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Tissue Plasminogen Activator Treatment of Juvenile Open Angle Glaucoma

Glaucoma is a group of eye diseases causing irreversible vision loss; it is the second leading cause of blindness worldwide. A common disease form is open-angle glaucoma (OAG) and the pathogenesis is unclear for the majority of cases. The most common genetic mutation associated with primary OAG occurs within the MYOC gene, which encodes the myocilin protein. While the precise intraocular function of this protein is unclear, mutations are known to cause damage within trabecular meshwork (TM) cells leading to severe intraocular pressure elevation early in life. Prior studies found a significant reduction in the
expression of matrix metalloproteinases (MMP-2 and MMP-9) in transgenic TM cells expressing the Tyr437His (Y437H) mutation in the MYOC gene. Our research into steroid-induced OAG showed that intraocular administration of tissue plasminogen activator (tPA) can enhance the expression of Mmp-2, Mmp-9 and Mmp-13 in the TM tissue of mice. tPA is a commercially available fibrinolytic agent used in post-stroke therapy. Our research sought to determine whether there are baseline alterations in the expression of fibrinolytic pathway components and MMPs in the TM tissue of a transgenic mouse model (Tg-MYOCY437H) of the disease. Following intravitreal injections of the tPA protein, outflow facility was measured and gene expression changes were assessed. This approach was compared to a previously published treatment using topical administration of sodium phenylbutarate (PBA). Our results show that Tg-MYOCY437H mice display a significant reduction in the TM expression of Mmp-2 and Mmp-9. Furthermore, though there was no reduction in tPA expression, its administration enhanced Mmp-9 expression and increased outflow facility. Finally, our treatment was as effective as PBA in this mouse model. Therefore, these experiments have widened the applicability of tPA to a model of genetic OAG. Future experiments may test this treatment in human cell models and larger scale animals.

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