

Aqueous Outflow Biology and Therapeutics: What's New?

P. Kaufman

Ophthalmology and Visual Sciences, University of Wisconsin, Madison, USA

Glaucoma pharmacotherapy has traditionally relied on the use of small molecules acting as mediators or at receptors in signaling pathways to enhance aqueous humor outflow or decrease aqueous inflow in order to lower IOP. Directly targeting the trabecular meshwork (TM) with agents that disrupt the actin cytoskeleton, cellular contractility and adhesions, and extracellular matrix (ECM) interactions is an effective strategy for enhancing outflow through the TM in important preclinical models.

Transforming growth factor beta (TGF β)-2 is thought to contribute to glaucoma pathogenesis by increasing ECM production and tissue rigidity in the TM. In monkey and pig organ culture systems TGF β -2 treatment led to increased cochlin levels in the tissue and media. Cochlin was shown by proteomics analysis of trabeculectomy samples from glaucomatous and age-matched normal donors to be uniquely present in glaucomatous TM. It may play a causal role in the development of IOP elevation by altering TM architecture and rendering components like collagen more susceptible to degradation and collapse. Cochlin overexpression alone may be sufficient to elevate IOP, and provide new experimental models that more closely match the actual pathophysiology of human glaucoma, and facilitate anterior and posterior segment physiology and pharmacology studies.

Viral vectors have been used extensively in animal and human gene therapy. Recent work has demonstrated that scAAV and FIV vectors can produce robust and long-term (>2 years) expression of reporter genes in the primate outflow pathway in vivo, with low immunogenicity. These vectors have potential as experimental and clinical gene transfer agents.