Cellular crosstalk regulates the aqueous humor outflow pathway and provides new targets for glaucoma therapies

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Primary congenital glaucoma (PCG) is a severe disease characterized by developmental defects in the trabecular meshwork (TM) and Schlemm's canal (SC) , comprising the conventional aqueous humor outflow pathway of the eye. Recently, heterozygous loss of function variants in TEK and ANGPT1 or compound variants in TEK/SVEP1 were identified in children with PCG. Moreover, common variants in ANGPT1and SVEP1 have been identified as risk alleles for primary open angle glaucoma (POAG) in GWAS studies.

Here, we show tissue-specific deletion of Angpt1 or Svep1 from the TM causes PCG in mice with severe defects in the adjacent SC. Single-cell transcriptomic analysis of normal and glaucomatous Angpt1 deficient eyes allowed us to identify distinct TM and SC cell populations and discover additional TM-SC signaling pathways. Furthermore, confirming the importance of angiopoietin signaling in SC, delivery of a recombinant ANGPT1-mimetic promotes developmental SC expansion in healthy and Angpt1 deficient eyes, blunts intraocular pressure (IOP) elevation and RGC loss in a mouse model of PCG and lowers IOP in healthy adult mice. Our data highlight the central role of ANGPT1-TEK signaling and TM-SC crosstalk in IOP homeostasis and provide new candidates for SC-targeted glaucoma therapy.

Nat Commun. 2021 Oct 18;12(1) :6072. doi: 10.1038/s41467-021-26346-0.

PMID: 34663817 PMCID: PMC8523664 DOI: 10.1038/s41467-021-26346-0