Maternal Microbiota and Immune Interactions in Neurodevelopmental Risk: A Review of Maternal Immune Activation Models

Written by Alexander Byrne

Abstract

Maternal Immune Activation (MIA) is a model used to study the impact of maternal infection and maternal inflammatory cues on fetal brain development and vulnerability to neurodevelopmental disorders (NDDs). Studies using the MIA model have confirmed the role of immune mediators, such as interleukin-17A (IL-17A), in disrupting the cortex's structural integrity and behavior. The maternal microbiota has also been recognized as a key modulator of these immune-fetal brain interactions. Microbes that inhabit the gut control TH17 cell differentiation—long-term players in MIA—and presence or absence can determine whether offspring become NDD-like following maternal inflammation. This association suggests the capacity of the microbiota to modulate maternal immune reactivity and thereby determine fetal neurodevelopmental processes. Together, these findings position MIA not as a singular immune event but as a systems-level interaction among microbes, cytokines, placental signaling, and fetal neuroimmune development.

Introduction

Neurodevelopmental disorders (NDDs) are some of the most notable and commonly discussed disorders in neuroscience. These disorders are dependent on prenatal environmental changes and are often studied in rodent models, though establishing one-to-one comparisons between rodents and humans remains difficult. While rodent models exhibit NDD-like symptoms, their mapping to human conditions is tentative. Significant stages of development are the prenatal and early postnatal periods, which are particularly sensitive to severe viral infections and the resulting immune response (Chalen, Caetano-Silva, et al., 2024; Otero and Antonson, 2022). This response can contribute to the development of NDD-like symptoms. The model used to study this interaction is known as Maternal Immune Activation (MIA), which occurs when a pregnant mother's immune system is triggered by infection, leading to changes in fetal brain development (Otero and Antonson, 2022; Chalen, Caetano-Silva, et al., 2024). The immune system plays a vital role in protecting the body from infection and disease, yet it can also have adverse effects. Research indicates that certain cell populations involved in immune responses can produce unexpected neurological side effects on fetal offspring. Beyond infection and immune response, other external factors, such as the maternal microbiome, have also been linked to NDDs. This review aims to understand the relationship between the maternal microbiome and the phenomenon of MIA.

Modeling MIA with Poly I:C

The study by Choi and collaborators demonstrates how gut microbes regulate maternal immune responses and influence fetal brain development (Choi et al., 2016). The molecule used to study this is Poly I: C, which was used to activate the immune system artificially, distinct from a live virus. This triggers the cell populations of the immune response known as T Helper 17 cells (TH17 cells), which are shown to be responsible for ASD-like symptoms in rodent offspring. Looking deeper into this, the effector cytokine interleukin-17a (IL-17a) is directly related to the microbiome

and is necessary and sufficient to cause abnormal behaviors and brain development in the rodent model (Choi et al., 2016). The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Normally, neurons in the cerebral cortex organize into distinct layers, but MIA leads to patches of disorganized neurons similar to those seen in ASD postmortem brains (Choi et al., 2016).

While it has been shown that MIA caused by infection can lead to the development of abnormal behaviors and brain development in rodent models' offspring, it remains to be seen the degree to which other factors, such as the microbiome, play as significant a role. During TH17 cell differentiation, the maternal microbiome and bacteria play an essential role. Segmented filamentous bacteria (SFB) are strongly associated with TH17 production and activity, and mice treated with vancomycin lack this but recover it when in contact with non-treated mice/waste (Kim et al., 2017). When treated with broad-spectrum antibiotics or minimally possessing TH17 cells in the small intestine, cortical patches consistent with ASD-like morphology in fetal offspring decreased. Therefore, maternal gut bacteria are indispensable to promote neurodevelopmental abnormalities in mouse offspring (Kim et al., 2017). Two genetically similar strains of mice, Taconic (Tac) and Jackson (Jax), differ in their TH17 cell populations due to the presence or absence of SFB. When subjected to MIA, Tac offspring display NDD-like behaviors, whereas Jax offspring do not. However, when Jax mothers are colonized with SFB, their offspring develop ASD-like behaviors, demonstrating that maternal gut bacteria influence neurodevelopment. Pregnant Jax mice colonized with human gut bacteria that promote TH17 cells also develop ASD-like offspring after MIA, reinforcing the idea that human microbiota may contribute to neurodevelopmental abnormalities.

Building on the IL-17A mechanism, Shin Yim and collaborators (Shin Yim et al., 2017) demonstrated that the neurodevelopmental outcomes of maternal immune activation (MIA) are not permanent and can indeed be reversed postnatally (Shin Yim et al., 2017). Utilizing a poly I:C model to mimic viral infection in pregnancy, offspring exhibited typical neurodevelopmental disorder (NDD)-like behaviors, such as decreased social interaction, augmented repetitive behaviors, and hyper ultrasonic vocalizations. These behaviors had already been linked to cortical disorganization in the form of loss of layer specific markers like SATB2 and TBR1 (Shin Yim et al., 2017). Notably, the study localized these defects to discrete cortical patches—primarily in the dysgranular zone of the primary somatosensory cortex (S1DZ)—and linked their presence and size with the severity of behavior. In Figure 1f, the S1 of MIA offspring had elevated c-Fos expression, indicative of elevated baseline neuronal activity, again implicating hyperexcitable cortical circuits as an etiology for the phenotypes. In a tour de force, the investigators then proceeded to employ postnatal intervention by optogenetically silencing this overactive cortical region, rescuing both behavior and cortical anatomy. Importantly, the behavioral rescue was most effective when performed during the early postnatal time points, emphasizing an early window of enhanced neuroplasticity. These findings contend that while MIA imposes structural and functional changes on fetal brain development, these changes are not permanent but rather are therapeutically accessible by virtue of neural activity manipulation within key cortical nodes like the S1DZ (Shin Yim et al., 2017).

Modeling MIA with Real Pathogens: The Use of Live Viruses in Research

The review by Otero and Antonson (Otero and Antonson, 2022) highlights maternal immune activation (MIA) as a multifaceted model for understanding how prenatal infections shape fetal neurodevelopment (Otero and Antonson, 2022). Central to their argument is the distinction between commonly used pathogen mimetics like poly I: C and live virus models such as influenza A virus (IAV) (Otero and Antonson, 2022). Whereas poly I:C triggers a brief, acute innate immune response, IAV triggers a long-term, multi-stage immune cascade along both innate and adaptive pathways of immunity. The paper notes that although both models activate the TH17/IL-17A pathway—a pathway previously demonstrated to interfere with cortical morphology and stimulate fetal microglia—IAV more accurately reflects in vivo infections. Importantly, they argue that poly I: C may oversimplify MIA by bypassing key interactions between maternal microbes, cytokines, and fetal immune cells. The review also underscores additional mechanisms, such as placental lack of oxygen and microglial priming, which could potentially operate independently or alongside IL-17A signaling.

Antonson and collaborators in their 2021 study provide critical insight into the threshold model of fetal vulnerability by studying the effects of moderately pathogenic IAV infection during pregnancy (Antonson, Kenney, et al., 2021). Pathogenicity is a major player in the MIA model, and the degree of infection is a crucial factor to consider. According to this study, moderate infection might have muted or even negligible effects on cortical formation and fetal brain inflammation, though there is a noted impact on placental health (Antonson, Kenney, et al., 2021). This observation underscores the important role of the placenta as a protective barrier against maternal inflammation (Antonson, Kenney, et al., 2021). Typical immune responses with moderate doses include systemic cytokine elevations, such as IL-6, albeit to a lesser extent than those seen with high-dose infections. Additionally, while cytokines in the placenta may lead to structural integrity breakdown, the absence of a fetal brain response suggests that the placenta acts as the first line of defense, a notion further supported by pathway analyses showing upregulation of inflammatory

and hypoxia-related genes (Antonson, Kenney, et al.).

In their 2024 study, Otero and collaborators explored how IAV infection during pregnancy affects fetal brain development in a dose- and time-dependent manner (Otero et al., 2024). Severity has been demonstrated to be a significant factor when considering the infection type for the MIA model. Although the model often focuses on IL-17A and TH17 pathways, activation by IAV does not elevate these components as one might suppose; instead, fetal microglia and border-associated macrophages emerge as the primary responders, increasing in both number and phagocytic behavior. While cytokines such as IL-6 and IFN-γ consistently rise with the level of infection—a constant feature of MIA— maternal IL-17A and TH17 cell numbers remain relatively constant. Consequently, high dose IAV infection results in a thinning of the cortical plate and disorganization of both deep and upper cortical layers, evidenced by altered distributions of TBR1+ and SATB2+ neurons (Otero et al., 2024). This disruption is absent in moderate IAV infection, further reinforcing the concept of a severity threshold. High-dose infection also alters gene regulation for neuronal development, inflammation, and microglial function, indicating that severe maternal inflammation disrupts normal cortical development.

The Microbiome and MIA

Other factors such as stressors, metabolites and others contribute to the complexity of the MIA model and the neurological realities within. Antonson and collaborators in their 2020 study investigated how prenatal stress alters both maternal immune function and gut microbiota composition (Chen, Antonson, et al., 2020). The study found that stress during gestation led to unique immune signatures in pregnant dams, including elevated cytokines such as IL-6 and CCL2, alongside shifts in microbial diversity. These changes were linked to disrupted microbial metabolic pathways, which influence neuroactive compound production. The study underscores the importance of the microbiome as a mediator between psychological stress and systemic immune activation during pregnancy. The altered microbial and immune landscape suggests a possible route by which prenatal stress exerts long-term effects on offspring brain development.

Chen and collaborators in their 2020 study similarly examined prenatal stress's effects on initiating disturbances in the immune system and neurochemistry with long term behavioral impacts in offspring (Chen, Antonson, et al., 2020). From their findings, prenatal stress generated intrauterine inflammation characterized by increased CCL2 expression that, in turn, affected serotonin signaling pathways responsible for neurodevelopment. Behavioral tests revealed that such offspring exposed to this inflammatory microenvironment had enduring impairments of anxiety-like behavior and social interaction.

“The altered microbial and immune landscape suggests a possible route by which prenatal stress exerts long-term effects on offspring brain development.”

Notably, these behaviors were dependent on both microbial colonization and CCL2 signaling, indicating that stress-induced behavioral phenotypes are regulated by microbiota-immune crosstalk. Galley and collaborators in their 2021 study studied the ways in which prenatal stress regulates tryptophan metabolism, a critical connection between the gut microbiome and neurodevelopment (J. Galley et al.,2021). The study demonstrated that stress during pregnancy disrupted both microbial and host tryptophan metabolic pathways, including those leading to the synthesis of serotonin and kynurenine. These were accompanied by alterations in fetal brain and placental tryptophan transporter expression, showing that maternal stress can impair neurotransmitter supply at critical developmental windows. The data suggests a mechanism where the maternal microbiome influences neurodevelopment via metabolite signaling, adding a biochemical dimension to the immune-mediated MIA framework.

Galley and collaborators in their 2023 study examined how other stressors impact developing offspring gut microbiomes (Galley et al., 2023). Using human cohorts and mouse models, the study revealed that high maternal psychological distress was associated with reduced bifidobacteria abundance and decreased microbial richness in offspring. Extending this work, (Galley et al., 2024) studied the effectiveness of probiotic intervention by modulating *Bifidobacterium dentium* administration during pregnancy (Galley et al., 2024). The study demonstrated that prenatal exposure to this specific strain had long-term intergenerational effects, including altered immune profiles, metabolic signaling, and improved social behaviors in offspring. Offspring of *B. dentium*-treated dams exhibited reduced pro-inflammatory cytokine expression and more balanced microbiota composition. These findings are significant in that they show intentional manipulation of maternal microbiota can have trans-generational protective effects.

Discussion and future directions

Taken together, these reports support a multi-aspect interaction among maternal stress, microbial ecology,

immune signaling, and neurodevelopment of the offspring. In their early phase, MIA experiments focused mostly on cytokines such as IL-6 and IL-17A, but emerging evidence hints toward the universal involvement of maternal microbiota in eliciting immunity and programming fetal fates. Pioneering experiments by (Choi et al., 2016) and (Kim et al., 2017) showed that gut microbiota in mothers—here specifically those triggering TH17 differentiation—are required to trigger pathogenic cascades that lead to cortical defects and autism-like behaviors in offspring (Choi et al, 2016.; Kim et al., 2017). However, recent work by (Otero et al., 2024) and (Antonson, Kenney, et al., 2021) has opened the paradigm using live influenza A virus (IAV) models, revealing immune dynamics that encompass placental hypoxia, microglial priming, and a threshold of severity for fetal brain effects—none of which are fully captured in synthetic mimetic models like poly I:C (Antonson, Kenney, et al., 2021; Otero et al., 2024). Other recent research has tried to explore the role of IL17A in the absence of microbes (Chalen, Wang, Jung, et al. 2022; Chalen, Wang, Florianowicz, et al., 2023).

In parallel, studies by Chen, Galley, and Antonson have extended this framework beyond infection, showing that non-infectious stressors such as psychological distress during pregnancy also disrupt maternal microbial communities and immune tone (Antonson, Evans, et al, 2020.; Galley et al, 2024.; Chen, Galley, et al., 2021). These disruptions—marked by altered tryptophan metabolism, inflammatory chemokine expression, and reduced bifidobacterial abundance—contribute to long-term changes in neurodevelopmental signaling pathways and behavior. Notably, (Galley et al., 2024) demonstrate that probiotic interventions using B. dentium during gestation can reverse or mitigate these effects, leading to improved social behavior and reduced inflammation in offspring, even across generations (Galley et al., 2024). This body of work supports a more integrative and systems-level approach to understanding MIA. Future studies should holistically account for the interactions among maternal microbial ecology, immune response, infection severity, psychological stress, and critical windows of neurodevelopment. COVID-19 in pregnant women acts as an example of MIA and has already been shown to cause the development of NDD-like symptoms (Duan et al., 2024). While the mechanism hasn't been figured out, the expansive scientific literature and research on influenza will likely inform future research pathways regarding Covid-MIA interactions. Future research will look at interactions between the microbiome and influenza infection in the mouse model and how both relate to the development of NDD.

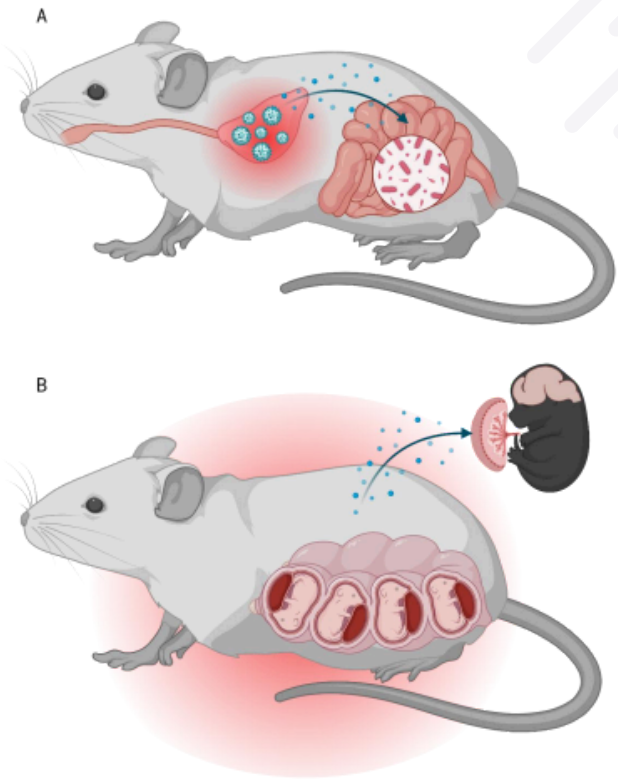

Figure 1. (A) Maternal respiratory infection can cause systemic inflammation and disrupt gut microbiota. (B) Maternal systemic inflammation can be detrimental to fetal neurodevelopment. (Source: BioRender)

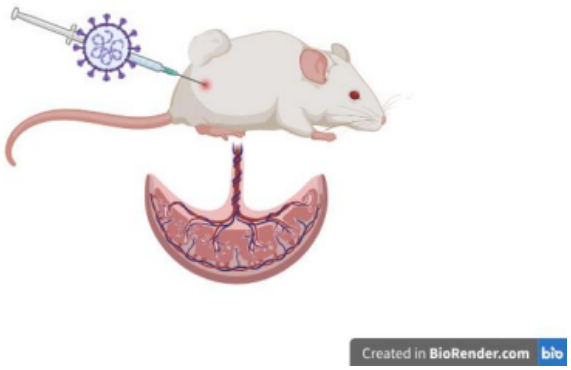

Figure 2. Infected Mouse and Placental Changes: (a) Pregnant Mice are innoculated with influenza on Gestational Day (GD) 9.5 and sacked and placentae extracted at GD 16.5. Placental integrity and morphology are then measured. (Source: BioRender)

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About the Author

Alexander Byrne, a native of the South Side of Chicago, has long fostered his fascination with science and narrative. Now a student pursuing a degree in Neuroscience, Alexander has focused his scholarly work on the overlap of maternal immune activation, neurodevelopmental disorders, and gut-brain microbiota interactions with the aim of determining how early immune signals influence the development of the brain and long-term behavioral outcomes.In addition to this study, he is deeply engaged in molecular neuroscience investigations into the structural processes of prion protein misfolding and aggregation. After finishing his undergraduate studies, Alexander plans to undertake a Ph.D. in neuroscience. His desire is to be involved in translational research that converts molecular biology into clinical knowledge.