Transforming Growth Factor-β2 Attenuates Bradykinin B2 Receptor Expression in Human Trabecular Meshwork Cells

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INTRODUCTION

Glaucoma is a leading cause of blindness, projected to affect nearly 80 million people worldwide by the year 2020.1 In the US, it is estimated that nearly 2 million individuals age 45 years and older have primary open angle glaucoma (POAG), the most prevalent form of the disease.2 Current treatment options for patients with POAG are aimed at lowering chronically elevated intraocular pressure (IOP), a poorly-understood risk factor associated with POAG.

In healthy eyes, normal IOP is maintained through balanced production and outflow of aqueous humor (AH). In adults, the majority (>50%) of AH exits the eye through the trabecular meshwork (TM),3 a process considered to be a significant contributor to abnormal elevation of IOP in POAG patients. The mechanism by which this occurs remains poorly defined.

In the anterior chamber of POAG patients, the levels of transforming growth factor (TGF)-β2 in AH is aberrantly elevated compared to healthy eyes.1 Conversely, perfusion of TGF-β2 through cultured human, bovine, and porcine anterior segments significantly elevates IOP ex vivo by increasing outflow resistance through the TM.4,5 In vitro, exogenous addition of TGF-β2 has been shown to increase content of a number of factors associated with elevated IOP, including extracellular matrix components as well as endothelin-1.6,7 However, there remains a paucity of data on the complete mechanism by which TGF-β2 promotes aberrantly elevated IOP.

In this study, we investigated the effects of TGF-β2 signaling on IOP and B2 receptor expression in porcine anterior segments and human TM cells, respectively.

METHODS

Cell Culture: Primary human TM (hTM) cells were harvested from discarded human cataractous eyes and cultured as described previously.8-10 SV40-transformed TM cells derived from a male glaucomatous patient (GTM3) and a male non-glaucomatous control (NTM5) were a kind gift from Dr. Gordon Faralli (University of Wisconsin-Madison) for their assistance with anterior segment perfusion experiments. This work was supported, in part, by grants from the American Glaucoma Society, the American Heart Association’s Great Lakes Affiliate and unrestricted grant support from Research to Prevent Blindness, Inc. (USA).

RESULTS

Activation of the bradykinin (Bk) receptor B2 has recently been shown to lower IOP in ocular hypertensive non-human primates.4-8 By contrast, TGF-β2 is known to modulate BK-associated signaling pathways.9 However, the relationship between TGF-β2 and BK signaling in TM cells remains undefined. In this study, we investigated the effects of TGF-β2 signaling on IOP and receptor expression in porcine anterior segments and human TM cells, respectively.

REFERENCES