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Immune contributions to cause and effect in autism spectrum disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder that appears during the first 3 years of life and presents with a variable set of symptoms that include impairments in social communication, narrow and restricted interests, and repetitive behavior. ASD is the most rapidly increasing neurodevelopmental disorder and current estimates are alarming, indicating 1 in 68 children and 1 in 42 boys in the United States are on the spectrum (1). Despite this growing public health emergency, few effective treatments exist for ASD and more research is needed to identify new therapies and alleviate the enormous personal, social and economic costs of ASD to our society.

Few therapies for ASD are currently available in large part because the field is still struggling to understand ASD and determine its underlying causes. The high rates of heritability of ASD strongly suggest a genetic component and recent research has identified a large number of genes associated with this disorder (2). In addition to genetic associations, there is a long list of diverse environmental factors that contribute to ASD (3) and it is currently thought that ASD is caused by a combination of genetic and environmental risk factors that either alone or together exceed a threshold for disease manifestation.

One of the most exciting recent hypotheses in the field is that immune dysregulation contributes to, and may cause, ASD. Indeed, many of the genetic associations and most of the environmental factors linked to ASD converge on immune dysregulation through alterations in immune-related genes and/or immune responses to environmental stimuli (4). ASD is linked to aberrations on chromosome 6, which is densely packed with genes for immune molecules, (5) and specific haplotypes of immune genes—especially MHC and cytokines—correlate with ASD (4, 6). Moreover, the expression of many immune-related genes in the brain is altered in individuals with ASD (7). These genetic associations, either alone or in combination with environmental exposures, may contribute to ongoing immune dysregulation in ASD, which manifests as altered cytokine levels in the blood, brain, and cerebrospinal fluid (CSF) (8–14) and abnormalities in peripheral immune cells and their responsiveness that correlate with behavioral symptoms in ASD (4, 15, 16). The archival report by Careaga et al. in this special issue (17) provides further evidence for the association between immune cell responsiveness and ASD and suggests that ASD subtypes can be defined by distinct profiles of immune dysregulation. Children whose blood cells

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respond to stimulation with excess pro-inflammatory cytokines exhibit more severe phenotypes including developmental and social impairments, aggression, and sleep disturbances.

Despite the mounting evidence for ongoing immune dysregulation in ASD, little is known about when immune dysregulation arises in development relative to the progression of the disorder. Using neonatal blood spots from the Childhood Autism Risks from Genetics and the Environment study, Krakowiak et al. (18) found that levels of several cytokines, including interleukin (IL) -1 β and IL-4, are elevated at birth in individuals with ASD compared to typically developing controls. Elevated IL-4 are associated with a higher likelihood of more severe ASD and in males, elevated IL-4 is negatively associated with nonverbal cognitive ability. In contrast, elevated IL-1 β is associated with mild/moderate ASD. These results suggest that immune dysregulation is present in ASD before diagnosable symptoms and thus, imply that immune dysfunction could contribute to the emergence of the disorder in addition to resulting from it. Moreover, these results are important in contributing to identification of a combined set of biomarkers that may aid in ASD diagnosis in the future.

If immune dysregulation is already present at birth in children that will go on to develop ASD, then these changes in immune responsiveness in the fetus must be caused either by genetics or by something else within the maternal environment. The review by Edmiston et al. (19) summarizes evidence linking a family history of autoimmune disease with increased risk of having children with ASD. This association may reflect a role for genes in ASD that cause autoimmune disorders, such as genes within the major histocompatibility complex, or the effect of abnormal maternal immunity on offspring (4). The Edmiston et al. review focuses on the potentially transformative discovery of autoantibodies that recognize proteins in the fetal brain generated by mothers of children with ASD compared to controls. The identity of the targets of these autoantibodies, and recent studies in animal models focused on determining their role in causing impaired brain development that might lead to ASD-related neuropathologies and behaviors in offspring, are detailed in this review (19). Together this research has led to the classification of a subtype of ASD called maternal autoantibody related (MAR) ASD, which will allow more precise diagnosis of this ASD subtype in the future and eventually new treatments for this specific form of ASD.

In addition to maternal autoantibodies, there is growing evidence that environmental exposures during pregnancy contribute to ASD risk. The risk for ASD is higher in offspring conceived in the winter months, consistent with a role for respiratory infections (20) and indeed, maternal infection greatly increases the risk for ASD in offspring (4, 21, 22). These correlations from epidemiological studies are supported by work from animal models of maternal infection. Adult offspring of pregnant mice, rats, and non-human primates from models of maternal immune activation (MIA) exhibit behavioral abnormalities and changes in gene expression, neuroanatomy, and neurochemistry consistent with ASD (4, 22). The Careaga et al. review in this special issue (23) covers this important topic from the epidemiology through animal models and discusses the advantages and limitations of these MIA models for translational research.

If immune dysregulation contributes to ASD risk, then why is ASD so extremely male biased? McCarthy and Wright (24) discuss this intriguing question of how immune dysregulation could lead to the extreme male bias in ASD in their review. They present recent evidence that inflammatory signaling molecules, especially the prostaglandin PGE₂, act through cells of the innate immune system—microglia—and astrocytes to regulate the masculinization of the brain. This review describes how this molecular pathway could contribute to ASD-related behaviors through altering development of the sexually dimorphic preoptic area of the brain as well as the cerebellum. This regulation by immune signaling could thus put the male brain at risk of being altered by maternal inflammation during fetal development.

In addition to immune dysregulation being associated with ASD, gastrointestinal (GI) issues are another common co-morbidity. Much excitement has been generated by the transformative discovery that the microbiome regulates GI physiology, as well as immune and nervous system development and function (25). Vuong and Hsiao (26) review recent discoveries of links between the presence of particular gut bacteria and ASD-related behaviors. Importantly, they also discuss the hypothesis that microbial dysbiosis may contribute to, and perhaps even cause, ASD either directly through producing imbalanced metabolites or indirectly through altering immune system development and function.

One particular molecule—the MET receptor kinase—appears to bridge all of these immune associations with ASD. The review by Eagleson et al. (27) details the exciting evidence that MET regulates homeostasis in the immune and GI systems and neural development and synapse maturation in the brain. The presence of the *MET* ‘C’ allele appears to increase susceptibility for the production of maternal autoantibodies to the fetal brain in MAR ASD (19). Importantly, this allele is also present in a subset of children with ASD and regulate specific circuits that mediate social behavior. Eagleson et al. (27) discuss evidence for the role for MET in regulating brain development and present a model showing that MET interacts with many other ASD-associated proteins in both mouse model and human neocortex to alter the development and function of multiple systems across the body—brain, immune, and gut—that have been implicated in ASD.

Finally, it is important to note that the association of maternal immune dysregulation with ASD, although strong, does not appear to be specific. Recently, associations have been reported linking maternal autoimmune disorders and maternal infection to several other psychiatric disorders including schizophrenia, bipolar disorder, and major depression (22). This list of psychiatric disorders associated with maternal immune diseases has now been expanded with the report by Instanes et al. (28) showing that offspring born to mothers with immune disorders have a higher risk for developing attention-deficit/hyperactivity disorder (ADHD). These links between immune dysregulation in utero and psychiatric illness in offspring suggest that common molecular pathways may be shared by these disorders and provides hope that new therapies directed at correcting the maternal immune dysregulation in ASD could prevent a wide range of human diseases.

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