Abstract—Growing evidence from epidemiological studies strongly suggests maternal infection as a risk factor for psychiatric disorders including bipolar disorder, schizophrenia, and autism. Animal studies support this association and demonstrate that maternal immune activation (MIA) changes brain morphology and inflammatory cytokines in the adult offspring. Evidence for changes in inflammatory cytokines is also demonstrated in human post-mortem brain and peripheral blood studies from subjects with psychiatric disorders. This perspective briefly highlights convincing evidence from epidemiological, preclinical and human pathological studies to support the role of MIA in major psychiatric disorders. A better understanding of the link between MIA and brain development in psychiatric disorders will lead to the development of novel immunomodulatory interventions for individuals at risk for psychiatric disorders.

Key words: maternal immune activation, inflammation, brain development, bipolar disorder, schizophrenia, autism.

PERSPECTIVE

The link between brain development and later onset of psychosis has increasingly emerged in the past two decades (Ploeger et al., 2010). Current research strongly postulates the complex interplay between genetic and environmental factors in directing and shaping brain development (Sullivan et al., 2012). Brain development is a highly elaborate process that occurs predominately during the prenatal period, which starts with the proliferation and migration of neurons to the appropriate location in the brain, followed by the establishment of proper neuronal connections (Knuesel et al., 2014). Considering the highly sophisticated processes of brain development, any small perturbations, such as maternal exposure to infectious or inflammatory insults, can potently compromise the developing architecture and function of the fetal brain (Knuesel et al., 2014). These perturbations from the trajectory of normal brain development during prenatal period may contribute to a sequence of events that can become progressively magnified over time, leading to long-term changes in brain and behavioral functions that may persist into adulthood (Bale et al., 2010).

Epidemiological studies suggest that exposure to prenatal infection such as influenza, rubella, measles, herpes simplex virus, and bacterial infections may increase the risk for the offspring to develop bipolar disorder (BD) (Parboosing et al., 2013), schizophrenia (SCZ) (Mortensen et al., 2010), or autism (Atladóttir et al., 2010). The diversity of infectious pathogens suggests that general immune activation during gestation, rather than the type of pathogen is associated with later onset of psychosis in the offspring. This notion is supported by a nationwide study in Denmark which found that children born to mothers who required hospitalization in the first or second trimester due to severe infections were associated with the diagnosis of autism (Atladóttir et al., 2010). In a more recent exploratory study, the same group reported that in children diagnosed with autism, mothers who had prolonged episodes of fever during the first or second trimester was associated with threefold increased risk of infantile autism (Atladóttir et al., 2012). This study is confirmed by a larger case–control study which found a strong association between maternal fever during pregnancy and autism risk (Zerbo et al., 2013). SCZ and BD had similarly been linked to a three- or fourfold increase risk respectively after exposure to maternal influenza during pregnancy (Brown and Derkits, 2010; Parboosing et al., 2013). In addition, the occurrence of “winter baby” was reported in autism (Zerbo et al., 2011), SCZ (Davies et al., 2003; Konrath et al., 2016), and BD (Torrey et al., 1996), where higher risk of these disorders was observed in babies conceived during the winter months possibly due to higher prevalence of influenza and infectious diseases. These epidemiological findings suggest that activation of the maternal immune response may be a shared underlying pathway conferring risks to these psychiatric disorders.
One prevailing hypothesis is that altered expression levels of inflammatory molecules in the fetal compartment in response to immune activation may disrupt brain development and neural connectivity, which may, in turn, have long-term effects on the individual’s mental functions later in life. (Knuesel et al., 2014; Miller and Raison, 2016). Cytokines are small signaling inflammatory proteins secreted by a wide range of immune and non-immune cells (Arango Duque and Descoteaux, 2014). Cytokines include an assortment of chemokines, interleukins (IL), interferons (IFN) and tumor necrosis factors (TNF) that are generally grouped into pro- or anti-inflammatory cytokines. Examples of pro-inflammatory cytokines include IL-1β, IL-6, and IFN-γ, which are involved in the magnification of inflammatory responses. In contrast, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 alleviate inflammatory responses. The balance between these cytokines regulates a wide variety of processes such as regulating the innate and adaptive immune systems, cellular proliferation, activation, and differentiation (Arango Duque and Descoteaux, 2014). In the central nervous system, cytokines regulate a variety of neurodevelopmental processes including neuronal cell differentiation, synaptic connectivity and pruning, neuronal plasticity and neuronal survival (Bauer et al., 2007). During prenatal brain development, there is constitutive expression of cytokines and their receptors on neuronal cells, suggesting that these molecules play a crucial role in directing and shaping brain development (Mousa and Bakhiet, 2013). Hence, alterations in the cytokine network may be associated with changes in brain development.

Several lines of evidence support the hypothesis that alterations in the expression levels of cytokines during early brain development are associated with a broad range of psychiatric disorders. First, epidemiological studies reported that higher levels of pro-inflammatory cytokines (TNF-α and IL-8) in the maternal serum are associated with increased odds of psychosis (Brown et al., 2004), while higher levels of maternal anti-inflammatory cytokines (IL-4, IL-5, and IL-13) are associated with decreased odds of psychosis (Allswede et al., 2016). Preclinical evidence for these epidemiological associations had been attained by exposing pregnant animals, such as mice and rats to immunological agents at a specific gestational age (Meyer, 2014). This involves maternal exposure to lipopolysaccharide (LPS), a bacterial endotoxin, or polyriboinosinic-polyribocytidylic acid [poly(I:C)], a synthetic double-stranded RNA, both of which induces immune activation and cytokine release (Meyer, 2014). Maternal exposure to these immunological insults was found to increase levels of pro-inflammatory cytokines (IL-6, TNF-α, IFN-β, and IL-1β) in the maternal serum, amniotic fluid, placenta, and the fetal brain of mice (Urakubo et al., 2001). Both IL-1β and IL-6 play an important role in activating the maternal immune response. Exposure of IL-1β to rat fetal neural progenitor cells was found to inhibit cell proliferation and neurogenesis (Crampton et al., 2012). While exposure of IL-6 to wild-type mice during mid-pregnancy was found to produce core features of autism and SCZ such as social and behavioral deficits in the adult offspring, which can be reversed with administration of IL-6 antibodies (Smith et al., 2007). These data suggest that cytokines are important mediators of maternal immune activation (MIA) on psychiatric phenotypes in the offspring.

While there is evidence that MIA induces cytokine imbalance and behavioral changes, little is known about how these cytokines alter brain development. One plausible explanation is that MIA leads to the production of inflammatory cytokines that are often prolonged and systemic in the maternal blood. These maternal cytokines can reach the fetal compartment by crossing the placental barrier (Zaretsky et al., 2004). Indeed, subtle levels of IL-1β, IL-6 and TNF-α were found to cross intact human fetal membranes, i.e. amnion, chorion, and decidua (Kent et al., 1994). The resulting cytokines in the fetal circulation can activate the fetal immune response to produce more cytokines. It is widely believed that the blood–brain barrier of the fetus is more fragile and immature when compared to adults, making it very likely that systemically generated cytokines from the fetus gain access into the fetal brain (Saunders et al., 2012). The exposure of cytokines to brain cells can alter functions of neurotransmitters such as serotonin, dopamine and glutamate, which in turn may lead to "sickness behaviors", comprising of altered appetite, fatigue, emotion, cognition, learning and memory (Zalcman et al., 1994; Dantzer et al., 2008; Yarlagadda et al., 2009; Felger and Lotrich, 2013). Thus it is likely that cytokine changes in the setting of maternal infection lead to long-term effects on brain function that would increase the risk for psychiatric disorders.

Studies have shown that MIA is accompanied by changes in brain cytokines throughout development and into adulthood of the offspring in a region-specific manner (Garay et al., 2013; Estes and McAllister, 2015). In the frontal and cingulate cortices, proinflammatory cytokines are found increased at birth and in the adult offspring (Garay et al., 2013). Changes in brain morphology such as SCZ- and autism-associated reduced cortical thickness, decreased hippocampal, prefrontal cortical and striatal volume, enlarged ventricles, as well as reduced Purkinje neurons in the cerebellum, are commonly observed in the adult offspring (Shi et al., 2009; Plonkewitz et al., 2011; Patrick et al., 2016). A study has also reported reduced dendritic spine density and synaptic proteins involved in neurotransmission (Coiro et al., 2015). Neurotransmission of serotonin and dopamine, two of the major neurotransmitters involved in controlling reward, pleasure and emotion are in part, regulated by cytokines such as IL-1β and TNF-α (Wischhof et al., 2015; Luchicchi et al., 2016; Miller and Raison, 2015). These cytokines have been shown to alter the release of dopamine and serotonin from neurons which may underlie the manifestations of psychiatric disorders (Miller and Raison, 2016). Reduced serotonin and dopamine neurotransmission is commonly observed in the brains of adult MIA offspring (Baharoomi et al., 2013; Depino, 2015). Also, gamma-Aminobutyric acid (GABA) signaling, a neurotransmitter involved in controlling the activity of highly excited neurons, is found
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات