RESEARCH HIGHLIGHT

Objection non-responsive! How maternal immune activation in pregnancy weakens subsequent microglial immune response

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Virus-like immunological stress during pregnancy diminishes subsequent microglia reactivity, elevating astrocyte inflammatory state and reducing synaptic activity in medium spiny neurons of the ventral striatum.

The developing immune system and central nervous system (CNS) in the fetus are especially sensitive to both external and endogenous signals. Early immune system activation has been proposed to cause lifetime changes, and additional evidence suggests that immunological dysregulation in the developing brain may play a role in neurodevelopmental disorders such as autism or schizophrenia by affecting the primary parenchymal immune cells of the CNS called microglia.[1,2]

Evoked responses to early immune stress may differ in their extent depending on the type of stressor (i.e., virus, bacteria, and other) and the timing of immunological dysregulation in relation to gestational age and fetal neurologic development. The primary query in the current study by Lindsay N. Hayes and colleagues[3] was the long-term changes of microglia following prenatal immune stress (Fig. 1). The authors used maternal immune activation (MIA) in mice to induce prenatal immune stress, in which the virus infection-mimicking immune activator polyinosinic:polycytidylic acid (PIC) was applied to pregnant dams at embryonic day (E) 9.5. When challenged with lipopolysaccharide (LPS) later after birth, microglial innate immune response pathways, including type I interferon signaling, were severely compromised. The quantification of secreted interleukin (IL)-6 and tumor necrosis factor alpha (TNFα) from LPS-stimulated microglia in vitro revealed a reduction already at E18 only in MIA-challenged microglia. Thus, MIA caused decreased microglial reactivity in both the neonatal and adult stages. What were the mechanisms of this phenomenon?

The authors observed in microglia from adult mice after LPS application only in MIA-exposed individuals more open differentially accessible regions (DARs) by performing an assay for transposase accessible chromatin with sequencing (ATAC-seq). However, transcription factors occupied fewer DARs in MIA-treated microglia. Among them were crucial transcription factors that preferentially control the interferon immune response like GATA4, SMAD3, and STAT1. In support of these findings, a network analysis of combined ATAC-seq and RNA-seq data revealed reduced transcription factor–target interactions in the type I interferon pathway in MIA-challenged microglia in response to LPS exposure. When the authors treated pregnant dams with a CSF1R antagonist (PLX5622) between E9.5 and E12.5 to remove embryonic microglia (but also other CSFR1-dependent cells), the subsequent LPS response in the repopulated microglia in MIA was improved, as revealed by protein and transcriptional data. Following LPS treatment, the cytokine protein expression of astrocytes and non-microglial/non-astrocytic (negative) cells was examined. The increased IL-6 production by astrocytes in MIA offspring suggests that astrocytes have an increased immune response. Prenatal microglia replacement corrected astrocyte pathology, indicating that defective microglia reactivity is likely to be the cause of astrocyte aberrations in MIA offspring. The authors then used electrophysiological recordings to assess the function of medium spiny neurons (MSNs) in the ventral striatum of adult MIA offspring in order to determine the cell non-autonomous influence of MIA microglia on brain development and neuronal function in general. The paired pulse ratio of dopamine receptor type-2 (D2R) MSNs was increased but not that of dopamine receptor type 1 (D1R) MSNs, indicating a lower likelihood of glutamatergic presynaptic vesicle release onto D2R MSNs in adult MIA offspring. Notably, prenatal microglial replacement restored the lower release probability to control levels. These findings show that immune-responsive microglia are beneficial and necessary during brain development. In the developing thalamus, for instance, IL-33, which is released by astroglial cells, controls microglia synaptic phagocytosis through the interleukin 1 receptor-like 1 (IL1RL1).[4]

Typically, chromatin accessibility is thought to be a feature of active regulatory regions where transcription factors are drawn in by interactions with specific DNA sequences. The fact that the opposite scenario exists in MIA-exposed microglia, with fewer transcription factors occupying these open regions, is certainly worth investigating further.[5] This is especially true given that epigenetic mechanisms are the molecular basis for a suppressed immune response in MIA microglia. Environmental stressors, such as immunological challenges, have the power to significantly change how many different fetal organ systems, including the brain, develop.[6] Microglia have already shown long-term impacts of MIA in mice, displaying ongoing modifications in their process motility patterns far into adulthood.[7] These changes undoubtedly impact how microglia communicate with their surrounding cells. Proper microglia–neuron interactions are crucial for brain growth and homeostasis, according to a growing body of research. By inciting embryonic microglia to create proinflammatory cytokines that lead to neuro-inflammation, which may ultimately impact

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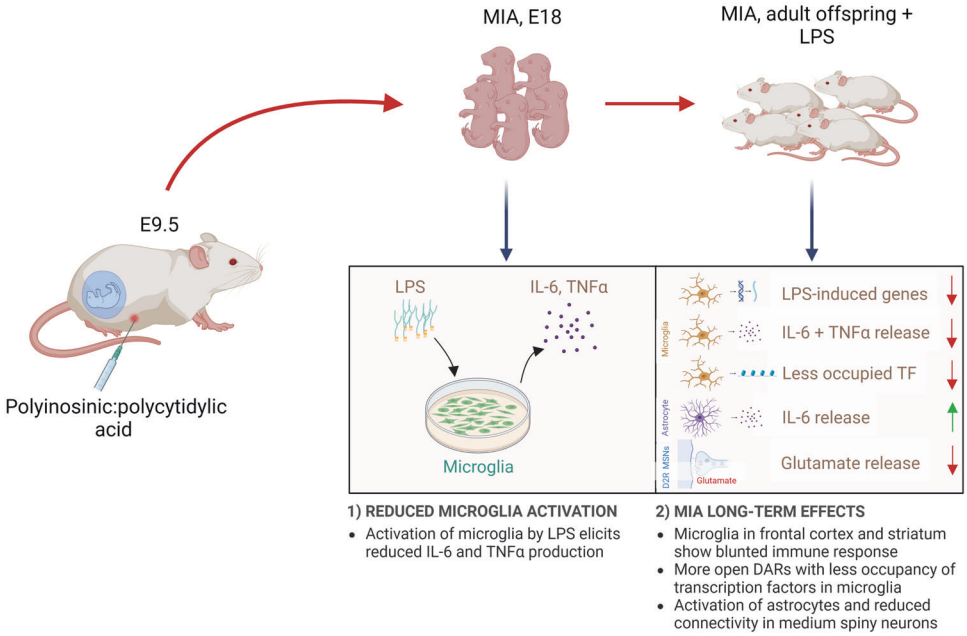

Fig. 1 MIA generates blunted immune response in microglia. Abbreviations: MIA maternal immune activation, E embryonic day, LPS lipopolysaccharides, IL-6 interleukin-6, TNFα tumor necrosis factor α, TF transcription factor, DARs differentially accessible regions, D2R dopamine receptor type-2, MSNs medium spiny neurons.

brain development, MIA is seen as one of the causes changing these cell–cell interactions.

In sum, Hayes et al.[3] report that MIA-exposed microglia enhance the expression of astrocytic IL-6 and create malfunctioning synaptic connections of the ventral striatum by simply remaining "non-responsive" and not by becoming chronically activated, a finding that might be regarded as a shift in paradigm. Synaptic functions are most likely not only impeded in the striatal region but also in other brain regions, which heightens the risk for behavioral abnormalities, including cognitive impairment, autism spectrum disorders, and schizophrenia in the progeny.[8,9] Therefore, this study presents an important next step to better understand the complex pathophysiology of those neuropsychiatric conditions.

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ADDITIONAL INFORMATION

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