Major Histocompatibility Complex I in Brain Development and Schizophrenia

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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. MHC class I (MHCI) molecules might 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 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.

Key Words: Cytokines, infection, maternal immune activation, 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). Schizophrenia is a chronic and disabling brain disorder that affects approximately 1% of the population worldwide and seems to be caused by interactions between genetic mutations and environmental insults during early development (1,2).

Many of the genetic associations linked to SZ converge on immune dysregulation through alterations in immune-related genes and/or immune responses (3,4). Schizophrenia 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), which are thoroughly reviewed in the Corvin and Morris paper in this Special Issue. Individuals with SZ and their relatives also have an increased incidence of autoimmune 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 central nervous system (CNS) is present in postmortem brains, and cytokine levels are altered in the blood, brain, and cerebrospinal fluid in SZ (4,16,17). Indeed, specific cytokines might 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 linked to, and might 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 intranasal 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 nonhuman primate MIA model (Bauman and Amaral paper, 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, might 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, might 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 seem 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

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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 nonclassical MHCI genes, especially in rodents (33), but the function of most of these is unknown (36).

The 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, comprising a transmembrane heavy chain, a light chain called β2-microglobulin (β2m), 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 after infection or internalization of antigen through phagocytosis and these MHCI/non-self peptide 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 approximately 15 years ago when the Shatz laboratory made the surprising discovery that MHCI molecules are expressed in the CNS throughout development (41). Messenger RNA 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 [sMHCI]) (49,50). The 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 nonfunctional or missing in the brain (55), TCR co-receptors, including CD3ζ and CD3ε, 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 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), its role in neurogenesis and migration has 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, whereas enhancing CD3ζ levels decreases it (57). Finally, the LY49 family might 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 whether 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 *β2m*, 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 seem to alter synapse density in mature, cultured hippocampal neurons from $\beta2m^{-/-}TAP1^{-/-}$ mice (50), but it does limit glutamatergic synapse density between neurons from the visual cortex, both in vivo and in vitro, in $\beta2m^{-/-}$ mice (49). Synapse density is elevated in $\beta2m^{-/-}$ cortex throughout development in vivo (49). Similarly, lowering sMHCI levels on young cultured cortical neurons using small interfering RNAs to β2m increases both glutamatergic and γ-aminobutyric acid (GABA)ergic synapse density, whereas 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 *β2m*$^{-/-}$*TAP1*$^{-/-}$ 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 *β2m*$^{-/-}$*TAP1*$^{-/-}$ mice (50). The lack of change in mEPSC amplitude suggests that MHCI does not alter α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) 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 3-week-old *β2m*$^{-/-}$*TAP1*$^{-/-}$ mice, with no change in mEPSC amplitude (50). Similarly, mEPSC frequency is also increased in young cortical neurons after β2m knockdown, whereas MHCI overexpression decreases mEPSC frequency (49). However, MHCI also negatively regulates mEPSC amplitude in these cortical cultures, suggesting that MHCI might 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 on cortical neurons (49). This role for MHCI might mediate part of its contribution to SZ, because an altered balance of excitation to inhibition 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 *N*-methyl-D-aspartate receptor (NMDAR) function (79). MHCI controls the development of structural and functional asymmetries in NMDAR expression in hippocampal circuitry in rodents (80). In addition, the AMPAR/NMDAR ratio is lower in hippocampal slices from *β2m*$^{-/-}$*TAP1*$^{-/-}$ mice. Because NMDAR-mediated excitatory postsynaptic potentials and field excitatory postsynaptic potentials are larger in the absence of sMHCI, while AMPAR-mediated responses are normal, MHCI seems to alter this ratio through specifically repressing NMDAR function. MHCI likely inhibits the channel properties of NMDARs, because their expression, composition, and distribution are not changed in *β2m*$^{-/-}$*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) might 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 messenger RNA levels in the lateral geniculate nucleus. 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 is lowered and long-term depression is absent in the hippocampus of *β2m*$^{-/-}$*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 might require CD3ζ, because *CD3ζ*$^{-/-}$ mice phenocopy the defects in long-term plasticity and long-term depression found in *β2m*$^{-/-}$*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 might 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 might 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 paper describing a non-immune role for MHCI in CNS development reported aberrant activity-dependent refinement of projections from the retina to the lateral geniculate nucleus in *β2m*$^{-/-}$ and *β2m*$^{-/-}$*TAP1*$^{-/-}$ mice (56). Mice deficient in *H2-Kb* and *H2-Db* (*KbDb*$^{-/-}$), or *CD3ζ*, 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 seem 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 seems to restrict ocular dominance plasticity, but not ocular dominance formation, through PirB (59,87).

It is important to note that most of the transgenic mice used to study MHCI and its receptors are nonconditional 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 *CD3ζ* 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 indicate that neuronal MHCI plays a direct role in development and plasticity, it is not known whether MHCI in the periphery or MHCI expressed on glia modulates 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 might 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 with 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 might 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 a 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 antipsychotic 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 after 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). In particular, the increase in interleukin (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 whether 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 importantly, 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. 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 whether 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 might 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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