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Inflammation and Autism: From Maternal Gut to Fetal Brain

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Abstract

Maternal immune activation (MIA) during pregnancy is associated with an increased risk of behavioral disorders in the offspring of affected mothers. Two recent studies highlight how maternal inflammation disrupts inhibitory interneuron networks and suggest that the maternal gut microbiome may be a contributing risk factor for MIA-induced behavioral abnormalities.

Autism spectrum disorders (ASD) are characterized by pervasive and potentially severe developmental deficits in communication, socialization, and behavior. Both genetic and environmental factors are thought to contribute to the pathogenesis of ASD[1], and maternal inflammation during pregnancy, particularly as a consequence of infection, is being increasingly recognized as a potential risk to developing ASD[2]. The association between maternal wellbeing and fetal development leads to novel avenues of translational investigation into the immunological, neurological, and developmental factors underlying ASD severity and pathogenesis. Indeed, these may ultimately lead to candidate therapeutic and preventative strategies to combat ASD.

Experimental work on the link between maternal inflammation and ASD was pioneered in the early 2000's, when it was discovered that maternal immune activation (MIA) in pregnant rodents, either through infection or administration of pro-inflammatory adjuvants, induced schizophrenia- and ASD-like behaviors in their offspring[3]. Two years ago, the field took a leap forward when Gloria Choi, Jun Huh, and colleagues demonstrated that MIA could induce abnormal patches of neuronal architecture in areas of the cerebral cortex through the direct, intracerebral action of the proinflammatory cytokine, interleukin-17a (IL-17a)[4]. This remarkable work also revealed that the source of IL-17 was that of T helper 17 (Th17) cells, a $CD4^+$ T cell subset that plays a key role in combatting bacterial and fungal infections, and in maintaining gut homeostasis. Thus, IL-17a, produced by maternal Th17 cells, was hypothesized to reach the fetal circulation, which would then allow it to affect fetal brain development.

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In companion publications in the September 2017 *Nature* issue, the same researchers now describe additional discoveries regarding both the neurological and immunological components of the IL-17a MIA pathway. The article focusing on the neurological pathway (Yim et al.) elegantly dissects the neural circuits involved in MIA-induced cortical pathology and associated behavioral abnormalities[5]. The authors first determined that polyinosinic:polycytidylic acid (poly(I:C))-induced MIA in pregnant mice led to a localized loss of inhibitory interneuron networks in the brains of adult offspring, primarily in the dysgranular zone of the primary somatosensory cortex (S1DZ)[5]. Moreover, upon optical stimulation of adult wild type mice (in the absence of MIA), the authors were able to recapitulate an ASD-like behavior (consisting of repetitive marble burying, anxiety (time spent at the center of an open field) and decreased sociability), by either enhancing the activation of excitatory neurons within the S1DZ, or by reducing the function of inhibitory interneurons. This suggested the possibility that MIA-induced ASD-like behaviors might arise from enhanced cortical activation following the loss of inhibitory interneuron networks.[5] Moreover, separate optogenetic targeting of the connections between the S1DZ and two of its downstream targets, the striatum and the temporal cortex, reproduced or rescued discrete components of MIA-induced behavioral abnormalities, repetitive behaviors and socialization defects, respectively. These data implicated S1DZ as a central node connecting multiple behavioral pathways disrupted by MIA. A seminal finding from this work was that optogenetic inhibition of S1DZ in adult MIA offspring abrogated the behavioral abnormalities of these mice, thus demonstrating the potential of reversing MIA-induced developmental abnormalities, even into adulthood.[5]

Although maternal inflammation is associated with increased risk of ASD, the incidence of ASD among children of mothers hospitalized from infection is still relatively low[2]. This suggests that other maternal or fetal factors may modify the risk of ASD in the context of an inflammatory illness. Accordingly, the immunological experiments described in the companion article (Kim et al.) revealed that the maternal gut microbiome is another critical determinant of MIA-induced behavioral abnormalities[6]. This work took advantage of the fact that C57BL/6 mice purchased from Taconic Biosciences (Tac) contain a high number of gut Th17 cells because they are colonized with a strain of segmented filamentous bacteria (SFB). In contrast, mice purchased from The Jackson Laboratory (JAX) lack gut Th17 cells and are not colonized by SFB. The authors found a striking result in that only the offspring of Tac mice are susceptible to MIA-induced behavioral pathology; furthermore, such susceptibility-- concomitant with the induction of gut Th17 cells-- could be conferred to JAX mice by co-housing the animals, or via gastrointestinal gavage[6]. In addition, the study demonstrated that elevated IL-17a responses during MIA were due to the activation of dendritic cells (a key antigen presenting cell type), interacting with pre-established memory Th17 cells within the SFB-colonized gut.

Together, these murine studies provide further definition to the mechanisms of MIA-induced behavioral changes, and also open up new ways of thinking about how ASD pathogenesis intersects with maternal inflammation, brain development, and environment. For instance, the known effects of diet on gut microbial composition[7] might help explain the emerging link between diet and ASD incidence[8];this in turn, may suggest ways to harness specific dietary modifications during pregnancy to reduce ASD risk. Furthermore, MIA cortical

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pathology possesses a narrow developmental window[5], suggesting that developing neural networks may have a restricted window of sensitivity to IL-17a, or, that MIA-induced IL-17a production by gut Th17 cells is itself somehow regulated over the course of gestation. Indeed, Kim et al. showed that systemic inflammation does not activate gut dendritic cells (and hence Th17 cells) when the mice are not pregnant. How this additional layer of regulation relates to the multitude of dynamic physiologic, hormonal, and immunologic changes that accompany pregnancy remains to be determined.

These pregnancy-specific issues are also relevant when considering how IL-17a, produced by maternal Th17 cells might reach the fetal brain, and whether this process might be regulated by the placenta, which separates maternal and fetal circulation, and which tightly controls the communication between the two compartments. One possibility is that the cytokine itself is transported across the placenta; another is that Th17 cells migrate from the maternal gut to the fetus. Both possibilities, however, would be consistent with the emerging association between ASD risk and certain pathologies of the placenta[9,10].

It is important to note that the murine MIA model used by the Choi and Huh laboratories simulates viral infection, but bacterial infections and autoimmune events are also associated with an increased risk of ASD[2]. It is thus possible that nonspecific memory Th17 activation could serve as a final common pathway for different inflammatory challenges, or, alternatively, that other yet-to-be-defined mechanisms can account for increased ASD risk under different inflammatory circumstances. Lastly, although many hurdles remain, the work by Choi, Huh and colleagues now point the way towards envisioning how therapies that target discrete regions of the brain might eventually be developed to ameliorate ASD symptoms.[5,6]

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