Toward the Establishment of an In-Vitro Model of Glaucoma Using Human Induced Pluripotent Stem Cells

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Glaucoma is a severe neurodegenerative disease of the retina, leading to eventual irreversible blindness. A crucial element in the pathophysiology of all forms of glaucoma is the death of retinal ganglion cells (RGCs), a population of CNS neurons with their soma in the inner retina and axons fasciculating together to form the optic nerve. Retinal astrocytes have also been associated with glaucomatous neurodegeneration, although the direct or indirect role for these cells in the disease process remains unclear. Human induced pluripotent stem cells (iPSCs) provide a promising approach to develop cellular models to study such neurodegenerative diseases in vitro. Directed differentiation of several somatic cell types from human iPSCs have been successfully achieved with great implications for disease modeling and cell replacement strategies. Using existing lines of iPSCs, efforts were undertaken to successfully differentiate and characterize RGCs and astrocytes, the affected cell types in glaucoma. Using a previously described protocol, these cells were directed to differentiate toward a retinal fate through a step-wise process that proceeds through all of the major stages of neuroretinal development. The differentiation of RGCs was observed within the first forty days of differentiation whereas astrocytes were observed only after at least 70 days of differentiation. Using techniques including immunocytochemistry and RT-PCR, the individually derived somatic cells types were characterized by the expression of developmentally associated transcription factors specific to each cell type. Further approaches were undertaken to characterize the morphological differences between RGCs and other neuroretinal cell types derived in the process. Overall, this study demonstrates a robust method to derive the complex cell types associated with glaucoma, with prospects for further investigations into the developmental progression of the disease.

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