

Regulation of Plasticity and Fibrogenic Activity of Trabecular Meshwork Cells by Rho GTPase Signaling

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Glaucoma, a prevalent blinding disease is commonly associated with increased intraocular pressure due to impaired aqueous humor (AH) drainage through the trabecular meshwork (TM). Although increased TM tissue contraction and stiffness in association with accumulation of extracellular matrix (ECM) are believed to be partly responsible for increased resistance to AH outflow, the extracellular cues and intracellular mechanisms regulating TM cell contraction and ECM production are not well defined.

This study tested the hypothesis that sustained activation of Rho GTPase signaling induced by lysophosphatidic acid (LPA), TGF- β and connective tissue growth factor (CTGF) influences TM cell plasticity and fibrogenic activity which may eventually impact resistance to AH outflow. Various experiments performed using human TM cells revealed that constitutively active RhoA (RhoA^{V14}), TGF- β 2, LPA and CTGF significantly increase the levels and expression of Fibroblast Specific Protein-1 (FSP-1), α -smooth muscle actin (α SMA), collagen-1A1 and secretory total collagen, as determined by q-RT-PCR, immunofluorescence, immunoblot, flow cytometry and the Sircol assay.

Significantly, these changes appear to be mediated by Serum Response Factor (SRF), myocardin-related transcription factor (MRTF-A), Slug and Twist-1, which are transcriptional regulators known to control cell plasticity, myofibroblast generation/activation and fibrogenic activity.

Additionally, the Rho kinase inhibitor-Y27632 and anti-fibrotic agent-pirfenidone were both found to suppress the TGF- β 2-induced expression of α SMA, FSP-1 and collagen-1A1. Taken together, these observations demonstrate the significance of RhoA/Rho kinase signaling in regulation of TM cell plasticity, fibrogenic activity and myofibroblast activation, events with potential implications for the pathobiology of elevated intraocular pressure in glaucoma patients.

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