Cooperation of Angiopoietin-2 and Angiopoietin-4 in Schlemm's Canal Maintenance

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PURPOSE: Defects in the iridocorneal angle tissues, including the trabecular meshwork (TM) and Schlemm's canal (SC) , impair aqueous humor flow and increase the intraocular pressure (IOP) , eventually resulting in glaucoma. Activation of endothelial tyrosine kinase receptor Tie2 by angiopoietin-1 (Angpt1) has been demonstrated to be essential for SC formation, but roles of the other two Tie2 ligands, Angpt2 and Angpt4, have been controversial or not yet characterized, respectively.

METHODS: Angpt4 expression was investigated using genetic cell fate mapping and reporter mice. Congenital deletion of Angpt2 and Angpt4 and tamoxifen-inducible deletion of Angpt1 in mice were used to study the effects of Angpt4 deletion alone and in combination with the other angiopoietins. SC morphology was examined with immunofluorescent staining. IOP measurements, electron microscopy, and histologic evaluation were used to study glaucomatous changes.

RESULTS: Angpt4 was postnatally expressed in the TM. While Angpt4 deletion alone did not affect SC and Angpt4 deletion did not aggravate Angpt1 deletion phenotype, absence of Angpt4 combined with Angpt2 deletion had detrimental effects on SC morphology in adult mice. Consequently, Angpt2-/-;Angpt4-/- mice displayed glaucomatous changes in the eye. Mice with Angpt2 deletion alone showed only moderate SC defects, but Angpt2 was necessary for proper limbal vasculature development. Mechanistically, analysis of Tie2 phosphorylation suggested that Angpt2 and Angpt4 cooperate as agonistic Tie2 ligands in maintaining SC integrity.

CONCLUSIONS: Our results indicated an additive effect of Angpt4 in SC maintenance and Tie2 activation and a spatiotemporally regulated interplay between the angiopoietins in the mouse iridocorneal angle.

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