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PERSPECTIVE
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Maternal Immune Activation and Related Factors in the Risk of Offspring Psychiatric Disorders

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Maternal immune activation (MIA) at the time of gestation has been linked to increased risk of neurodevelopmental psychiatric disorders. Animal and human models have been used to evaluate the relationship between MIA and these outcomes. Given that each of these two disciplines of study have their benefits and limitations, a translational perspective is expected to illuminate more than by the use of any single approach. In this article, we discuss this translational framework and explore how it may be enhanced by the utilization of epigenetic studies and by investigating the microbiome. In this perspectives piece, we focus on the impact of epidemiologic studies, animal models, and preclinical studies in the literature on MIA as well as the potential for greater integration between fields.

Keywords: autism, schizophrenia, maternal immune activation, stress, microbiome

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INTRODUCTION

Fetal developmental events occurring *in utero* are implicated in the postnatal health of offspring through adulthood. Environmental exposures during gestation, including maternal infection, nutritional deficiencies, toxic exposures, and other factors that cause stress during pregnancy are particularly insidious during gestation. Central nervous system (CNS) disorders, particularly schizophrenia, autism spectrum disorder (ASD), and bipolar disorder likely result from both genetic and environmental contributions. Epidemiologic studies have revealed strong connections between conditions associated with heighted maternal immune activation (MIA), resulting from infection and stress, and schizophrenia (1, 2), ASD (3, 4), and bipolar disorder (5) in offspring. At the same time, substantial advances have been made through animal models to understand the mechanisms underlying these diagnoses. More recent studies have begun to address potential mediating pathways including epigenetics, and the role of the microbiome in these disorders.

IMPACT AND LIMITATIONS OF EPIDEMIOLOGIC STUDIES OF MIA

Epidemiologic studies offer important potential inferences into etiologic processes through the direct study of human populations. Results from early ecologic studies, which focused on the comparison of groups instead of on individuals, were consistent with associations historically found between schizophrenia and prenatal exposure to influenza outbreaks (6). Later, ecologic studies, with larger cohorts and those investigating other infectious agents, showed inconsistent results and generally weak effects. However, these types of studies are imprecise in their measurement of this exposure, as individual-level data are missing. About 70% of those who were *in utero* during the influenza

epidemic of 1957, but were unexposed, were incorrectly classified as exposed because ecologic studies are based on dates of birth to establish fetal exposure (7).

To address this limitation, individual-level information has been garnered through the use of birth cohort studies, by which exposures occurring during pregnancy can be documented with questionnaires, medical histories or biological samples. Individuals studied can then be longitudinally monitored for diagnoses such as ASD or schizophrenia. Birth cohort studies have shown that offspring of mothers with antibodies to certain infections, including influenza, and/or elevated C-reactive protein levels during pregnancy, were at increased risk for schizophrenia (1, 2, 8), ASD (3, 9, 10), and bipolar disorder (5, 11). This is discussed in a recent review [see Ref. (12)].

One key limitation of birth cohort studies is that they cannot be used to identify biological mechanisms underlying the pathology. The potential to draw causal inferences is further limited by potential bias and confounding, though our group and others have utilized epidemiologic and statistical approaches to reduce the impact of these factors. Since a myriad of infectious agents produce cytokines and other inflammatory markers, they can be used as a common indicator of these exposures and may operate as a shared mechanism by which neurodevelopment of offspring may be prenatally modified, thus increasing the risk for schizophrenia, bipolar disorder, and other psychiatric conditions (2, 13, 14).

IMPACT AND LIMITATIONS OF ANIMAL AND HUMAN MODELS OF MIA

The abovementioned epidemiological studies have inspired research on prenatal infection and MIA using rodent and primate models. Animal models have provided unique experimental tools to overcome the limitations of epidemiological studies, such as longitudinal evaluation of neurobiological processes as well as establishing causality. They also facilitate the unraveling of cellular and molecular mechanisms, which is not possible in epidemiologic studies. Through studies of animal models, cytokines were found to act on the developing fetal brain as inflammatory signaling proteins of detrimental environmental exposures. Cytokines play critical roles in normal fetal development, including neuron proliferation, and synaptogenesis (15). However, elevated maternal proinflammatory cytokine levels cause changes in these processes and have been associated with abnormal neurodevelopment (16). The MIA models in animals allow for in-depth tracking of biologically-relevant phenotypes over time from gestation to adulthood (17). These models involve triggering the maternal immune system during fetal development using a variety of immunogens, such as lipopolysaccharide (LPS) and polyinosinic:polycytidylic acid (poly I:C), and then observing changes in the brain and behavioral development of offspring for features corresponding to human neurological disorders (18, 19). It is possible that prenatal immune challenge acts as a "disease primer" which, when combined with other environmental, genetic, and epigenetic factors, alters the trajectory of fetal neurodevelopment and may ultimately result in the emergence of a number of CNS disorders (17).

Rodents have historically been the principal species utilized in animal model studies. For example, deficits in sensorimotor gating (17, 18), depression-like behaviors (20), and high levels of repetitive behaviors (18, 21, 22) have been noted in offspring of rodent MIA models. One particular mouse study (8) reported neural and behavioral abnormalities resembling those found in schizophrenia as a result of prenatal exposure to MIA interacting synergistically with traumatizing experiences in puberty (23). Studies have also included nonhuman primates, such as rhesus monkeys (24). These models have provided greater comparability with regard to biological phenotypes and neurodevelopmental processes to humans. In one rhesus monkey model, MIA produced progeny that displayed irregular social interactions, abnormal communication, and repetitive behaviors. These results extended rodent MIA findings to behaviors that more closely mirror human behaviors, such as those in both ASD and, to some degree, in schizophrenia (25). More recently, novel evidence implicating MIA exposure with alterations of nonhuman primate dendritic morphology was found (26). This may offer insight into revealing the neuropathology of CNS disorders related to MIA and pave the way for clinical investigations.

Recent clinical studies have served to help bridge the gap between non-human and human primate basic science by evaluating relationships between maternal immune function and neuroanatomic abnormalities. Maternal pro-inflammatory cytokine interleukin-6 concentrations were associated with offspring frontolimbic white matter microstructural properties, including maturational changes in the first 12 months postnatally (27). Another clinical study linked high maternal inflammatory concentration of interleukin-6, a pro-inflammatory cytokine, during pregnancy with abnormal development in offspring at 2 years of age in brain regions associated with sensory processing and impulse control (28).

STRESS AND MIA

Many studies have suggested a correlation between maternal stress during pregnancy and a myriad of negative neurodevelopmental effects in offspring (29, 30). Stressful experiences during pregnancy, including death in the family, war, natural disasters, and more recently socioeconomic disadvantage have been linked with schizophrenia in offspring (31–34). These results provide evidence for an association between maternal stress and schizophrenia in offspring. The impact of prenatal exposure to maternal stress has been investigated by several birth cohort studies. Distressing experiences while the mother was pregnant were recorded and used to anticipate potential risk of psychiatric disorders among offspring in a Danish cohort (35). There is a growing body of evidence implicating stress during prenatal development to ASD (36, 37).These results corroborate epidemiological research on birth cohorts from the Dutch Hunger Winter of 1944–45 which reported relationships between prenatal famine and offspring long-term cognitive and mental health development (38–40), including schizophrenia and affective disorders. Although nutritional deficiency is regarded as the likely cause of the findings, it is possible that maternal stress due to the exposure played a role. However, conflicting results were found

in a population-based cohort study, regarding maternal exposure to death of a relative and risk for ASD in offspring, in which no correlation was reported (41).

Although the precise mechanisms for the associations between maternal stress, immune activation, and subsequent offspring pathology are still not well known, it is thought that psychological stress, through the inflammatory response, may exert an influence on human health (42). One study has examined the cytokine profiles of umbilical cord blood, in association with prenatal stress, as a marker of their effects on the immune system. The findings suggest that both adaptive and innate immune responses were altered by prenatal stress (43). A more recent birth cohort investigation implicated maternal psychological stress in alterations of perinatal cytokine profile in offspring. In particular, prenatal maternal stress was associated with higher levels of interleukin-4, interleukin-5, interleukin-6, interleukin-8, and interleukin-1ß (44).

THE MICROBIOME AND MIA

The microbiome is a relatively new topic that has been explored as a potential etiologic factor in central nervous system disorders and the remediation of their symptoms. An imbalance in the microbiome is correlated with a variety of adverse consequences, including lasting behavioral abnormalities, neuropathology, immune dysfunction, and deficient gastrointestinal integrity. Abnormalities in immune function are reported in ASD and other psychiatric disorders, and recent studies suggest that microbiota is an important factor in this dysregulation (45, 46). The gut microbiome composition has been determined to not only be affected by neuroinflammation (46) but to reciprocally affect specific regional immune responses in the brain (47).

Animal Models

Experimental studies have shown that MIA brings about enduring changes in immune system activity as well as ubiquitous alterations in the balance of offspring microbiota in adulthood (48–50). One study reported changing the microbiome of mice using human commensal *B. fragilis* enhanced not only gastrointestinal health, but also execution of certain tasks used to measure behaviors principally associated with ASD (49). In another study, investigators found that mice that had more Th17 cells in their intestine, and in which there was more colonization with segmented filamentous bacteria (SFB), were more prone to behavioral pathology caused by MIA (50). This susceptibility was passed to other mice by induction of Th17 cells and colonization of SFB. In addition, during MIA, elevated interleukin-17a responses were caused by the activation of dendritic cells, a key cell type involved in CNS pathology, interacting with SFB colonized Th17 cells (50).

MIA and the Human Microbiome

When the maternal immune system is activated during pregnancy, the inflammatory cytokines released affect the offspring's vagal system and consequently their CNS regulation (51). MIA activation also affects maternal gut bacteria, which in turn can affect the microbiome of offspring. The microbiome of offspring has been shown to be populated and affected by the prenatal environment (52), mode of delivery (53), diet, and other aspects of postnatal care (54). The microbiome of children with ASD, when compared with controls, is less diverse, with overgrowth of certain microbes, such as *Desulfovibrio* (55), *Alistipes*, and *Akkermansia* (56), being more common.

Probiotics are hypothesized to aid autism symptoms by colonizing the gastrointestinal system with beneficial bacteria. However, clinical trials of probiotic supplementation have shown mixed results for the effectiveness of probiotics on the behavioral symptoms of ASD (57). A more recent open-label study using microbiota transfer therapy (MTT), which consists of round of an antibiotic, a colon cleanse, and fecal transplant therapy, resulted in an 80% decrease in problematic GI symptoms using the Gastrointestinal Symptom Rating Scale and increased diversity of the microbiome of participants (58). This therapy also resulted in improved ASD behavioral symptoms which continued for 8 weeks post-treatment completion. This therapy will need to be studied more extensively with larger sample sizes, but these results are promising for a potential treatment option.

It has recently been reported that oral probiotic supplementation during pregnancy reduced MIA cytokine levels and subsequent offspring ASD symptoms, such as depression, anxiety, and social deficits, in mouse models (59). Some of these results may be due to the prevention of Poly(I:C)-induced weight loss of dams, another result of the oral probiotic supplementation. Although this has yet to be studied in humans, this offers insight into potential preventative measures for expecting mothers.

EPIGENETICS AND MIA

It has been found that epigenetic modifications occur beyond early embryonic development and are dynamic throughout fetal development and over one's lifetime (60, 61). Epigenetic alterations offer possible mechanisms by which immune insults during prenatal development affect offspring outcomes. Maternal distress has been reported to be a leading cause in epigenetic alterations (61). Birth cohort studies investigating the effects of the Dutch Hunger Winter have examined whether standard DNA methylation is modified as a result of maternal famine and stress. Hypo-methylation during gestation alters the accessibility of offspring DNA to translation and therefore changes gene expression in these regions. Several genes, including ABCA1, insulin-like growth factor II, interleukin-10, GNASAS, and MEG3 have been found to have modified levels of DNA methylation in offspring, thus implicating extensive epigenetic effects of maternal famine (62, 63).

In mouse models of MIA, adult offspring have displayed hypo-methylation, and transcriptional changes, in genes related to GABAergic signaling and neural development (64). In a more recent review, maternal depression, and its associated immunological alterations in cytokines and reactive oxygen species levels, was linked to offspring DNA methylation (65). Experimental evidence from animal models has indicated that MIA can result in widespread DNA hypo-methylation in the

hypothalamus (66). This can be a potential factor for dysregulation of the hypothalamus–pituitary–adrenal gland (HPA) axis, which has been linked to the pathophysiology of schizophrenia (67). Alterations in the gray-matter composition of the hypothalamus have also been linked to ASD (68). Another study reported that, in MIA exposed mice, 80% of hypo-methylated sites were stabilized with a diet high in anti-inflammatory fats (69). Although this is yet to be studied in humans, this has profound implications for possible dietary interventions to mitigate the effects of MIA induced hypo-methylation in addition to standard treatment.

MIA also alters histone acetylation. Adult female offspring of MIA mice expressed anhedonic behavior, which was correlated with global histone acetylation changes in the hippocampus (70). Histone modification caused by MIA may alter hippocampal serotonin transporter (SERT) expression, a critical component to the etiology of depression and which may play a significant role in schizophrenia (70, 71).

FUTURE RESEARCH AND PERSPECTIVES

Great strides have been made through both epidemiologic work and basic science to explore the potential role of MIA in neuropsychiatric disorders. The addition of epigenetics to the MIA model as a mediating mechanism may shed more light on pathogenic processes that underlie these disorders. A key challenge regarding a suitable translational approach (12) is the Research Domain Criteria (RDOC) (72), which is aimed at deconstructing psychiatric disorders into their most basic psycho- and neuropathological components. Further insights for future translational research may be gleaned from standardization of immune activating agents and methods, integrating postmortem pathology, and longitudinal neuroimaging (73–75).

Although stress has been conceptualized as a teratogen, and may activate the maternal immune system in a way similar to infection, the biological framework for how it may affect offspring is still not well understood. Beyond cytokines, maternal cortisol levels have also been implicated in offspring neuropathology (76). Further elucidation of the biological mechanism by which maternal stress may act as an inflammatory agent, and influence offspring neuropathology relevant to psychiatry disorders, is necessary.

Although investigation of the microbiome offers the potential for important findings linking the immune system and psychopathology, several issues remain. For example, whether exposure to known risk factors for ASD and other psychiatric outcomes also result in microbiome alterations requires further investigation. Another question of interest relates to the cause-effect relationship between MIA and the maternal microbiota, on offspring neurodevelopment. Studies comparing psychiatric outcomes following C-section versus natural birth creates opportunities to address this question given the differences in exposure to the vaginal microbiome between the two delivery methods (77).

CONCLUSIONS

In conclusion, we propose it is vital to consider MIA in the context of not only infection but also other factors, such as maternal psychological stress, in the etiology of neurodevelopmental disorders. Epigenetic events may represent mediating or modifying factors in the putative pathogenesis of psychiatric disorders following MIA. The microbiome is another promising area of investigation in the MIA hypothesis of mental disorders. We believe that a translational approach that incorporates knowledge of these processes will be necessary to broaden our understanding of the effects of prenatal MIA on offspring susceptibility to psychiatric disorders.

AUTHOR CONTRIBUTIONS

FC wrote the first draft of the manuscript. AB contributed to the conception, editing, and research for the manuscript. Both authors contributed to manuscript revision and have read and approved the final manuscript.

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