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Maternal inflammation and its ramifications on fetal neurodevelopment

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Abstract

Exposure to heightened inflammation in pregnancy caused by infections or other inflammatory insults has been associated with the onset of neurodevelopmental and psychiatric disorders in children. Rodent models have provided unique insights into how this maternal immune activation (MIA) disrupts brain development. Here, we discuss the key immune factors involved, highlight recent advances in determining the molecular and cellular pathways of MIA, and review how the maternal immune system affects fetal development. We also examine the roles of microbiomes in shaping maternal immune function and the development of autism-like phenotypes. A comprehensive understanding of the gut bacteria-immune-neuro interaction in MIA is essential for developing diagnostic and therapeutic measures for high-risk pregnant women and identifying targets for treating inflammation-induced neurodevelopmental disorders.

Maternal immune activation

A developing fetus absorbs nutrients and other key resources from maternal circulation while avoiding potentially harmful effectors, including those produced from the maternal immune system that might view the fetus as foreign [1]. Mechanisms ensuring mammalian

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Declaration of interests

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immunological tolerance (e.g., regulatory T cells [Tregs]; See Glossary) contribute to protecting fetuses from pregnancy-associated complications, such as preterm labor, preeclampsia, fetal growth restriction, and miscarriages [2]. Exposure to heightened inflammation during pregnancy, such as respiratory infection and autoimmunity, can lead to various neurological manifestations, including alterations in brain connectivity, variations in cognitive development, and abnormal neural activity [3,4]. Moreover, epidemiological and preclinical studies indicate a strong association between maternal immune activation (MIA) and several psychiatric and neurological disorders, including schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD), cerebral palsy, developmental delay, cognitive dysfunction, anxiety/depression, and autism spectrum disorders (ASD) [5]. Therefore, determining the underlying mechanisms of MIA is essential for developing preventive and therapeutic measures for various immune-dependent psychiatric disorders. This review summarizes recent findings of how MIA affects brain development and can promote neurodevelopmental illness in the offspring (Figure 1). Postnatal exposure to inflammation also induces long-term consequences in animal health and has been recently reviewed [6]. Here, we focus on the ramifications of prenatal exposure to MIA.

Maternal infections and neuropsychiatric disorders

In addition to genetic components, environmental factors likely contribute to the onset of neuropsychiatric and neurodevelopmental disorders, such as bipolar disorder, schizophrenia, and ASD. Epidemiological data indicate a strong association between increased infection rates and neurodevelopmental disorders. For example, the 1918–1919 influenza virus pandemic was suggested to increase the risk of schizophrenia [7]. After the 1964 rubella epidemic, the incidence of neurodevelopmental disorders (including ASD and schizophrenia) in children with congenital rubella increased significantly [8]. Consistently, ecological and maternal studies have shown strong associations between prenatal influenza virus infection during the second trimester and a 2- to 8-fold increased risk of schizophrenia [9,10]. Of note, a recent study highlighted seasonal effects in the risk of autism in more than 8,000,000 children born from 1990 to 2002, noting a slight but significant higher risk of ASD in children conceived in December to March, compared to those conceived in July, possibly owing to higher rates of respiratory infections during the colder months [11], although this remains to be fully explored.

The association between infection in pregnancy and an increased risk for neurodevelopmental disorders is not restricted to a specific type of virus [12]. Studies have indicated that both viral- (food-borne viruses, cytomegalovirus, measles, mumps, chickenpox, and polio) and bacterial-induced (*Escherichia coli*, pneumonia, and *Toxoplasma gondii*) infections at prenatal stages can trigger psychiatric disorders in mouse offspring [13,14]. A large-scale human study performed on 1,612,342 children born in Denmark from 1980 to 2005 [15] also supports the same notion—infection or inflammation requiring hospitalization of pregnant women was associated with the risk of developing psychiatric disorders in their children. Therefore, pathogen-induced MIA and not specific pathogens, has been deemed a pivotal factor in driving persistent changes in brain development and behaviors in offspring. In line with this idea, various inflammatory conditions during pregnancy are shown to enhance the risk of neurodevelopmental disorders. For instance,

maternal autoimmune disorders, allergies, and asthma have been reported as risk factors for developing ASD and schizophrenia in humans [16,17]. Additionally, other factors, such as acute stress [18], exposure to environmental pollutants [19], and nutrient conditions [20] that directly or indirectly elevate immune responses, have also been linked to an increased risk of ASD [2,5]. Mechanistically, a series of recent human studies have shown that pregnant mothers exposed to MIA can have dysregulated cytokine production, such as for interleukins 6 (IL-6) and 17a (IL-17a), which are associated with cognitive impairment and the risk of developing ASD in their children [3,21–23]. Although further studies are needed to clarify which key inflammatory markers or pathways are triggered by different pathogenic infections and which genetic or environmental factors elicit or contribute to the development of certain brain disorders, the available evidence suggests that MIA can act as a prenatal "primer" that can instigate a range of neurodevelopmental and neuropsychiatric disorders in offspring.

Presently, rapid globalization, exploding population growth, emerging novel infectious agents, and a resurgence of classical contagious diseases (including measles, mumps, and polio) may be laying the groundwork for increased rates of opportunistic infections in pregnant women. Combined with the rising rates of inflammatory conditions, which may include autoimmune disorders, allergies, and asthma, these factors might account for or contribute to recent increases in neurodevelopmental disorders in the global pediatric population [24]. The current coronavirus disease 2019 (COVID-19) pandemic has already affected more than 2.5 billion individuals (at the time this article was written), including pregnant women. These alarming cases make it imperative to understand how MIA affects inflammatory responses in pregnant women and can contribute to promoting neurodevelopmental disorders in affected children. Indeed, data already indicate that SARS-CoV-2 infection, like some other respiratory infections, can elicit pregnancy complications, including fetal growth restriction, fetal distress, and preterm birth [25]. We describe various ways of inducing MIA, maternal immune pathways eliciting neurodevelopmental pathologies, and the role of gut bacteria in contributing to MIA-induced pathologies. We also highlight key unanswered questions and future directions.

MIA animal models

Animal models have facilitated studies of complex human brain diseases. Earlier rodent models of MIA were established with an initial focus on schizophrenia [26,27]. A seminal paper reported that infecting mice with influenza virus or treating the animals with the long double-stranded RNA (dsRNA), polyinosinic:polycytidylic acid (poly[I:C]) as a viral mimetic, triggered ASD- and schizophrenia-like behavioral abnormalities in the offspring, as evidenced by cognitive tests, such as the three-chamber and marble-burying assays [28,29]. These and other studies extensively characterized behavioral abnormalities in MIA-affected offspring, particularly those reminiscent of human ASD and schizophrenia patients, including alteration and deficits in pre-pulse inhibition, cognition, sociability, repetitive behavior, and increased sensitivity to antipsychotic drugs compared with controls [13]. Importantly, these MIA-induced behavioral abnormalities have been similarly reproduced in nonhuman primate (NHP) models [30,31]. Subsequently, MIA animal models have been extensively used, allowing researchers to employ various environmental insults to trigger

MIA during pregnancy. Those triggers include infectious agents (pathogens, pathogen mimicry), autoimmunity, dietary factors (high-fat, high-salt diet), environmental risk factors (exposure to diesel, fine particles), and even psychiatric stress (social and restraint stressors) [20,32].

Non-infectious stimuli inducing MIA

Metabolic factors

Maternal diabetes conditions, including gestational diabetes mellitus, display a strong co-morbidity with neurodevelopmental deficits, including language delay, poor motor development, impaired recognition memory, and ASD in humans [33]. Indeed, increased incidence of ASD and other developmental delays have significantly correlated with maternal diabetes and hypertension among more than 1000 pregnant women [34]. Consistently, rodent offspring from dams exposed to a high-fat diet (HFD) during gestation display significant deficits in cognitive function, heightened anxiety, and abnormal social behaviors [35]. NHP studies have also resulted in similar outcomes [36,37]. Moreover, maternal obesity in pregnancy has also been attributed to enhanced autism-like phenotypes in offspring. In rodents, a HFD has triggered both systemic and local immune activation in pregnant mice. Specifically, a HFD during gestation increased the production of inflammatory cytokines, including IL-1β, IL-6, and TNF-α, in the plasma, liver, and brain in both the mother and the fetus [38,39]. A HFD also induced changes in immune responses in the placenta, such as the dysregulated NK cell activity [40], and altered gene expression in the mouse fetal brain [41]. Additionally, offspring born to HFD-fed mothers displayed heightened anxiety [35], impaired sociability [42,43], and cognitive decline [43]. In humans, excessive weight gain in pregnancy has been associated with increased concentrations of inflammatory and metabolic factors in maternal serum (e.g., monocyte chemoattractant protein-1, high-sensitivity C-reactive protein, and leptin) [44]. Furthermore, maternal obesity may also affect an offspring's neurodevelopment; recent epidemiological studies suggest that obesity (defined by body mass index) during pregnancy influences an offspring's brain development, the dysregulation of which may affect cognitive and motor performance [45,46] and contribute to an increased risk of developing psychiatric disorders, including ASD [47,48], ADHD [49], schizophrenia [50], and anxiety/depression [51].

Altogether, these findings suggest that dysregulated metabolism during pregnancy likely results in heightened inflammation that can negatively impact the proper brain development of fetuses, potentially leading to an enhanced susceptibility to developing certain neurodevelopmental disorders.

Environmental risk factors

Exposure to various environmental factors during pregnancy has been proposed to affect fetal brain development and induce psychiatric disorders in offspring. Risk factors include (but are not limited to) pesticides, air pollutants (fine particles, diesel, NO_2, and heavy metals), and phthalates [32,52]. A recent study with more than 1,700 children born from 1990 to 2002 in the U.S. revealed a strong association specifically in the third trimester between maternal exposure to fine particles, or particulate matter 2.5 (PM2.5), and increased

ASD prevalence [19]. Moreover, prenatal exposure to PM2.5 during pregnancy has led to behavioral abnormalities in rat offspring [53]. Additionally, exposure to traffic-related air pollutants, such as diesel fumes, during prenatal and early life strongly correlates with the incidence of ASD in humans [54,55] and mice [32,56]. Of note, particulates from air pollution also trigger particle-induced inflammation in humans (e.g., increased cytokine and chemokine responses) [57]. However, it is still unclear, by and large, how environmental risk factors cause excessive inflammation, perturb fetal neurodevelopment, or contribute to neurodevelopmental disorders in children. Therefore, further rigorous investigations are needed to conclusively assess a causal relationship between various environmental risk factors, MIA, and its long-term pediatric consequences.

Stress

In humans, studies have shown a strong association between excessive maternal stress, such as traumatic experiences, anxiety, and depression, with prenatal inflammation, impaired brain development, and psychiatric disorders in offspring [58,59]. These epidemiological findings have been reproduced in the rodent prenatal stress model, enabling researchers to study how maternal stresses might prompt prenatal inflammation and influence fetal development. For instance, exposing pregnant mice to repetitive restraint stress (RSS) during gestation has promoted autism-like behaviors, including anxiety-like behavior, decreased sociability, and locomotor inhibition in offspring [60]. Along with behavioral abnormalities, prenatal RSS has affected immune responses, leading to increased IL-6 and ILβ in maternal serum and altered kynurenine metabolite concentrations in the placenta relative to control mice [61,62]. Blocking the IL-6 pathway with an anti-IL-6 antibody has ameliorated maternal stress-induced microglial dysfunction in offspring, as evidenced by increased sociability and reduced anxiety-like behaviors [63]. Similarly, other prenatal or early life stresses, such as bright light exposure, tail shocks, and noise exposure, increase feto-maternal inflammation as well as neurodevelopmental phenotypes, including irregular brain development and reduced sociability, in laboratory rodents [64]. While fetal microglia are a key mediator producing stress-induced neuroinflammation in fetal brains [65], the identities and functions of the responsible immune cells in pregnant mothers underlying maternal stress-induced neurodevelopmental changes remain to be investigated. These data collectively suggest that the immune system may play a key function in priming maternal stress-induced neurodevelopmental disorders in offspring.

MIA-inducing stimulants

Respiratory viral infections

Influenza viral infection in animal models has been associated with psychiatric and neurodevelopmental diseases in offspring. Rodent and NHP offspring born to influenza virus-infected mothers display core behavioral abnormalities of ASD and schizophrenia, including decreased sensitivity to auditory stimulation, increased anxiety, social deficits, and repetitive behaviors [28,66,67]. Influenza (H1N1) viral infection has led to vascular inflammation, the production of excessive inflammatory mediators such as IL-1β, TNF-α, and IFN-γ, and the infiltration of immune cells, including $Ly6C^{low}$ and $Ly6C^{high}$ monocytes, neutrophils, and T cells, into the vascular tissues of pregnant dams [68].

Studying respiratory viral infection-induced MIA models can enable researchers to further elucidate the molecular and cellular mechanisms of MIA pathogenesis. Of note, it will be essential to test if SARS-CoV-2 infection leads to behavioral abnormalities in pregnant dams expressing SARS-CoV-2 specific receptors, such as human angiotensin-converting enzyme 2 (ACE2)[69].

Non-infectious agents inducing MIA

Unlike pathogenic insults, mimetic agents do not fully recapitulate all the immunological consequences of MIA, such as antigen-specific T and B cell responses and antibody production. However, treating pregnant mice with bacterial and viral mimetics produces a set of core behavioral and neurological abnormalities reminiscent of those observed in human ASD and schizophrenia patients [13,70,71]. Furthermore, non-infectious mimetics have enabled researchers to induce MIA with uniform intensity and in a controlled fashion. Over the years, both viral and bacterial mimetics, including poly(I:C) and LPS (lipopolysaccharides), have been widely used to investigate MIA (Box 1).

Other TLR ligands

Injecting pregnant mice with different Toll-like receptor (TLR) ligands, such as synthetic oligodeoxynucleotides containing CpG motifs, has led to fetal demise [72]. However, more extensive analyses are required as different amounts of the CpG motifs might induce MIA and alter immune responses in pregnant mice and developmental phenotypes in offspring. Similarly, it will be informative to assess if fungal or parasitic infections and other inflammatory stimuli induce MIA responses and autism-like phenotypes, and assess whether their actions might converge on IL-6 and IL-17a pathways.

Two-hit MIA models

In the two-hit MIA model, TLR agents (e.g., poly(I:C) and LPS) are used sequentially to induce MIA and postnatal immune activation in mice, leading to the manifestation of core autism-like, behavioral phenotypes in a sex-biased manner [73]. Whether the same immune and neurological pathways that function in the poly(I:C)-MIA model (Box 1) play a role in the two-hit model, however, remains to be investigated. Regardless, given that human fetuses are exposed to distinct pathogens before and after birth, rodent studies employing the two-hit model can provide unique mechanistic insights into the pathogenesis of multi-immune stimuli-induced neurodevelopmental disorders.

Mechanisms underlying MIA-induced neurodevelopmental disorders

Most of the work on MIA has been done using poly(I:C) in rodent models; thus, this section primarily focuses on findings acquired with this model.

Poly(I:C)-driven MIA model

The maternal immune system recognizes and responds to dynamic environmental stimuli to protect the mother and fetus during pregnancy. However, we lack a comprehensive understanding of the cellular, molecular, and immunological mechanisms of how pregnancy shapes the maternal immune system and how, in turn, the immune system affects pregnancy.

This gap in knowledge poses a significant challenge to maternal-fetal health. For example, pregnant women are more susceptible to respiratory viral infections and other inflammatory insults compared to age-matched non-pregnant women, warranting revived and refocused efforts to understand the long-term effects of inflammation in pregnancy.

The poly(I:C)-driven MIA rodent model has provided a wealth of information on immune responses in pregnancy following immunological challenges. It is well established that poly(I:C) injection increases inflammatory cytokine concentrations in maternal serum, as well as in amniotic fluid. These observations raise the question of whether maternal cytokines can mediate the effects of MIA on fetal development and cause ensuing behavioral changes in offspring. Administration of IL-6 at embryonic day 12.5 (E12.5) has produced the characteristic behavioral changes of MIA-affected offspring reminiscent of schizophrenia and autism [74]. However, MIA-associated behavioral abnormalities require IL-6 to be present in pregnant mothers given that poly(I:C) injection to IL-6-deficient mice no longer produces MIA-induced behavioral abnormalities in offspring [29].

IL-6

Initially identified as a pleiotropic cytokine that promotes the activation and effector function of various immune cell populations, IL-6 has subsequently been found to play a central role in protecting the host against various infections [75]. In humans, a deficiency in IL-6 function, caused by autoantibodies against IL-6 or autosomal mutations in the Stat3 pathway (the primary IL-6 downstream signaling module), impairs innate and adaptive immunity against viral, parasitic, and bacterial infections, and causes premature death from pneumonia [75]. Such phenotypes have been successfully recapitulated in rodent systems. However, uncontrolled IL-6 activity can also promote chronic inflammation in various inflammatory disorders, such as hyper IgE syndrome, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, colitis, and even cancer.

As stated earlier, IL-6 is a key cytokine in promoting MIA-induced autism-like abnormalities in mice [29]. IL-6 amounts have been reported to be increased in both MIA-affected rodent fetal brains [76] and human brain tissues derived from autistic patients [77]. Furthermore, a functional magnetic resonance imaging study identified elevated IL-6 during pregnancy in maternal sera, suggesting that this cytokine might affect brain connectivity and working memory in human newborns [3]. How does maternal IL-6 bridge maternal inflammation and fetal brain development? IL-6 has been proposed to cross the placenta barrier, leading to the loss of Purkinje cells in fetal hindbrain regions; indeed, the removal of IL-6 receptors in placental trophoblasts has prevented this phenotype [78]. Moreover, Purkinje cell dysfunction has been associated with some cases of autism in humans [79]. A recent finding following *Yersinia pseudotuberculosis* bacterial infection in mice during pregnancy also showed that maternal IL-6 crosses the placental barrier and acts on its receptor expressed in the fetal gut epithelial cells of offspring, influencing their long-term immunological responses against pathogenic infection occurring in adulthood [80]. Furthermore, IL-6 injection to fetal brains has led to synaptogenesis in glutamatergic neurons [81]. These data suggest that on the one hand, IL-6 might promote MIA phenotypes by directly acting on its receptor in fetal tissues (Figure 2). On the other hand, IL-6

might also indirectly enhance MIA phenotypes. For example, IL-6 functions as an upstream cytokine that stimulates the differentiation of naïve $CD4^+$ T cells into Th17 cells [82], which play a crucial role in MIA (see below section)[83]. Supporting this idea, blocking maternal IL-6 function with an anti-IL-6 antibody injection in pregnant mice has impaired poly(I:C)-induced upregulation of IL-17a protein in maternal circulation; however, intra-ventricle injection of IL-17a, but not IL-6, into fetal brains at E12.5 has recapitulated MIA effects in offspring [83]. These results suggest that there are direct as well as indirect roles of maternal IL-6, as an inflammatory cytokine, in inducing MIA.

IL-17a

IL-17a received much attention after its discovery as the signature cytokine of a specific subset of T helper cells, later dubbed Th17 cells [84]. IL-17a maintains barrier function, aids in the tissue repair process, and induces innate immune-like defenses by promoting the production of antimicrobial peptides, such as β-defensin, and enhancing the recruitment of neutrophils into infected or injured sites [85]. IL-17a has also been associated with inflammation that drives various autoimmune diseases, such as rheumatoid arthritis (RA), psoriasis, and multiple sclerosis (MS) [85].

Recent mouse studies have also uncovered non-immunological functions of IL-17a, especially in the brain. For example, IL-17a produced from gamma delta T (γδT) cells in the meninges was reported to control synaptic plasticity and short-term memory by increasing the glutamatergic synaptic plasticity of hippocampal neurons [86]. Enhanced production of IL-17a by a high-salt diet has elicited brain endothelial damage and cognitive dysfunction, as measured by behavioral changes [87]. IL-17a-producing cells have also been implicated in promoting anxiety- and depression-like behaviors in mice [88,89]. Along with the extensively studied function of IL-17a in promoting neuroinflammation in the brain [90], these data suggest that IL-17a can directly or indirectly affect brain cells and induce neurological phenotypes.

Both IL-17a and Th17 cells might also play a role in ASD. Certain autistic patients display elevated IL-17a serum concentrations [91,92]. In rodent models, we and others previously showed that poly(I:C)-induced MIA in mice increased IL-17a production in maternal circulation [83,93–96]. Consistent with these findings, increased IL-17a concentrations or enhanced expression of RAR-related orphan receptor gamma t (RORγt)—the key transcription factor driving Th17 cell programming [97]—in pregnant mice, promoted autism-like behavioral abnormalities (e.g., increased repetitive behaviors and reduced sociability) in offspring [98–100] (Figure 2). Conversely, reducing IL-17a production or blocking its activity with anti-IL17a antibody prevented the development of autism-like behavioral abnormalities in MIA offspring [83,101]. Genetic removal of RORγt selectively in maternal $CD4^+$ T cells (CD4-Cre/*rorc*$^{fl/fl}$) or intraperitoneal administration of IL-17a blocking antibody in pregnant dams prevented MIA-induced cortical malformation and autism-like behaviors in offspring [83]. Direct introduction of IL-17a into the fetal brain at E14.5 induced MIA-associated phenotypes and microglial activation [83,99]. Conversely, neuron-specific removal of IL-17 receptor subunit A (IL-17RA; Nestin-Cre/*il17ra*$^{fl/fl}$) in developing embryos prevented poly(I:C)-induced MIA effects, including dysregulated neural

activity and behavioral abnormalities [4], indicating that maternally derived IL-17a exerted its function by acting on its receptor expressed in fetal brains. Maternal IL-17a also augmented the integrated stress response (ISR) in mouse fetal brains; ISR was required for the manifestation of MIA-associated behavioral and neurological phenotypes, as MIA offspring carrying $eIF2\alpha^{S51A/+}$ mutations no longer displayed such phenotypes [102,103]. As mentioned earlier, IL-17a is essential for promoting autism-like symptoms in offspring exposed to LPS-induced MIA [100]. Altogether, these data suggest that IL-17a may represent a relevant diagnostic and therapeutic candidate target to test the prevention of specific neurodevelopmental disorders in offspring exposed to prenatal inflammation. However, whether these findings translate to humans, requires robust research.

Other cytokines

Besides IL-6 and IL-17a, poly(I:C)-MIA triggers the production of other cytokines, including IL-1β, IFN-γ, TNF-α, and type I interferons (IFN) in both maternal and fetal mouse tissues [83,104]. A recent study examining induced MIA in *Ifna* receptor-deficient mice highlighted a contributing role of IFN signaling in promoting MIA-associated phenotypes [104]. However, more studies are needed to assess epistatic relationships between type I IFNs and other key inflammatory cytokines, such as IL-6 and IL-17a, in MIA. Furthermore, it will be informative to systematically test the modulatory role of each cytokine in MIA by administering individual cytokines to pregnant mice and/or fetal brains.

The gut microbiome and MIA

Mounting evidence supports pivotal roles for the gut microbiome in the developmental and cellular processes in health and disease. Earlier studies primarily focused on possible links between the gut microbiome and various diseases, including type 1 diabetes, asthma, inflammatory bowel disease, and cancer [105]. Recent research suggests that the gut microbiome affects the central nervous system (CNS) and CNS-related disorders, often dubbed as the “gut-brain axis” [106]. Observations made with germ-free mice indicated that commensal bacteria deficiency led to neuro/behavioral abnormalities, including deficits in memory formation [107], increased motor activity [108], reduced anxiety-like behaviors [109], increased stress-induced hypothalamic-pituitary-adrenal responses [110], reduced social behaviors [111], impaired blood-brain barrier function [112], and changes in the expression of various neurotrophic factors (e.g., brain-derived neurotrophic factor and N-methyl-D-aspartate receptor) relative to control mice[108,110]. Moreover, emerging evidence from animal models and clinical samples suggests causative roles for the microbiome in modulating many different neurological conditions, such as depression, anxiety, ASD, schizophrenia, and neurodegenerative disorders [93,113–115] (see below).

Maternal gut bacteria and MIA

The maternal gut microbiome likely functions as one of the key players promoting MIA-associated phenotypes (Figure 3). In pregnant dams, vancomycin antibiotic treatment prevented offspring from developing MIA-induced neural deficits and autism-like behaviors [93]. In 2009, one research group serendipitously observed significant differences in Th17 cell numbers in the intestines of mice obtained from two commercial vendors: mice from

the Jackson Laboratory had low Th17 cell numbers while mice from Taconic Biosciences had high Th17 cell numbers [116]. This observation led to the identification of the Th17 cell-promoting role of a single commensal bacterial species, segmented filamentous bacteria (SFB) [116,117]. By inducing MIA in Jackson and Taconic-derived dams and using other means, we and others showed that SFB or other Th17 cell-inducing bacteria in the maternal gut promoted MIA-induced pathogenesis in offspring [93,101]. Consistent with these results, infecting pregnant mice with the food-borne pathogen *Yersinia pseudotuberculosis* did not induce behavioral changes in offspring if their mothers lacked SFB, while the same inflammation led to long-lasting protective immunity against bacterial pathogens such as *Salmonella* Typhimurium serovar in affected offspring [80]. These results indicated that maternal gut bacteria were a crucial environmental trigger in an offspring's increased susceptibility to inflammation-associated neurodevelopmental disorders.

A recent report summarized various efforts to improve the rigor and reproducibility of MIA models among research groups and institutions [118]. The authors rightly emphasize the importance of using the appropriate immunogen by considering the vendor-to-vendor and lot-to-lot variation of poly(I:C) agents. However, less consideration has been given to harmonizing the efforts to assess the gut bacterial community in mice exposed to MIA, although gut microbiota in pregnant mice can have a significant impact on an offspring's phenotypes [93,94,101]. Furthermore, given that gut bacteria not only enhance Th17 cell responses but also likely mitigate their activity by augmenting anti-inflammatory Treg pathways [119,120], in an ideal scenario, it might be beneficial to consider the relative ratio of Th17 cell-promoting and -suppressing bacteria before inducing MIA (Box 2). Unfortunately, however, we lack a comprehensive list of gut bacteria that modulate Th17 cell responses. Even Taconic-derived mice, depending on their respective barrier facility, do not always carry SFB in their guts [121]. Therefore, at a minimum, we advocate qPCR testing of SFB amounts in stools from MIA-exposed mice [122] to minimize experiment-to-experiment variation. If SFB is absent in the vivarium, colonizing mice with SFB might likely produce more robust MIA phenotypes than those under different housing conditions—a key parameter for consideration.

The gut microbiome in other autism mouse models and in humans

Accumulating data suggest the importance of the host gut microbiome in affecting autism-related phenotypes. Several recent studies have found an altered microbiome in ASD patients, compared with healthy controls, suggesting a putative link between the gut microbiome and autism [123]. Moreover, transplanting gut microbiota from ASD patients into germ-free mice has been shown to promote autism-like behavioral changes in animal recipients [115]. However, a recent large-scale metagenomic study assessing the gut microbiota community in human ASD patients suggests that microbiome differences in ASD may be linked to dietary preference, cautioning against oversimplifying the importance of the gut microbiome in modulating either immunological or neurodevelopmental outcomes [124].

In mice, MIA offspring and several monogenic mouse models for autism such as BTBR or *Shank3* mutant mice display gut microbiome dysbiosis [125,126]. Oral gavage with anti-

inflammatory bacteria, such as *Bacteroides fragilis* or *Lactobacillus reuteri*, has mitigated autism-like behavioral abnormalities, such as social deficits [115,125,127]. Furthermore, oral administration of specific microbial metabolites, including 5AV and taurine, has reduced autism-related repetitive and social behaviors in ASD mouse models [115], while other metabolites, such as 4-ethylphenylsulfate, have exacerbated autism-related anxiety [128]; this has suggested a versatile role of microbial metabolites in affecting brain function and animal behaviors. While a mechanistic understanding is still missing, these studies indicate that non-genetic factors (e.g., microbiome) may interact with genetic factors in modulating ASD pathogenesis.

Concluding remarks

Growing evidence indicates that MIA affects the health of offspring in immunological, metabolic, and neurological disorders [2,129]. In this review, while we primarily focused on autism, many preclinical and human studies have linked MIA with other neurodevelopmental disorders, including anxiety, major depressive disorders, and bipolar disorders [130,131], which often harbor both genetic and environmental contributions to the inherent pathology. Hence, MIA may be considered a surrogate model for studying certain human psychiatric diseases under conditions in which inflammation and immunology are relevant. Accordingly, it would be interesting to investigate whether MIA offspring become susceptible to developing other inflammatory and metabolic disorders, such as diabetes, allergy, multiple sclerosis, and inflammatory bowel disease, since MIA may substantially impact the physiology of the developing fetus. Indeed, we recently demonstrated that pregnant mothers exposed to MIA-induced IL-17a presented altered gut microbiota, and their offspring exhibited primed immunological phenotypes, as evidenced by an enhanced susceptibility to gut inflammation caused by *Citrobacter* infection in mice [132]. In this study, we reported that this immune priming was due to alterations in the chromatin accessibility of genes linked to the regulation of $CD4^+$ T cell activity. As a result, in experiments such as these, MIA offspring developed heightened susceptibility to autoimmune inflammation in adulthood. By contrast, bacterially-induced MIA in the absence of SFB rendered offspring more resistant to pathogenic *Salmonella* infection through an IL-6-dependent mechanism by promoting epigenetic memory in intestinal epithelial cells. [80]. Collectively, these data demonstrate the complexities arising from different types of MIA that can modulate maternal gut bacteria (composition and frequencies), and which can lead to different immunological outcomes in the offspring.

From another angle, genetic factors are key drivers for ASD, supported by many twin concordance studies [133]. Hence, ASD research has centered on identifying genetic factors that drive ASD phenotypes with high penetrance. However, major genetic factors that govern ASD pathogenesis remain elusive, despite numerous efforts. The notion that non-CNS-derived factors, such as the gut microbiome, peripheral immune system, and their interactions (known as the gut-immune-brain axis [134]) play a role in ASD pathogenesis is gaining traction. Thus, understanding how these factors combine with or modulate genetic susceptibility and affect brain development represents an imminent research area that might potentially transform how ASD pathologies are diagnosed and prevented (see outstanding questions).

We posit that MIA rodent models can facilitate the development of potential preventive and therapeutic approaches to treating human ASD and other specific psychiatric disorders. Studies have identified maternal factors as potential targets for MIA-induced neural deficits and abnormal behaviors. For example, blocking maternal cytokines (e.g., IL-6 and IL-17a) during pregnancy suppresses MIA-induced autism-like phenotypes in rodent offspring [74,83]. In addition, performing bacteria-driven intervention to affect the maternal microbiome using a particular bacterial species or a defined consortium of the latter might be developed and tested as a putative therapeutic approach to ASD-like maladies. Altogether, we argue that MIA mouse models, in addition to other monogenic mouse models for autism, can provide invaluable avenues and complementary approaches for identifying ways to prevent and treat autism and/or other immune-mediated psychiatric illnesses – certainly representing a fruitful area of future investigation.

Whether or not the findings generated with MIA mouse models can be translated to human patients with neurodevelopmental disorders evidently awaits future validation. Large-scale, longitudinal studies following children born to pregnant mothers infected with pathogens or exposed to severe inflammation are thus warranted. Lastly, a special focus needs to be placed on acquiring samples for immunological and microbiome analyses during the course of pregnancy with or without exposure to inflammation.

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Glossary

Regulatory T cells
specialized subset of T cells that maintain homeostasis and self-tolerance.

Maternal immune activation
Immune stimulation during pregnancy, due to pathogenic infection or exposure to other inflammatory stimuli.

Pre-pulse inhibition
neurological phenomenon in which a weaker pre-stimulus inhibits the organism’s reaction to a subsequent, strong, reflex-eliciting stimulus.

Gestational diabetes mellitus
common metabolic disorder during pregnancy that causes considerable morbidity and pregnancy complications.

Phthalates
group of chemicals used to make plastics more durable, which induce various pathological effects, including neurotoxicity and anti-androgenic effects.

Toll-like receptor
class of receptor proteins; play crucial roles in recognizing pathogen-associated molecular patterns derived from various microbes to initiate an innate immune response.

Integrated stress response
conserved cellular stress response in eukaryotic cells; downregulates protein synthesis and upregulates specific gene expression in response to internal or environmental stressors.

The primary somatosensory cortex, the dysgranular zone of the S1
area of the cerebral cortex that receives sensory information, including from the somatic, proprioceptive, and from certain visceral senses.

T helper type 1 (Th1) cells
subset of $CD4^+$ effector T cells; promote cell-mediated immune responses and are required for host defense against intracellular viral and bacterial pathogens.

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Box 1:

Widely used agents to stimulate MIA responses in rodent models

Poly (I:C) is structurally similar to viral double-stranded RNA that stimulates immune responses through TLR3 and MDA5/RIG-1 RNA sensors. Research using poly(I:C) has significantly contributed to understanding the immunological and neurobiological mechanisms of MIA [2,14]. Studies identified a crucial gestation window, between embryonic days 9 to 15, in which poly(I:C) injection promotes behavioral abnormalities in offspring in mice [135]. Extensive efforts have been made to determine the levels of inflammation during which neurodevelopmental abnormalities in offspring ensue following injection with various amounts of poly(I:C) [28]. One study used the poly(I:C) model to demonstrate that IL-6, and not IFN-γ, was a key effector mediating MIA-induced behavioral abnormalities—the first major discovery into the mechanisms of MIA. We and others uncovered pivotal roles for Th17 cells and segmented filamentous bacteria (SFB) in promoting MIA pathogenesis. The poly(I:C) model has also been used to elucidate how MIA influences fetal brain development by affecting cortical architecture [4], ISR in fetal brains [103], and immune cell function in the choroid plexus [136]. Furthermore, this model identified dysregulated tactile hypersensitivity [137] and the emergence of heightened neural activity in the sub-region of the primary somatosensory cortex, the dysgranular zone of the **S1** (S1DZ), which is connected to different brain areas (including the temporal association area (TeA) and the striatum) in adult MIA offspring [83] (Figure 2). The effects of poly(I:C)-MIA on offspring include a strong male bias [103] and dysregulated immune responses, such as increased production of inflammatory cytokines upon stimulation [138,139], both of which are observed in human ASD patients [140]. This is an intriguing finding, and the significance of the male bias remains to be elucidated.

Bacterial infections, especially during the second trimester of pregnancy, are strongly associated with an increased risk of developing neurodevelopmental disorders in children [15]. During pregnancy, infections with various bacterial pathogens, including *Toxoplasma gondii*, *Chlamydophila pneumonia*, and *Mycoplasma*, increase the risk of ASD and schizophrenia in humans [141,142]. *T. gondii* or *Escherichia coli* infection in pregnant rodent dams promotes feto-maternal inflammation and behavioral abnormalities in offspring [143], and *T. gondii* antigen induces MIA-associated behavioral and neurodevelopmental changes [144,145]. Likewise, injection of lipopolysaccharide, a cell wall component of gram-negative bacteria, or *Staphylococcal* Enterotoxin A and B into dams promotes autism- or schizophrenia-like behavioral abnormalities, including deficits in social interaction, pre-pulse inhibition of acoustic startle response, decreased learning and memory, and increased repetitive behavior, in offspring [14,146–148]. While less is known about the downstream effector mechanisms, prenatal administration of LPS elicits the production of inflammatory cytokines (TNF-α, IL-1β, and IL-6) in maternal circulation and fetal brain [100,149]. Indeed, A recent study in mice demonstrated a role for IL-17a in triggering LPS-dependent, autism-like behaviors [100] (see main text).

Box 2:

Anti-inflammatory factors suppressing MIA

While many studies have shown that inflammatory factors can promote MIA-associated phenotypes, less attention has been given to identifying protective factors that can suppress the development of MIA and prevent offspring from developing MIA-induced neural deficits and psychiatric disorders. In humans, adverse conditions in pregnancy, such as preterm delivery, are strongly associated with loss-of-function mutations in IL-10, a widely studied anti-inflammatory factor [150]. Pregnant IL-10 mutant mice (*Il10* knockout) develop more severe inflammation to a low-dose LPS injection at late gestation, leading to significantly enhanced fetal loss, compared to wild-type mice [151]. Conversely, exogenous IL-10 given intraperitoneally to pregnant mice prevents fetal loss by restraining the production of LPS-induced inflammatory cytokines [151]. Likewise, ectopic expression of IL-10 in macrophages is sufficient to attenuate poly(I:C)-induced MIA during pregnancy and protect mouse offspring from long-term behavioral abnormalities [152], highlighting IL-10 as a maternal bulwark against MIA. Together with IL-10, $Foxp3^+$ regulatory T cells (Tregs) (which play key roles in immunological homeostasis) are thought to presumably help maintain a healthy pregnancy and feto-maternal tolerance against MIA [153]. Indeed, the functional impairment of Tregs has been reported to contribute to various human pregnancy complications, including implantation failure, miscarriage, and preeclampsia [153]. Moreover, Earlier studies have described the functional significance of peripherally induced Tregs in maintaining feto-maternal tolerance [153]. Transient depletion of Tregs (using the $Foxp3^{DTR}$ knock-in mouse line) in pregnant mice resulted in fetal resorption phenotypes accompanied by an expansion of IFN-γ-producing, fetal-specific **T helper type 1 (Th1) cells** in the spleen. Treg depletion in other contexts often triggers devastating inflammation, leading to various types of auto-inflammation. By contrast, Treg supplementation in offspring via an intravenous route has been reported to yield beneficial effects by dampening T cell inflammatory responses in MIA offspring [145]. One consideration is that perhaps Treg dysfunction during pregnancy might also give rise to MIA, potentially leading to neural deficits and psychiatric disorders in offspring, although this remains conjectural.

Outstanding questions

- Is there a specific time during fetal development when MIA induces long-lasting behavioral and neurodevelopmental changes? Human and mouse studies suggest that the timing at which developing fetuses are exposed to inflammation matters. However, a mechanistic understanding is lacking. Studies are needed to determine whether this time-dependent “immune sensitivity” reflects differences in the magnitude of maternal immune responses (e.g., amuonts of MIA-inducing cytokines), particular stages of fetal neurogenesis (e.g., cortical formation and neuronal migration), or the transfer of maternal immune molecules into the fetal compartment (e.g., the establishment of the blood-brain barrier in the fetus).
- What are the downstream events of MIA? It is largely unknown how IL-17 receptor signaling leads to enhanced ISR and how, in turn, it results in dysregulated neural activity in the S1DZ area. Additionally, the mechanisms by which MIA primes an offspring’s immune responses require further investigation.
- What are the upstream events of MIA? Studies need to be done to determine how poly(I:C) injection stimulates IL-6 and IL-17a responses in pregnant mice.
- What determines MIA-induced behavioral changes in male but not in female offspring? Male, not female, MIA offspring display enhanced ISR and behavioral abnormalities. The mechanisms underlying the enhanced male susceptibility to MIA-associated changes requires robust investigation.
- What other inflammatory stimuli induce MIA? The contributing roles in pregnancy of autoimmune and inflammatory conditions, such as inflammatory bowel disease (IBD), psoriasis, and asthma, need to be extensively tested. Given that the anti-fungal response in humans constitutes a major Th17 cell program, understanding how fungal infections in pregnancy affect fetal brain development remain to be investigated.
- What are the main limitations of the current MIA model? Most MIA work has been done using poly(I:C) injection of pregnant mice. Findings made from this model need to be confirmed or expanded to pathogenic viral or bacterial infections. In addition, more studies are needed to dissect the MIA-induced immunological and neurological phenotypes in non-human primate models, which will provide insights towards clinical relevance.

Highlights

- An increased risk of neurodevelopmental and psychiatric disorders in children has been associated with their exposure to heightened inflammation in the womb caused by respiratory infections or other inflammatory stimuli.
- Rodent models have provided a wealth of information on how maternal immune activation (MIA) influences brain development and animal behaviors.
- Maternal gut bacteria shape maternal immune function and influence the development of autism-like phenotypes in offspring.
- A comprehensive understanding of the gut bacteria-immune-neuro interaction in MIA is crucial to developing diagnostic and preventive measures for high-risk pregnant women and identifying targets for treating inflammation-induced neurodevelopmental disorders.

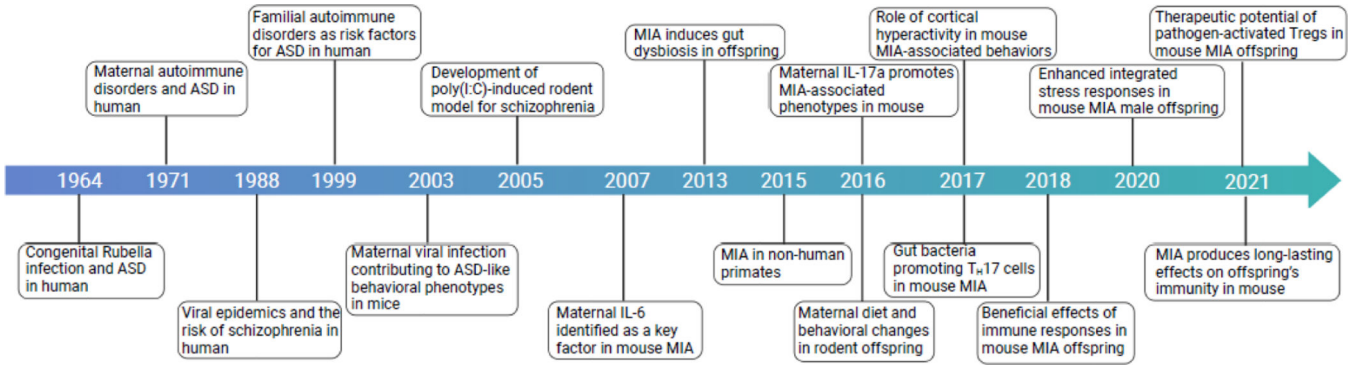

Figure 1. A brief history of MIA research leading to the identification of key players.

Timeline illustrating key events in MIA research. Abbreviations: ASD, Autism spectrum disorder; IL-6, interleukin-6; IL-17a, interleukin-17a; ISR, integrated stress response (ISR); MIA, maternal immune activation; Poly(I:C), polyinosinic:polycytidylic acid.

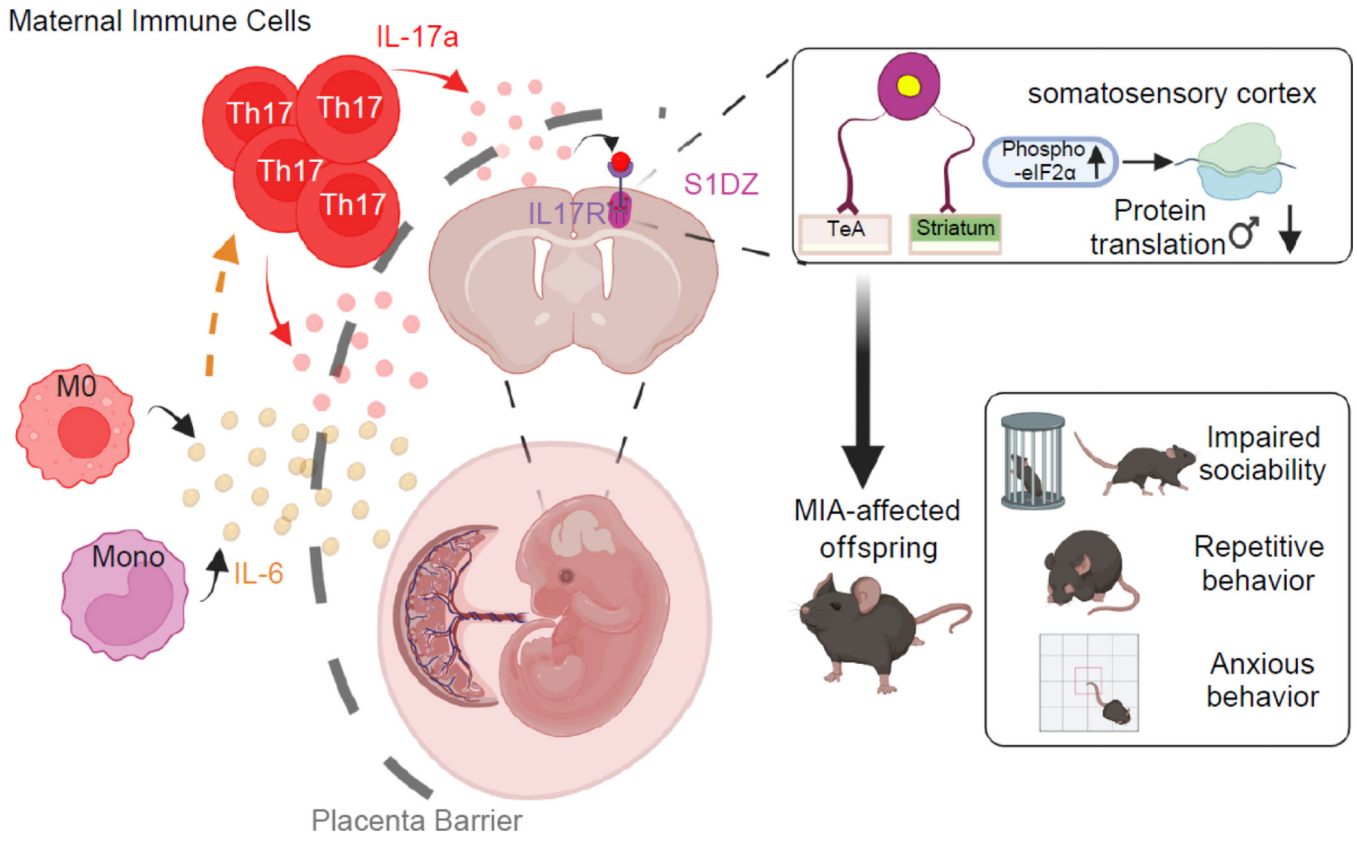

Figure 2. IL-6 and IL-17a promote MIA-associated phenotypes in mice.

This schematic reflects the current understanding of how MIA leads to the abnormal development of the fetal brain and autism-like behavioral abnormalities in offspring. i) MIA leads to enhanced production of interleukin-6 (IL-6) in pregnant dams. ii) IL-6 promotes the differentiation of naïve T cells into T_H17 cells, which produce interleukin-17a (IL-17a) in mice exposed to poly(I:C)-induced inflammation. iii) Both IL-6 and IL-17a may act on or across the placental barrier. iv) Exposure to maternally derived IL-17a stimulates the integrated stress response (enhanced phosphorylation of elongation initiation factor 2B [eIF2B]), leading to delayed translation in male, but not female, fetal brains. v) The IL-17-receptor (IL17R) is expressed in the cortical areas, including the primary somatosensory cortex dysgranular zone (S1DZ), which is connected to different brain areas, such as the temporal association area (TeA) and the striatum. Dysregulated neural activity in these regions contributes to autism-like behavioral phenotypes, including impaired sociability and increased repetitive and anxiety behaviors, in MIA-affected offspring. M0, macrophages; Mono, monocytes.

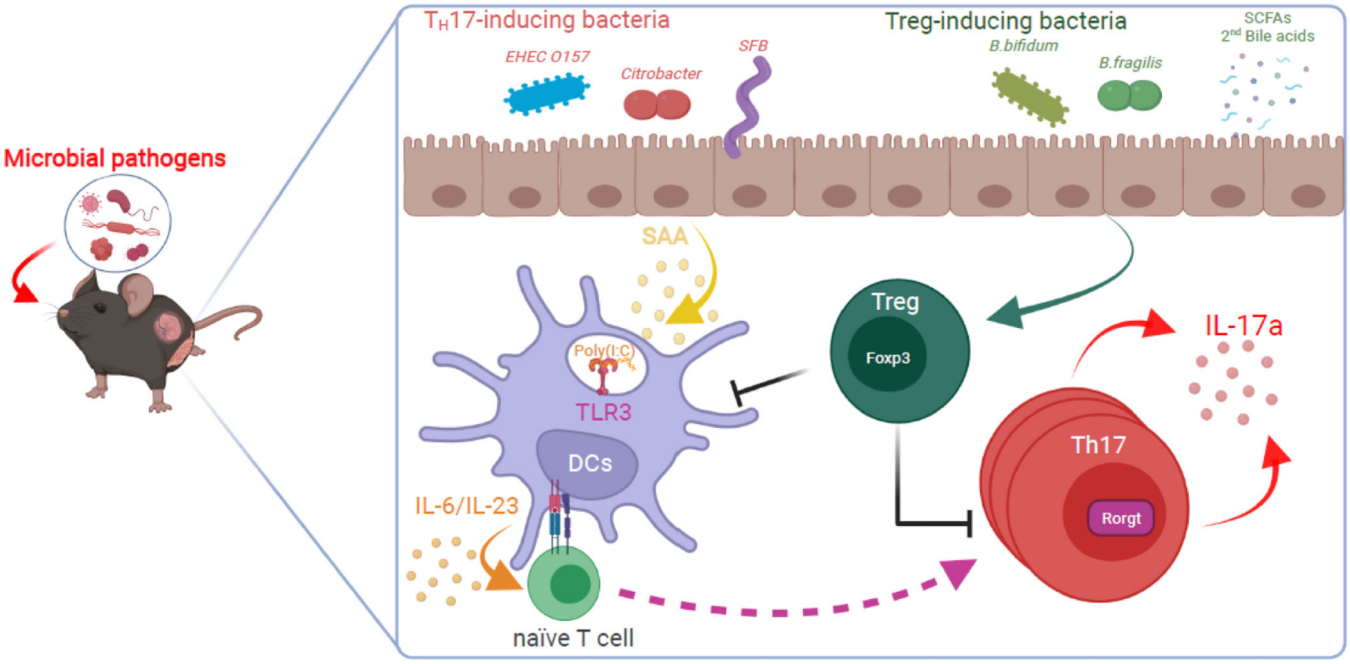

Figure 3. Gut commensal bacteria in pregnant mice contribute to MIA responses by regulating Th17 cell biogenesis and function.

The schematic represents the pathological T_H17 responses in the maternal intestine upon exposure to prenatal viral or bacterial infection. i) Gut commensal bacteria promote the differentiation of inflammatory T_H17 and anti-inflammatory Treg cells. ii) Commensal bacteria, such as SFB, stimulate intestinal epithelial cells to produce serum amyloid A (SAA). iii) SAA then acts on dendritic cells (DCs) and T cells and differentiates naïve T cells into IL-17a-producing T_H17 cells in the gut lamina propria. iv) DCs are further stimulated by poly(I:C) or other pathogenic insults. v) However, commensal bacteria, such as *Bifidobacterium bifidum* or bacterial metabolites (e.g., short-chain fatty acids [SCFAs] or secondary bile acids), enhance the production of Tregs, which may counteract MIA-stimulated Th17 cell responses.