THE HARTWELL FOUNDATION

2015 Individual Biomedical Research Award

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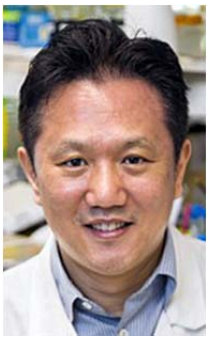

Hippocampal Nerve Cell Networks in Autism Spectrum Disorders

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that imposes enormous burden on patients, their families, and society. More than 3.5 million children in the U.S. are currently diagnosed with the disorder. In the past three decades, the diagnosis of ASD has not advanced appreciably and continues to rely upon questionnaires and physician/family observations to describe the child's behavior. With no proven cure, early detection and subsequent behavioral therapies combined with certain drugs to ameliorate various symptoms have been the standard of care. Unfortunately, drugs that globally affect "brain chemistry" often have unpleasant and unwanted side effects because they indiscriminately impact both affected and unaffected brain areas. Moreover, the compelling question remains whether ASD is the result of chemical imbalances in the brain, or does the structure of the brain also play an important role. Recent genetic analysis has provided a "unifying pathway" that can link the various autism genotypes to common autism phenotypes, where the majority of autism-associated genes apparently control common aspects of neuronal development, neural migration, and neural connectivity. Nonetheless, the question remains complicated by the behavioral heterogeneity of the disorder. Brain neurons are continuously being generated into neural circuits in the hippocampus region, making a myriad of connections with other parts of the brain, especially the cerebral cortex. The neural circuits connecting the hippocampus and the cortex ensure the information flow necessary for learning, memory, emotion, language and social interaction. The implication is that impaired formation of structural and functional neural circuits in the hippocampus leads to autism specific cognitive and social impairments. To address the contribution of such nerve-cell networks in the etiology of ASD, Hoonkyu hypothesizes that aberrant hippocampal neural circuits formed during fetal development and early childhood cause autism; and that appropriately changing these abnormal neural circuits would reverse autistic behavior. To evaluate the contribution of aberrant hippocampal neural circuits to autism pathology, he will map and manipulate brain neural circuits in a mouse model. Using a cutting-edge rabies virus-mediated tracing system, he will determine whether structural and functional impairments of primary projection neurons that connect the cortex to the deeper layer of the hippocampus contribute to the formation of autism-specific neural circuits. If Hoonkyu is successful in determining how such neural circuits are anatomically and functionally altered in animal models of the disorder, it will provide a compelling foundation to develop therapies for children affected by ASD by specifically targeting aberrant neural circuits in the hippocampus.