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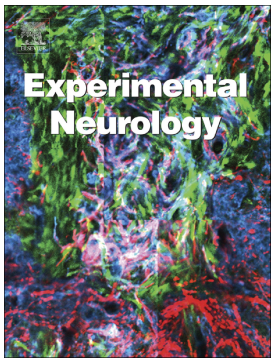

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Maternal IL-17A in autism

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Highlights

- Prenatal exposure to maternal immune activation (MIA) has been linked to ASD risk.
- Offspring in MIA mouse models exhibit ASD-like behaviors and cortical dysplasia.
- The pro-inflammatory cytokine IL-17A may play a causal role in MIA-associated ASD.
- IL-17A injection into the fetal brain can phenocopy MIA-induced effects.
- Potential mechanisms of IL-17A signaling effects on neurodevelopment are proposed.

I. Immune dysregulation in autism spectrum disorder

Autism spectrum disorder (ASD) constitutes a group of neurodevelopmental disorders with overlapping but variable behavioral and cognitive symptoms, severity, and comorbid conditions. The core diagnostic features of ASD are impaired social interaction, communication challenges, and expression of repetitive or perseverative behaviors (Kanner, 1943; Moldin et al., 2006). Although ASD has a strong genetic basis, its etiology is complex, with several genetic factors likely to be involved as well as interactions with environmental influences (Betancur, 2011; DiCicco-Bloom et al., 2006; Goines and Ashwood, 2013; Risch et al., 1999). ASD therefore represents a collection of conditions with heterogeneous causes, but they may converge on common molecular pathways to bring about the features that characterize this disorder. Immune dysregulation has gained significant attention as a pathway for the pathogenesis of ASD (Depino, 2013; Korvatska et al., 2002).

Immune system abnormalities have been observed widely in the brain and periphery of ASD individuals. Studies have found chronic neuroinflammation in ASD, indicated by increased activation of microglia and astrocytes and production of cytokines and chemokines in the brain (Li et al., 2009; Morgan et al., 2010; Vargas et al., 2005). Transcriptome analyses of ASD brains also have indicated an upregulation of immune response genes (Garbett et al., 2008; Voineagu et al., 2011; Ziats and Rennert, 2011). Similarly, in the periphery, studies have found elevated expression of pro-inflammatory cytokines and other immune factors in the blood and gastrointestinal tract of ASD individuals (Ashwood et al., 2004; Ashwood et al., 2011; Enstrom et al., 2010). Additionally, ASD has been associated with inflammatory disorders and autoimmunity in not only the affected individuals but also their mothers (Atladottir et al., 2009; Buie et al., 2010; Jonakait, 2007). Moreover, prenatal exposure to maternal immune activation (MIA) has been implicated as an environmental risk factor for ASD.

Several epidemiological studies have found that maternal infection during pregnancy correlated with an increased frequency of ASD in the children (Atladottir et al., 2010; Brown et al., 2014; Chess, 1977; Wilkerson et al., 2002). The infection activates a maternal immune reaction in which the molecular signaling cascades are thought to adversely affect