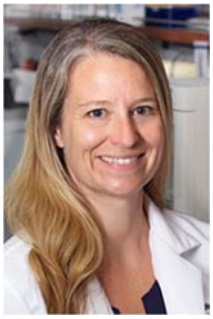
THE HARTWELL FOUNDATION

2018 Individual Biomedical Research Award

Nicole G. Coufal, MD, Ph.D.



Assistant Professor
Department of Pediatrics

University of California, San Diego

Inflammatory Developmental Hypothesis for Autism Spectrum Disorder and Associated Developmental Delay

Autism spectrum disorder (ASD) is one of the most common and devastating disorders of childhood. Characterized by persistent challenges in social communication and restricted/repetitive behaviors, 70% of affected children will also exhibit significant delay in reaching age-appropriate milestones (e.g., rolling over, crawling, walking, etc.), with 20% of children regressing from the developmental milestones they had previously reached. While research on the causes of ASD have focused primarily on nerve cell connections and neuronal networks, an increasing body of evidence suggests inflammation in the mother during pregnancy plays a prominent role framing fetal development and the origin of ASD. However, associated developmental delay and the loss of previously learned skills would suggest ongoing changes may occur rather than just a prenatal insult. In this regard, research on brain development unrelated to autism has shown that microglia, as the resident macrophage cells that are active in immune defense and mediate inflammation in the central nervous system, help regulate and modulate neuronal connections. Moreover, postmortem examination of brain tissue from individuals with autism have shown marked microglial activation. Based upon these data, I propose that there is an underlying and ongoing inflammatory component to ASD mediated by microglia that has not been previously recognized. In support of this hypothesis, I have found that many genes implicated in genetic causes of autism help regulate microglia function. Incipient and latent dysregulation of microglia could explain the loss of previously learned skills in developmental regression as the loss of neuronal connections that were previously established during development. To understand how changes in the regulation of microglia may lead to autism and associated developmental delay I will examine microglia obtained from pluripotent stem cells derived from patients diagnosed with single gene mutations leading to autism, or from cell lines deficient in other transcription factors/ genes expressed in primary human microglia that have been deleted by CRISPER. I will then seek to determine in cell culture any altered response to treatment with anti-inflammatory interferon beta versus pro-inflammatory stimuli, and how the transformed response (phenotype) contributes to autism severity. Using a specific immunocompromised mouse as an in vivo model suitable for generating preclinical data, I will also determine the phenotype for the interaction of human autism-derived microglia in the mouse brain. This information will then make it possible to screen FDA approved immunomodulatory drugs to ameliorate the inflammatory phenotype in autism-associated microglia in cell culture and in the mouse model. If I am successful, a drug therapy for ASD may be possible, especially for the prevention of associated developmental delay and its potential for regression in affected children.