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Neuroimmunology in Brain Development and Disease

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Although neural-immune cross-talk during disease and/or trauma has been studied for many years, the dogma has been that there is little interaction between the immune and nervous systems in healthy individuals. This belief was historically based on indications that the blood-brain barrier (BBB) blocks immune cell infiltration into the central nervous system (CNS), leading to limited immune responses in the CNS, and by a lack of classical immune proteins in the brain (Murphy and Sturm 1923; Joly et al. 1991). However, recent observations from both clinical and basic science research have caused a paradigm shift in our understanding of neural-immune interactions, indicating clearly that there is extensive communication between these systems (McAllister and van de Water 2009). There is now clear evidence that environmental insults that alter the immune response can affect brain development as well as behavior (Meyer et al. 2011; Patterson 2009). Moreover, mouse models of neurodevelopmental disorders have provided strong support for immune involvement in CNS development and disease (Patterson 2009; Patterson 2011). Finally, several different kinds of immune molecules, including cytokines, major histocompatibility complex (MHC) proteins, and complement, are expressed in the developing and adult brain and have critical functions in brain development and plasticity (Stephan et al. 2012; Garay and McAllister 2009; Shatz 2009; Elmer and McAllister 2012). In this Special Issue, we include reviews covering a range of topics from epidemiology, indicating a role for immune dysregulation in neurodevelopmental disorders, to basic mechanisms underlying the effects of immune molecules in brain development and disease.

Interest in neural-immune crosstalk has gained momentum as evidence accumulates regarding the potential involvement of immune dysregulation in many neurological and psychiatric disorders, as well as in healthy brain function. In addition to its well-documented role in trauma, neural inflammation is clearly present in several degenerative diseases, including Alzheimer's and Parkinson's disease (Lucin and Wyss-Coray, 2009). CNS resident immune cells, called microglia, may lose activity with age, leading to inefficient clearance of toxic protein aggregates that characterize neurodegenerative diseases. Moreover, the BBB becomes more permeable with healthy aging, which is accompanied by increased immune activation, expression of stress-induced and inflammatory genes, and CNS immune cell infiltration (Lucin and Wyss-Coray, 2009). Finally, neural-immune crosstalk may even occur in the non-diseased brain since BBB permeability is altered by

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many factors, including addictive drugs, toxins, subclinical infection, stress, and some medications (van den Pol, 2009).

In addition to a clear role for neural-immune crosstalk in degenerative disorders, there is rapidly increasing evidence for immune involvement in neurodevelopmental disorders. Although several neurodevelopmental disorders are caused by mutations in single genes, two of the most common disorders of neural development—autism spectrum disorders (ASD) and schizophrenia (SZ)—appear to be caused by a combination of mutations and environmental exposures. Interestingly, many of the diverse range of environmental factors that confer elevated risk for these disorders converge on an altered immune response. Each of the reviews included in this Special Issue discuss this issue from distinct perspectives. Alan Brown describes the increasingly compelling epidemiological evidence that several types of maternal infection increase the risk for offspring to develop ASD or SZ. This review also summarizes recent studies that report correlations between maternal cytokines, which are immune signaling molecules, and risk for these disorders. In addition to maternal infection, there is also ample evidence for changes in expression of immune genes in ASD and SZ patients. Michel and Mirnics summarize evidence that immune genes contribute to increased risk for ASD and SZ and expression of these genes is altered in postmortem ASD and SZ brains. Needleman and McAllister focus specifically on the evidence for a role for the diverse array of genes within the major histocompatibility complex (MHC) in conferring increased risk for ASD. Finally, in addition to ASD and SZ, immune dysregulation is also centrally involved in fetal alcohol spectrum disorder (FASD); Kane, Phelan, and Drew comprehensively describe this disorder and the role of immune cells in mediating it. Together, data from several of the approaches covered in these reviews converges on the conclusion that environmental and genetic changes in immune responses contribute significantly to ASD, SZ, and FASD.

Neuroimmunology research has also recently made dramatic advances in understanding how maternal infection and prenatal exposures contribute to neurodevelopmental disorders. An understudied, but clearly critical, component of this pathway is the placenta. Hsiao and Patterson describe how the placenta regulates maternal-fetal interactions, focusing on placental regulation of the effects of maternal immune activation (MIA) on the developing fetus. This review also discusses the intriguing evidence for a role for the placenta in prenatal programming of neurodevelopmental disorders. The placenta is generally thought to limit the maternal immune response from negatively impacting fetal development. While maternal antibodies are passed across the placenta to the fetus to confer passive immunity, some mothers generate antibodies that cross into the fetus and target fetal tissues. Because the BBB is not fully developed during this period of gestation, these maternal antibodies can enter the brain. It is well-known that autoantibodies from mothers with autoimmune disorders cross the BBB and may contribute to cognitive impairments in offspring (Bhat and Steinman, 2009). van de Water, Fox, and Amaral describe recent findings showing that specific maternal antibodies that cross the BBB in offspring and recognize fetal brain proteins are associated with increased risk for ASD.

The neural-immune theory of many neurodevelopmental disorders is also supported by extensive evidence from animal models. Mouse models of the MIA risk factor demonstrate

that maternal infection leads to abnormal behaviors in offspring that are consistent with SZ and include the three core symptoms of ASD. These models are being studied in many laboratories and their ability to model the anatomical, pharmacological, and behavioral changes in ASD and SZ are discussed in several reviews in this Special Issue. Michel and Mirnics introduce the mouse MIA model and this model is further discussed in the context of genes within the MHC by Needleman and McAllister. The role of the placenta in regulating and facilitating the effects of MIA in the offspring is discussed by Hsiao and Patterson. Harvey and Boksa compare and contrast the many pre- and postnatal MIA mouse models. This review critically assesses the strengths and potential pitfalls of these models and their relevance to neurodevelopmental disorders in general, and to ASD and SZ in particular. Mouse models of FASD have also revealed underlying pathology and the role of microglia in this disorder as reviewed by Kane, Phelan, and Drew. Finally, van de Water, Fox, and Amaral discuss recent reports in both mouse and non-human primate models that have revealed detrimental effects of maternal antibodies on brain development and lead to ASD-like behaviors.

Although the epidemiological evidence suggesting that immune dysregulation predisposes offspring to ASD and SZ is increasingly compelling, little is known about how immune dysregulation during early development causes behaviors and neuropathology characteristic of ASD, SZ, or FASD in offspring. The role of microglia in contributing to FASD is reviewed by Kane, Phelan, and Drew. Several microglial proteins within the MHC may also contribute to ASD, as summarized by Needleman and McAllister. Most of the evidence to date, however, strongly suggests that immune signaling molecules called cytokines are essential for a peripheral immune response to alter brain development. The central role for both maternal and fetal cytokines in mediating the effects of MIA on brain development are described by Michel and Mirnics, Needleman and McAllister, Hsiao and Patterson, and Harvey and Boksa. Although the effects of many cytokines remain to be investigated, one in particular, the chemokine CXCL12 (also known as SDF-1) has been extensively studied for its role in brain development. Zhu and Murakami summarize that the influence that CXCL12 has on many stages of neural development and illustrate the point that the timing of changes in cytokine levels caused by genetic or environmental factors will strongly influence the types of developmental processes affected.

Despite the rapid recent progress in the field of neuroimmunology in the past few years, many questions remain to be addressed. First, how central is immune dysregulation to neurodevelopmental disorders such as ASD, SZ, and FASD? Does immune dysregulation generally predispose individuals to neurodevelopmental disorders or is it the primary cause of subsets of these disorders (an important question debated by Harvey and Boksa)? What role does the placenta play in this process and can transfer of detrimental maternal cytokines or antibodies to the fetus be prevented at the level of the placenta? What is the molecular pathway triggered by maternal cytokines resulting from MIA that leads to the neuropathology and altered behaviors characteristic of ASD and SZ? Finally, which cytokines are the most important in causing neurodevelopmental disorders and can they, or their receptors and/or signaling cascades, be targeted to prevent the MIA phenotype? Answering these questions is essential to determine if immune molecules present novel therapeutic approaches in the near future for these complex neurodevelopmental disorders.

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