in SZ, including the decreased cortical thickness and enlarged ventricles characteristic of SZ (27, 99, 100).

Despite recent progress in characterizing rodent MIA models, little is known about how MIA alters brain development to cause SZ-like pathology and behaviors. An increasingly attractive hypothesis is that immune signaling molecules called cytokines mediate this process in both the mother and fetus. Cytokine expression is altered in blood from pregnant dams and in the fetal brain hours after poly(I:C) injection (4, 101, 102). Cytokines remain altered in the blood and brain of offspring following MIA throughout development and into adulthood (28). As expected, several, mostly pro-inflammatory, cytokines are elevated at birth in the frontal cortex (FC) of MIA offspring. Surprisingly, however, many cytokines are decreased during postnatal periods of synaptogenesis and plasticity and a few are elevated again in the adult FC. The pattern of change in cytokines in the hippocampus is distinct from that found in the cortex. Cytokines are also altered throughout development in the serum of MIA offspring, but these changes do not correlate with those in brain cytokines. Finally, MIA does not alter blood–brain barrier permeability or the density of immune cells including microglia in the brains of offspring (28). Importantly, these long-lasting changes in cytokine levels in the blood and brain of MIA offspring are similar to reports of altered blood and brain cytokines in individuals with SZ (4, 18, 103). The increase in IL-6 expression in human prefrontal cortex (103) is similar to the increase in IL-6 protein levels reported in FC of MIA mouse offspring (28), suggesting a potentially important role for brain IL-6 in SZ.

The cytokine hypothesis of SZ proposes that chronically altered brain cytokines cause changes in neural connectivity that underlie SZ-like behaviors in the rodent MIA model. However, until recently, it has been unknown if neural connections are altered in the brains of MIA offspring. Consistent with this hypothesis, MIA was recently found to alter cortical connectivity in offspring through an MHCI signaling pathway (29). MIA causes a profound deficit in the ability of cortical neurons to form synapses during early postnatal development. Neurons cultured from newborn MIA FC form half as many synapses as control neurons. These cortical neurons from MIA offspring also exhibit dramatically elevated sMHCI levels (29). Most important, the MIA-induced deficit in the ability of neurons to form synapses requires increased MHCI signaling. Returning sMHCI expression to control levels in MIA neurons rescues the MIA-induced deficit in synapse density (29).

Together, these results imply that MIA requires an MHCI signaling pathway to limit the ability of cortical neurons to form synapses. In order to fully understand the contribution of MHCI signaling to SZ, it will be important to determine whether the MIA-induced increase

in cytokines in offspring directly regulates neuronal MHCI levels, whether this pathway regulates the formation, dynamics, and strength of neural connections throughout development, and most critically, whether it mediates SZ-linked behaviors in offspring in the MIA mouse model. Nevertheless, these recent results provide the first evidence that an environmental risk factor for SZ, maternal infection, alters MHCI expression in the brains of offspring, which subsequently mediates MIA-induced changes in cortical connectivity. Determining if other environmental risk factors for SZ, such as maternal bacterial or parasitic infections, obstetric complications, urban stress, heavy cannabis use, and trauma (2) alter neural connectivity and function through neuronal MHCI is an important goal for the future.

Concluding remarks

Recent advances from many facets of SZ research have converged on the hypothesis that genetic and environmental risk factors cause a chronic immune-dysregulated state in offspring that alters brain development and causes SZ. MHCI signaling represents a common molecular pathway downstream of both genetic mutations and environmental factors that contribute to SZ. Because MHCI molecules play critical roles in the development, plasticity, and function of the brain, understanding MHCI signaling in the CNS may illuminate not only novel mechanisms of neural development, but also new pathways to target for treating SZ and other neural-immune-based psychiatric disorders.

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