Another Piece of the Puzzle: MYOC and Myocilin Glaucoma

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MYOC, encoding the secreted protein myocilin, was the first gene linked to familial forms of primary open angle glaucoma (POAG).[1] "Myocilin glaucoma" is characterized by very high eye pressures due to reduced aqueous outflow through the trabecular meshwork and Schlemm's canal. Pathogenic variants are thought to lead to a toxic gain-of-function due to misfolding and intracellular aggregation of the mutant protein.

A large number of *MYOC* mutations are now recognized (http://www.myocilin.com, in the public domain), primarily located within the C-terminal olfactomedin (OLF) domain. Recently the crystal structure of the MYOC OLF domain was solved, revealing its membership in the five-bladed β-propeller family. This structure is best known as a hub for protein–protein interactions.[2]

Two proteins that interact specifically with the normal MYOC OLF domain have been identified to date: FLOT1 and OLFM3. In this issue of *Investigative Ophthalmology & Visual Science*, Joe et al.[3] report use of a shotgun proteomic approach for discovery of new MYOC interacting partners. They identify TIMP3 as the third MYOC OLF binding protein. Significantly, TIMP3 did not bind to a MYOC OLF mutant.

A member of the tissue inhibitor of metalloproteinase family, TIMP3 inhibits the activity of matrix metalloproteinases (MMPs), a family of enzymes with broad roles in tissue morphogenesis, remodeling, and disease. MMP cleavage of extracellular matrix substrates has been implicated in facilitation of aqueous outflow. In a seeming paradox, MYOC markedly enhanced the inhibitory activity of TIMP3 toward MMP2, a representative MMP that is abundant in the trabecular meshwork. However, TIMP3 also has functions that are independent of its MMP inhibitory activity (e.g., it serves as a potent angiogenesis inhibitor that is mutated in Sorsby's fundus dystrophy).[4]

Despite intensive effort over the last two decades, the function of MYOC in ocular health is still not understood. It seems likely that identification of MYOC OLF binding partners and elucidation of their functional relevance will provide important clues toward solving the puzzle.

References

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