Generating patient-specific iPSC-derived choroidal endothelium to study and treat macular degeneration

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Age-related macular degeneration (AMD) is the leading cause of incurable blindness in western countries. In the United States alone, there are two million people with advanced AMD and an additional seven million with early AMD. Individuals with advanced AMD have severely impaired central vision, making everyday activities very difficult. Although AMD is a common blinding disease, it is not well understood how the disease progresses. There is strong evidence showing that the choroidal vasculature bed behind the retina is the first tissue to degenerate in AMD. Therefore, it is crucial to study these special blood vessels involved in AMD at a cellular level to identify its cause and develop cures to help patients regain their lost vision.

The work described in this dissertation used mouse and human induced pluripotent stem cells (iPSCs) to generate the choroidal vascular tissue behind the retina. Co-culture systems, RNA-seq analysis, and statistical screens were used to identify connective tissue growth factor as the key component required for driving choroidal vascular development. To our knowledge, this work is the first in the field to regenerate the choroidal tissue from control and AMD patient stem cells. The choroidal endothelium generated from patient AMD stem cells also showed disease-like signs, such as increased membrane attack complex formation and cytolysis, indicating that the AMD choroidal endothelium modeled the disease in vitro. Therefore, this work provides an invaluable tool for researchers to perform in depth studies on the choroidal tissue to better understand AMD pathophysiology and develop cell replacement therapies.

Overall, the work presented in this dissertation will push the AMD research field forward by providing a way to directly study AMD patient-specific iPSC-derived choroidal endothelium. In combination with retinal pigment epithelium and photoreceptors, patient-specific choroidal endothelium will make it possible to better understand AMD pathogenesis and to develop autologous cell replacement therapies to rebuild patients’ damaged choroids.

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