

# 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).<sup>1</sup> “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  $\beta$ -propeller family. This structure is best known as a hub for protein–protein interactions.<sup>2</sup>

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.<sup>3</sup> 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).<sup>4</sup>

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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