Modelling the Impact of the Autism Gene SCN2A on Retinal Development Using Human Stem Cell-Derived Organoid Models

Jarryll Uy[1], BHSc, Karun Singh[1], PhD,

[1]Department of Laboratory Medicine and Pathobiology, University of Toronto

Introduction: De novo protein-truncating or missense variants in the central nervous system-specific neuronal voltage-gated sodium channel, SCN2A (Nav1.2), is responsible for a range of neurological disorders that includes autism spectrum disorder/intellectual disability (ASD/ID) and visual impairment. While the source of vision disorders in SCN2A patients is thought to be cortical, SCN2A is expressed in many cell types in the eye (eg. retinal ganglion cells and bipolar cells) and in retinal organoids (ROs), suggesting impaired SCN2A function in the retina may contribute to vision disorders. Given that loss-of-function mutations in SCN2A, generally associated with ASD, impair excitatory synaptic transmission in cortical neurons, SCN2A may a play a role in synaptic transmission in the retina. Therefore, we hypothesize that ASD-mutations in SCN2A cause vision disorders by impairing the development and function of retinal synapses.

Methods: I have generated two isogenic human embryonic stem cell lines – one heterozygous for a novel ASD-specific G1744* mutation and one homozygous knock-out (KO), to reveal how complete or partial loss of SCN2A function impacts human retinal development and synaptic function. ROs and cerebral organoids (COs) are an emerging 3D stem cell-derived model that recapitulates most aspects of retinal development and gene expression patterns compared to the human retina and brain in vivo. We first examined the impact SCN2A would have in cortical development using COs given its primary expression in the brain. COs were generated using STEMdiffTM Cerebral Organoid Kit by STEMCELL Technologies and assayed at Day 90, a time of high neuron diversity of maturation, for cytoarchitecture and single-cell RNAseq.

Results: Using single-cell RNAseq, we found cell type-specific changes in developmental trajectories in mutant organoids. Specifically, SCN2A mutant organoids showed reduced proportion of deep- and upper-layer neurons. Conversely, we observe precocious production of DLX+ inhibitory neurons resembling those derived from the caudal ganglionic eminence.

Conclusions: Our results suggest that the loss of SCN2A leads to impaired neuron development and disrupts normal excitatory-inhibitory balance. Given these findings in a cortical forebrain model, it is possible SCN2A may regulate similar aspects in the retina and contribute to the pathophysiology of vision disorders observed in some SCN2A patients.