Title

Fetal Environment and Neurodevelopment: The Role of Maternal Immune System and Microbiota in Autism Spectrum Disorder

Abbreviated Title

Maternal Immune-Microbiome Axis in Autism Spectrum Disorder

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Abstract

The prevalence of Autism Spectrum Disorder (ASD) is increasing globally, making it urgent to elucidate its underlying mechanisms. While ASD is thought to result from complex interactions between genetic and environmental factors, recent attention has focused on fetal environment, particularly maternal conditions. This review examines the roles of Maternal Immune Activation (MIA) and gut microbiota in ASD development. MIA influences fetal neurodevelopment through inflammatory cytokines, while alterations in gut microbiota affect brain function via the gut-brain axis. These factors interact, impacting various neurodevelopmental processes including synapse formation, neural circuit construction, and neurotransmitter balance. Recent studies also report effects on epigenetics and mitochondrial function. These findings suggest possibilities for early ASD diagnosis and novel therapeutic approaches. Further research in this field is expected to contribute to improving the quality of life for individuals with ASD and their families.

Keywords: Autism Spectrum Disorder, Maternal Immune Activation, Gut Microbiota, Neurodevelopment, Gut-Brain Axis

1. Introduction

The escalating prevalence of Autism Spectrum Disorder (ASD) on a global scale underscores the pressing need to unravel its intricate underlying mechanisms. ASD, a neurodevelopmental disorder characterized by impairments in social communication and restricted, repetitive behaviors and interests (1), is now understood to be influenced by a complex interplay of genetic and environmental factors (2). Notably, maternal immune activation (MIA) during fetal development and alterations in the gut microbiome have emerged as significant environmental risk factors for ASD (3,4).

2. Maternal Immune Activation and ASD Pathogenesis

MIA refers to the activation of the maternal immune system during pregnancy, which can be triggered by various factors, including viral infections, bacterial infections, or autoimmune diseases (5). Characteristic features of MIA include elevated levels of pro-inflammatory cytokines (e.g., IL-6, IL-17, TNF-α, IL-1β) in the bloodstream, increased acute phase proteins (e.g., C-reactive protein), and activation of the complement system (6,7). Epidemiological studies have demonstrated that maternal infections or inflammatory conditions during pregnancy increase the risk of ASD in offspring (8,9). In particular, MIA during early to mid-gestation has been identified as a crucial risk factor for ASD (10).

The Role of Interleukin-17 (IL-17)

Animal studies have consistently shown that offspring of MIA model animals exhibit ASD-like behavioral abnormalities, including reduced sociability, increased repetitive behaviors, and communication deficits (11). The mechanisms by which MIA affects fetal brain development include the transplacental passage of inflammatory cytokines, alterations in placental function, and impacts on the fetal immune system (12,13).

Recent studies have highlighted the role of interleukin-17 (IL-17) in mediating the effects of MIA on fetal brain development (14–16). In MIA mouse models, IL-17A produced by maternal Th17 cells has been shown to cross the placenta and affect fetal brain development. Specifically, IL-17A has been reported to induce cortical abnormalities in the fetal brain and elicit ASD-like behaviors (14). This discovery provides a clear mechanistic link between MIA and increased ASD risk.

4. Gut Microbiota and ASD

The gut microbiota is crucial in maintaining host health, significantly influencing immune system development and regulation, metabolic functions, and neurodevelopment (17). Numerous studies have reported characteristic alterations in the gut microbiota of ASD patients compared to typically developing individuals. These changes include reduced microbial diversity, increased Bacteroidetes

and decreased Firmicutes phyla, elevated levels of specific bacterial species (e.g., *Clostridium*, *Desulfovibrio*, *Sutterella*), and reduced short-chain fatty acid-producing bacteria (17–19). These alterations have been associated with ASD symptoms and severity (20).

5. Interaction between MIA and Gut Microbiota

The relationship between IL-17 and the gut microbiota has become increasingly apparent. Certain gut bacteria (e.g., segmented filamentous bacteria) have been shown to promote Th17 cell differentiation and increase IL-17 production. This increased IL-17 is thought to amplify the effects of MIA (21), highlighting the complex interplay between MIA and the gut microbiota.

The gut microbiota influences ASD symptoms through various mechanisms, with the gut-brain axis playing a crucial role. This axis, which affects brain function through neural, endocrine, and immune pathways (22), is significantly influenced by the gut microbiota. Alterations in the gut microbiota in ASD may influence brain function and behavior through this pathway. Additionally, metabolic products derived from the gut microbiota, particularly short-chain fatty acids (e.g., butyrate, propionate), have been shown to impact brain function and behavior (23). Imbalances in these metabolites have been reported in ASD patients (24).

MIA and the gut microbiota interact bidirectionally, and this interaction is thought to increase the risk of ASD. Multiple studies have reported that MIA significantly alters maternal gut microbiota. Fundamental changes include reduced microbial diversity, increases in specific bacterial species (e.g., *Bacteroides*, *Clostridium*), and decreases in short-chain fatty acid-producing bacteria (25,26). These alterations are closely associated with immune system changes and inflammatory responses during pregnancy (27).

Recent studies have demonstrated that MIA-induced changes in maternal gut microbiota can be transmitted to the fetus, influencing ASD-like behaviors after birth. IL-17 is believed to play a crucial role in this process (28). These findings reveal the complex interplay between MIA, gut microbiota, and IL-17 influencing ASD risk. The role of IL-17 in ASD patients has also garnered attention. Significantly elevated serum IL-17 levels have been reported in ASD patients compared to healthy controls (29). This result supports the hypothesis that IL-17 is involved in ASD pathophysiology and that MIA and gut microbiota alterations may influence ASD onset and symptoms through IL-17.

6. Impact on Immune System and Neurodevelopment

In MIA model mice, alterations in gut microbiota have been shown to increase the production of inflammatory cytokines, including IL-17, which is associated with ASD-like behaviors. Notably, administration of probiotics has been reported to partially ameliorate these changes (13). This finding

suggests that interventions targeting the gut microbiota may regulate IL-17 production, offering a promising avenue for developing new treatments for ASD symptoms.

The interaction between MIA and gut microbiota has been shown to influence fetal development and increase ASD risk through the following mechanisms:

1. Neurodevelopmental effects: These include abnormalities in synapse formation, neural circuit formation, and neurotransmitter imbalances. Inflammatory cytokines induced by MIA and metabolites derived from altered gut microbiota have been shown to affect synapse formation and pruning (30). MIA and gut microbiota alterations have also been demonstrated to influence the formation of specific neural circuits (e.g., those involved in social behavior) (31). Furthermore, gut microbiota is involved in the production of neurotransmitters such as serotonin and GABA. MIA-induced changes in gut microbiota have been shown to disrupt the balance of these neurotransmitters (32).

2. Immune system development and function: The inflammatory environment induced by MIA has been shown to impair the acquisition of immune tolerance and increase the risk of autoimmune reactions (13,33). MIA and gut microbiota alterations are thought to activate microglia in the brain, leading to a chronic neuroinflammatory state (34). Moreover, MIA and gut microbiota changes have been shown to influence postnatal immune cell cytokine production patterns, inducing a chronic inflammatory state (35).

7. Potential Therapeutic Approaches

Dysfunction of the gut-brain axis is implicated in the manifestation of ASD symptoms. Changes in gut microbiota have been shown to affect vagus nerve function, leading to alterations in brain function and behavior (36). Additionally, MIA and gut microbiota alterations have been reported to decrease intestinal barrier function and increase intestinal permeability, allowing intestinal substances (bacterial products and metabolites) to enter the bloodstream and affect brain function (37).

Recent research has demonstrated that MIA and gut microbiota alterations may contribute to ASD onset through epigenetic modifications. Lammert et al. (2023) reported changes in DNA methylation patterns in the brains of MIA model mouse offspring, particularly in gene regions involved in synapse formation and neurotransmission(28,38). MIA and gut microbiota alterations have also been shown to affect histone-modifying enzyme activity, altering gene expression patterns (39). Furthermore, the inflammatory environment induced by MIA has been found to alter the expression of specific non-coding RNAs (microRNAs and long non-coding RNAs), influencing the regulation of

neurodevelopment-related genes (40).

The impact on mitochondrial function has also garnered attention. A recent study demonstrated that MIA and gut microbiota alterations affect mitochondrial function in offspring brains (41). Decreased ATP production efficiency was observed in brain mitochondria of MIA model animal offspring. Additionally, mitochondrial dysfunction was associated with increased production of reactive oxygen species (ROS) and enhanced oxidative stress. MIA and gut microbiota alterations may also increase the mutation rate of mitochondrial DNA. These mitochondrial function changes are thought to influence neuronal energy metabolism, cell death, synaptic function, and other aspects of ASD pathophysiology.

8. Future Research Directions

As our understanding of the roles of MIA and gut microbiota deepens, new therapeutic approaches are being proposed. Administration of specific probiotic strains improved ASD-like behaviors in MIA model animals (42). This approach is expected to become a novel treatment that alleviates ASD symptoms through modulation of the gut microbiota. Specific dietary components (e.g., dietary fiber, omega-3 fatty acids) have also been shown to influence gut microbiota composition and metabolite production, leading to improvements in ASD symptoms (43). Furthermore, immunomodulatory therapies (e.g., use of anti-inflammatory drugs) to mitigate the effects of MIA are being considered as means of ASD prevention and early intervention (44). Microbiome transplantation is also attracting attention as a new treatment modality, although further research is needed to establish its safety and efficacy (45).

9. Conclusion

These findings reveal complex interactions between IL-17, gut microbiota, MIA, and ASD. IL-17 mediates the effects of MIA, and its production is regulated by changes in the gut microbiota. The combined action of these factors influences ASD risk and symptom severity. However, many of these studies are based on animal experiments, and direct evidence in humans still needs to be improved. Many aspects still require further research, such as the relative contributions of individual factors and interactions with other environmental factors.

Future research should focus on elucidating the detailed interactions between IL-17-centered immune responses, MIA, and gut microbiota. This may lead to the development of new approaches for ASD prevention and treatment. For example, management of maternal gut microbiota during pregnancy or immunomodulatory therapies targeting IL-17 could be considered, but their safety and efficacy require careful evaluation.

While research on the involvement of MIA and gut microbiota in ASD development is rapidly progressing, many challenges remain. Much of the current evidence is based on animal experiments, and caution is needed when directly applying these results to humans. Long-term epidemiological and interventional studies in humans are necessary. Additionally, the effects of MIA and gut microbiota are likely to vary greatly depending on genetic background and environmental factors, necessitating the development of precision medicine approaches that consider individual differences. Furthermore, the impacts of MIA and gut microbiota may differ across developmental stages (fetal period, infancy), and elucidating these stage-specific effects is crucial. Identifying the optimal timing for ASD prevention and early intervention is also a challenge. It is necessary to determine which period (during pregnancy, immediately after birth, during infancy) is most effective for intervention. Moreover, a more comprehensive understanding of ASD development mechanisms is required, including interactions with environmental factors other than MIA and gut microbiota (e.g., environmental pollutants, stress).

MIA and gut microbiota have been shown to increase ASD risk through complex and multi-layered mechanisms. These factors influence various physiological processes, including neurodevelopment, immune system function, and regulation of the gut-brain axis. Recent research has begun to elucidate mechanisms from new perspectives, such as epigenetics and mitochondrial function. These insights are expected not only to deepen our understanding of ASD pathophysiology but also to lead to the development of new prevention and treatment strategies.

Future research should focus on expanding human studies, developing approaches that consider individual differences, and elucidating complex factors. Approaches focusing on MIA and gut microbiota are expected to provide an essential foundation for ASD prevention, early intervention, and the realization of personalized medicine. Ultimately, these research outcomes are anticipated to improve the quality of life for individuals with ASD and their families and promote the well-being of society as a whole.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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