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Wnt and inflammatory pathway mediated differential expression of water channel protein in glaucomatous trabecular meshwork

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Abstract

Aquaporin (AQP) is an integral membrane protein which helps in the transport of water and small solutes [1]. The functions of AQP0 and AQP6 have not been studied in Glaucomatous trabecular meshwork. Intra-ocular Pressure (IOP) is regulated by Wnt signaling but till date no report has been published in patient trabecular meshwork tissue [2]. Effect of GSK3β (a Wnt signaling regulator) on IFNβ, an important immune-modulatory cytokine, has not been studied in Glaucoma. This study explores the cross talk between Wnt signaling and inflammatory pathway in context of water channel proteins' expression. Trabecular meshwork tissue after glaucoma surgery was collected with prior approval of the Institutional Ethics Committee and written informed consent. AXIN2, IFNβ, IL6, AQP0, AQP6 and AQP9 gene expression analysis was done in trabecular meshwork tissue from glaucoma filtration surgery patients (n=32) and cadaveric controls (n=20). Human Trabecular Meshwork (HTM) cells, cultured in DMEM with 10% FBS and 1% PSA were treated with Wnt activator (AZD2858; GSK3β inhibitor) or inhibitor (XAV939; β-catenin inhibitor) and analysed after 24 hrs for expression of the same genes. In patient TM samples, we observed a downregulation of AQP0, AQP9 ($p=0.002$) and significant gain in AQP6 ($p\leq0.03$) and IL6 ($p\leq0.04$) associated with increased Axin2 ($p=0.04$) and reduced IFNβ (0.01) when compared to controls. Activation of Wnt pathway (using chemical activator AZD2858) in HTM culture mimics the patient data demonstrating a reduction in AQP0, AQP9 and IFNβ expression, but significantly induced Axin2, AQP6 and IL6. Wnt inhibitor XAV939 reversed the same observations. This is the first study that illustrates the role for water channel proteins' expression such as AQP0, AQP6 and AQP9 in glaucomatous trabecular meshwork. An inverse correlation was observed between expression of AXIN2 (Up-regulated) and IFNβ (down-regulated) in Glaucomatous trabecular meshwork and HTM cells which may be associated with inhibition of GSK3β. The data reveals interaction between Wnt and IFNβ as a possible mechanism that regulates expression of critical AQPs i.e. AQP 0, 6 and 9 with subsequent loss of hydrostatic and osmotic balance in glaucoma. Our observations suggest feasible role of Wnt inhibitors as therapy for glaucoma.

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