Impaired TRPV4-eNOS signaling in trabecular meshwork elevates intraocular pressure in glaucoma

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Primary Open Angle Glaucoma (POAG) is the most common form of glaucoma that leads to irreversible vision loss. Dysfunction of trabecular meshwork (TM) tissue, a major regulator of aqueous humor (AH) outflow resistance, is associated with intraocular pressure (IOP) elevation in POAG. However, the underlying pathological mechanisms of TM dysfunction in POAG remain elusive. In this regard, transient receptor potential vanilloid 4 (TRPV4) cation channels are known to be important Ca2+ entry pathways in multiple cell types. Here, we provide direct evidence supporting Ca2+ entry through TRPV4 channels in human TM cells and show that TRPV4 channels in TM cells can be activated by increased fluid flow/shear stress. TM-specific TRPV4 channel knockout in mice elevated IOP, supporting a crucial role for TRPV4 channels in IOP regulation. Pharmacological activation of TRPV4 channels in mouse eyes also improved AH outflow facility and lowered IOP. Importantly, TRPV4 channels activated endothelial nitric oxide synthase (eNOS) in TM cells, and loss of eNOS abrogated TRPV4-induced lowering of IOP. Remarkably, TRPV4-eNOS signaling was significantly more pronounced in TM cells compared to Schlemm's canal cells. Furthermore, glaucomatous human TM cells show impaired activity of TRPV4 channels and disrupted TRPV4-eNOS signaling. Flow/shear stress activation of TRPV4 channels and subsequent NO release were also impaired in glaucomatous primary human TM cells. Together, our studies demonstrate a central role for TRPV4-eNOS signaling in IOP regulation. Our results also provide evidence that impaired TRPV4 channel activity in TM cells contributes to TM dysfunction and elevated IOP in glaucoma.

Proc Natl Acad Sci U S A. 2021 Apr 20;118(16) :e2022461118. doi: 10.1073/pnas.2022461118.

PMID: 33853948