Restoration of Aqueous Humor Outflow Following Transplantation of iPSC-Derived Trabecular Meshwork Cells in a Transgenic Mouse Model of Glaucoma

Zhu W (1) , Jain A (2) , Gramlich OW (3) , Tucker BA (3) , Sheffield VC (4) , Kuehn MH (1)

1 Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, Iowa, United States 2Center for the Prevention and Treatment of Visual Loss, Iowa City Veterans Affairs Medical Center, Iowa City, Iowa, United States.
2 Department of Pediatrics, University of Iowa, Iowa City, Iowa, United States.
3 Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, Iowa, United States.
4 Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, Iowa, United States 3Department of Pediatrics, University of Iowa, Iowa City, Iowa, United States 4Howard Hughes Medical Institute, University of Iowa College of Medicine, Iowa City, Iowa, United States.

PURPOSE: Primary open-angle glaucoma (POAG) is particularly common in older individuals and associated with pathologic degeneration of the trabecular meshwork (TM) . We have shown previously that transplantation of induced pluripotent stem cell (iPSC) derived TM cells restores aqueous humor dynamics in young transgenic mice expressing a pathogenic form of human myocilin (Tg-MYOCY437H) . This study was designed to determine if this approach is feasible in older mice with more pronounced TM dysfunction.

METHODS: Mouse iPSC were differentiated toward a TM cell phenotype (iPSC-TM) and injected into the anterior chamber of 6-month-old Tg-MYOCY437H or control mice. IOP and aqueous humor outflow facility were recorded for up to 3 months. Transmission electron microscopy, Western blot, and immunohistochemistry were performed to analyze TM morphology, quantify endoplasmic reticulum (ER) stress, and assess TM cellularity.

RESULTS: A 12 weeks after transplantation, IOP in iPSC-TM recipients was statistically lower and outflow facility was significantly improved compared to untreated controls. The number of endogenous TM cells increased significantly in iPSC-TM recipients along with the appearance of TM cells immmunopositive for a marker of cellular division. Morphologically, transplantation of iPSC-TM preserves ER structure 12 weeks after transplantation. However, myocilin and calnexin expression levels remain elevated in transplanted eyes of these 9-month-old Tg-MYOCY437H mice, indicating that ER stress persists within the TM.

CONCLUSIONS: Transplantation of iPSC-TM can restore IOP and outflow facility in aged Tg-MYOCY437H mice. This type of stem cell-based therapy is a promising possibility for restoration of IOP control in some glaucoma patients.

Invest Ophthalmol Vis Sci. 2017 Apr 1;58(4) :2054-2062. doi: 10.1167/iovs.16-20672.

http://www.ncbi.nlm.nih.gov/pubmed/28384726