THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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Targeting Gastrointestinal Deficits in Autism Spectrum Disorder

Many children with Autism Spectrum Disorder (ASD) suffer digestive problems. In the US, the number of children diagnosed with ASD is rising, with 1 in 36 children under the age of eight now affected, representing approximately 800,000 children. Among these affected children, 23% to 70% suffer from gastrointestinal distress and notably, the severity of digestive problems is linked to the severity of their brain-related symptoms. Most research has focused on how ASD affects the brain, where inflammatory conditions are known to increase the number of neurons and certain support cells called glia become "reactive" (more branched), leading brain circuits to malfunction and alter behavior. Despite the pervasiveness and gravity of digestive problems in children with ASD, less attention has been given to how it affects the gut. In this context, the gut has its own nervous system, called the enteric nervous system, made up of sensory neurons, motor neurons and a cell type called glia, which collectively control gut function and express many genes linked to ASD. However, the role of glial cells in the gut of children with ASD remains unclear. Analogous to glia in the brain, I have observed that enteric glia are diverse and may perform defined functions in a manner that parallel their varied role in the brain. Understanding how the gut works differently in children affected with ASD could lead to better treatments for digestive problems and improve their overall quality of life. To address this challenge, I have generated 3D, multi-cellular, miniature human intestine (“mini-guts”) in a dish using ASD patient stem cells. The mini-guts are cellularly and architecturally complex, retaining the same organization and cellular crosstalk present in vivo. With a novel approach I developed, the tissue uniquely maintains the complex genetic background of ASD. While glial cells in gut tissue are different from the brain, I discovered that glial cells in gut organoids derived from children with ASD have undergone increased expression of glial reactivity markers, including transcriptional changes and altered expression of genes related to neuron growth, migration, and nerve synapse integrity. I hypothesize that the observed molecular changes could be due to the formation of reactive glia promoting aberrant neuronal wiring or the formation of beneficial glia attempting to repair ASD gut wiring. In either case, fewer or weaker neuronal synapses in the ASD gut would lead to disruptions that ultimately could cause digestive problems. To discern functional changes in the developing ASD mini guts, I will employ state-of-the-art stem cell technologies, including electrophysiological methods, to pinpoint which cell types are contributing to pathology. If I am successful in discerning whether glial cells are responsible for impaired neuronal wiring in the ASD gut that lead to defects in neuron signaling, it will then be possible to identify druggable targets and therapeutic strategies to alleviate gastrointestinal symptoms in children affected with ASD.