PNAS COMMENTARY

When the BBB goes MIA

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Epidemiological studies implicate maternal immune activation (MIA) as a risk factor for a variety of neurodevelopmental disorders. Bacterial and viral infections including rubella, influenza, *Toxoplasma gondii,* and herpesvirus infections have been associated with autism spectrum disorder (ASD), schizophrenia, bipolar disorder, epilepsy, and cerebral palsy (1–4). The impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on the incidence of neurodevelopmental disorders in the offspring of infected mothers remains to be seen. MIA induces a maternal cytokine response, and exposure to these immunostimulants results in altered neural development in the fetus, a theory supported by several mouse and human studies (1–3). However, the underlying cause of lifetime cognitive defects in offspring due to MIA is unclear (Fig. 1). In PNAS, Zhao et al. (5) demonstrate that MIA is associated with increased blood–brain barrier (BBB) permeability and microglial activation in the offspring, leading to an inflammatory response in the fetal brain that persists into adulthood.

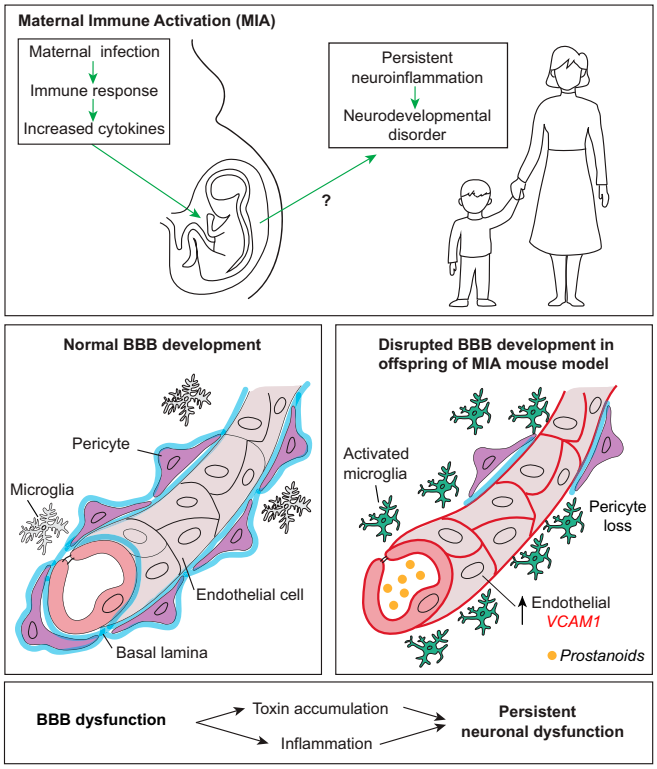

Fig. 1. MIA disrupts the BBB in the offspring. MIA increases inflammatory cytokines in the mother that lead to nonresolving inflammation in the offspring which, in turn, may underlie neurodevelopmental disorders associated with maternal infections (*Top*). MIA up-regulates COX-2 in microglia, leading to microglial activation, clustering of microglia around blood vessels, endothelial inflammation, pericyte loss, and increased permeability of the BBB in the offspring (*Middle*). The BBB dysfunction may promote persistent inflammation as well as the entry into the brain parenchyma of blood-derived toxins which may predispose to developmental alterations and neuronal dysfunction (*Bottom*).

MIA induces a maternal cytokine response, increasing the production of proinflammatory cytokines including interleukin (IL)-6, IL-17, tumor necrosis factor alpha (TNFα), and IL-1β (1, 2). It is thought that exposure to these factors causes an increase in cytokines in maternal serum, the placenta, amniotic fluid, and the fetal brain. While the link between MIA and neurodevelopmental disorder has been established, the mechanisms underlying neurodevelopmental defects and permanent neural disorder are unclear. During normal neurogenesis, the fetal brain expresses many different cytokine receptors in spatially and temporally distinct patterns. Mouse models have demonstrated that increased levels of IL-1β, IL-6, and IL-17a during fetal brain development result in behavioral traits associated with ASD and schizophrenia, neocortical malformations, enhancement of excitatory synapses, and hyperconnectivity in adult offspring (6–8). Thus, spatiotemporal changes in cytokine signaling can lead to developmental changes that cause long-lasting effects into adulthood, the mechanisms of which have remained elusive.

MIA can also permanently affect fetal immune mechanisms (1, 2, 9). The predominant immune cells in the brain are microglia that perform canonical roles such as phagocytosis. In response to injury or infection, microglia become activated, adopt a rounder "amoeboid" shape, and undergo transcriptional changes to carry out inflammatory responses (10, 11). Microglia also carry out a number of noncanonical functions including regulating neural progenitor cell number, synaptic pruning, neuronal maturation, programmed neuronal cell death, and brain vasculogenesis (10–14). Microglia contribute to neurovascular organogenesis and function and play an important role in the development and maintenance of the BBB (15–17). Prenatal exposure to MIA leads to microglial activation; studies demonstrate that suppression of microglial activation in MIA mouse models can attenuate inflammatory response, rescue neuronal deficits, and restore locomotor activity (1, 18). In vitro studies have demonstrated that prolonged microglial activation impairs BBB permeability, contributing to the progression of neurodegenerative disease in animal models (15, 19–22).

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However, it is unclear if microglial activation due to MIA disrupts BBB development in vivo and contributes to the neurodevelopmental deficits in the offspring.

The BBB, located at the level of the cerebral endothelial cells (ECs) lining cerebral blood vessels, controls the bidirectional molecular traffic between blood and brain (16). A critical early step in BBB development involves the recruitment of pericytes to the developing ECs in the capillary wall. Pericytes share a basement membrane with ECs and are essential for maintaining BBB integrity in the adult (15, 16). The BBB protects the brain parenchyma from potential blood-borne neurotoxins and pathogens. Disruption of BBB development or integrity results in accumulation of toxins and increased inflammation, leading to persistent neuronal dysfunction (Fig. 1) (16). Here, Zhao et al. (5) tested the hypothesis that MIA-induced microglial activation and inflammation disrupt the development of the BBB in the fetus, leading to hyperpermeability and to a long-lasting fetal inflammatory response that persist into adulthood.

To this end, Zhao et al. (5) utilized the polyinosinic:polycytidylic acid (polyI:C) model, injecting pregnant dams at embryonic day (E) 13.5 to induce MIA. They confirmed the induction of expected phenotypes in both the mother and offspring, including increased cytokine concentration in maternal blood serum, increased activated microglia, and anxiety and memory deficits in the adult offspring. Using dynamic contrast-enhanced MRI they went on to demonstrate increased blood-to-brain transfer of the tracer gadolinium diethylenetriamine pentaacetic acid (Gd-DPTA), confirming increased global BBB permeability in the adult offspring. Cellular phenotypes associated with BBB were also observed, including increased expression of inflammation marker vascular cell adhesion molecule 1 (VCAM1) in ECs and decreased pericyte–EC coverage. Given that capillary volume is unchanged in MIA-model offspring, the authors attribute the BBB disruption to reduced pericyte coverage. Interestingly, they show that the BBB dysfunction starts in the fetus. Decreased pericyte coverage, increased EC VCAM1 expression, and increased numbers of activated microglia (Fig. 1) was observed within 48 h of MIA. At this time, live MRI of pregnant dams elegantly demonstrated increased fetal BBB permeability to Gd-DPTA. This strikingly rapid disruption of BBB links the adult phenotype with a developmental pathogenic event affecting fetal cerebral microvessels and BBB formation.

COX2 expression is induced in response to inflammation and is involved in the production of prostaglandin E2 (PGE2) and other prostanoids. Zhao et al. (5) show that a subset of microglia express COX2 and in response to MIA this COX2+ population expands, becomes perivascular, and is associated with BBB disruption (Fig. 1). Concordantly, increased levels of PGE2 were detected in fetal brain, but not in the mothers, in response to MIA. Thus, MIA rapidly activates fetal microglia, up-regulates COX2 and PGE2, and results in the increased inflammatory responses seen in vivo.

In PNAS, Zhao et al. demonstrate that MIA is associated with increased blood–brain barrier (BBB) permeability and microglial activation in the offspring, leading to an inflammatory response in the fetal brain that persists into adulthood.

Zhao et al. (5) effectively established causality using pharmacological and genetic strategies. The COX2 inhibitor celecoxib reduced COX2 activity in the mothers and both COX2 and PGE2 in the fetal brains and normalized pericyte–EC coverage and BBB permeability. Microglial-specific COX2 down-regulation in transgenic mice also ameliorated microglial activation, perivascular localization, and proliferation and restored pericyte–EC coverage. Future studies will have to determine if PGE2 or another reaction product of the COX2 pathway is directly responsible for the BBB alteration and neuroinflammation. Furthermore, it will be of interest to determine whether MIA-associated behavioral deficits can also be ameliorated by perinatal celecoxib treatment.

The timing and severity of MIA determines the susceptibility of the fetus to neurodevelopmental disorder. Acute infections during the first trimester are more closely associated with neurodevelopmental defects (1–3). Zhao et al. (5) provide evidence that early MIA results in BBB disruption and inflammatory responses that lead to persistent postnatal structural and cellular defects associated with MIA, rescuable by celecoxib treatment. The findings of Zhao et al. advance our understanding of the developmental origins of MIA-associated cognitive deficits and unveil a potential therapeutic intervention for the BBB dysfunction and chronic inflammation associated with neurodevelopmental diseases. In addition, the data raise the possibility that the BBB alterations induced by MIA may also contribute to other diseases associated with chronic neuroinflammation. In this regard, MIA in the setting of the SARS-CoV-2 pandemic should alert health-care providers to this potential risk, warranting careful monitoring of the offspring in infected mothers.

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