

The Histopathological Findings of the Trabecular Outflow Pathway in Primary Open-Angle Glaucoma

What likely contributes to the pathogenesis of this disease?

BY HAIYAN GONG, MD, PhD

Primarily open-angle glaucoma (POAG) is a multifaceted optic neuropathy characterized by the loss of optic nerve axons and retinal ganglion cells. A primary risk factor for the development and progression of this disease is elevation of the IOP¹ resulting from increased resistance to aqueous humor outflow² in the trabecular meshwork (TM). The trabecular outflow pathway is the major drainage pathway of aqueous humor. The biological changes in cells and the extracellular matrix (ECM) that compromise the trabecular drainage pathway contribute to an increase in IOP and the pathogenesis of POAG. Seven histopathological findings are associated with POAG.

No. 1. A DECREASE IN TM CELLULARITY

A progressive age-related loss of trabecular cells has been reported in healthy eyes, but cellular loss beyond that of normal aging has been found in the TM of eyes with POAG (Figure 1A).³⁻⁵ The observed fusion of trabecular beams in eyes with advanced POAG may result from adhesions between denuded portions of adjacent trabecular beams (Figure 1B).

No. 2. AN ABNORMAL ACCUMULATION OF ECM

An increase in the amount of ECM or “plaque material” in the juxtacanalicular connective tissue (JCT) has been reported in eyes with POAG (Figure 1C and 1D), whether or not they are undergoing medical treat-

ment.^{6,7} This change is associated with increasing severity of optic nerve damage,⁸ but morphometric studies of such specimens have been unable to account for the greater outflow resistance in POAG. Numerous studies

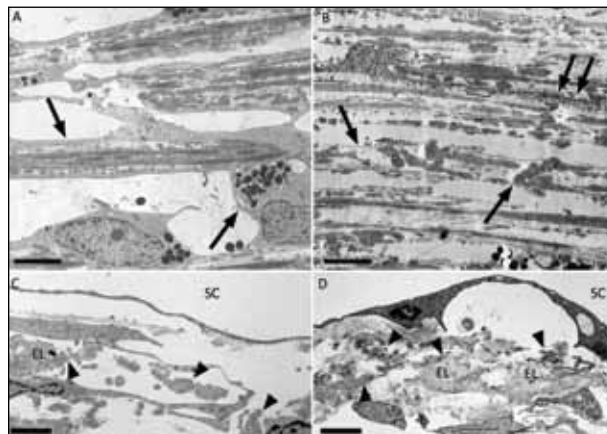


Figure 1. Morphological changes in the TM in POAG eyes compared to healthy eyes. Endothelial cells lined the trabecular beams (arrows) in healthy eyes (A). A loss of cellularity and more “naked” trabecular beams (arrows) were visible in POAG eyes. The decrease in cellularity might also cause the fusion of trabecular beams to one another (double arrows; B). Elastic fibers (EL) and sheath-derived plaques (arrowheads) were visible in the JCT region of a human eye (C). Compared to an age-matched healthy eye, a significant increase in sheath-derived plaques was evident in the JCT region of a POAG eye (arrowheads). A&B scale bar = 2 μ m; C&D scale bar = 5 μ m.

“[Research] findings strongly suggest that the obstruction of collector channels contributes to increased outflow resistance.”

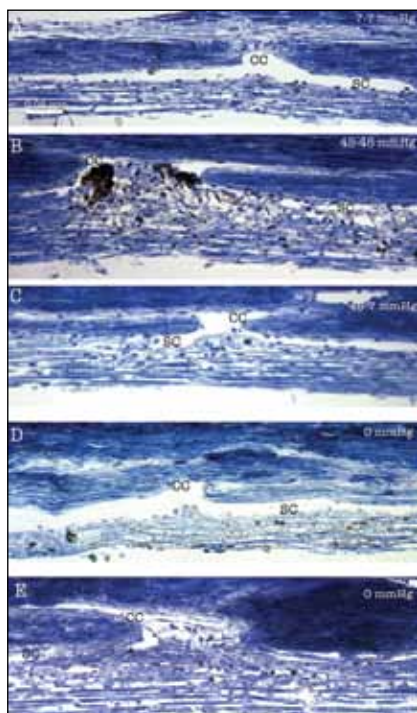
have demonstrated that transforming growth factor- β 2 (TGF- β 2) is elevated in the aqueous humor of patients with POAG.⁹⁻¹³ High levels of TGF- β 2 promote ECM formation and inhibit ECM degradation in the TM, both of which contribute to an increase in IOP.¹⁴⁻¹⁸

No. 3. A DECREASE IN GIANT VACUOLES AND PORES

Eyes with POAG exhibit fewer giant vacuoles¹⁹ and pores^{20,21} in the inner wall of Schlemm canal (SC) than do healthy eyes. This finding suggests that the endothelial cells lining SC lose their ability to passively permit aqueous humor to enter the lumen of the canal, possibly contributing to increased outflow resistance in eyes with POAG. It was recently reported that TM stiffness is significantly higher in glaucomatous eyes than in healthy eyes,²² which may account in part for the decreased ability of the inner-wall cells to form the giant vacuoles and pores.

No. 4. THE COLLAPSE OF SC

Increasing IOP leads to the progressive collapse of SC (Figure 2A-2C).^{23,24} As SC crumples, the outflow resistance grows, and the IOP rises even more.^{25,26} The dimensions of SC in eyes with POAG are significantly smaller than in healthy eyes (Figures 2D-2E and 3),²⁷ a finding recently confirmed by spectral-domain optical coherence tomographic assessment in patients with POAG.²⁸ The shrinking of SC accounted for nearly half of the decrease in outflow facility observed in eyes with POAG.²⁷



Additionally, SC became smaller after successful filtration surgery, most likely due to underperfusion of the TM.²⁹ The decrease in the size of SC after successful filtration surgery could make glaucoma more difficult to control if the filter ultimately fails.

No. 5. HERNIATIONS BLOCK THE COLLECTOR CHANNEL OSTIA

When the IOP rises, the TM extends toward the outer wall of SC and leads to the progressive collapse of SC.^{23,24} Because there is no outer wall of SC in the region of the collector channel (CC) ostia, the JCT and inner-wall tissue herniate into the CC ostia.²⁴ Under experimental conditions in healthy eyes, the herniations were reversible when the IOP decreased from high to normal levels.³⁰ Permanent herniations were common among eyes with POAG, even when the eyes were fixed at zero pressure³¹ (also H.G., unpublished data, 2013). The obstruction of CCs was also detected in patients with POAG through an evaluation of the fluorescein egress from SC to the episcleral veins and blood reflux from the episcleral veins to SC.³² These findings strongly suggest that the obstruction of CCs contributes to increased outflow resistance.

No. 6. A SHORTER SCLERAL SPUR

A shorter scleral spur was reported in eyes with POAG compared with healthy eyes (Figure 3).^{33,34} Upon contraction of the ciliary muscle, the scleral spur moves

Figure 2. Collapse of SC and herniation into the CC ostia with increased IOP in healthy human eyes and in a POAG eye. When a healthy human eye was continually perfused at 7 mm Hg (normal IOP for an enucleated eye without episcleral venous pressure), SC was open, and no herniation into the CC ostium was visible (A). When the eye was continually perfused at 45 mm Hg, SC collapsed, and the TM herniated into the CC ostium (B). When the eye was first perfused at 45 mm Hg and then the IOP was reduced to 7 mm Hg, the herniation into the CC ostia observed at 45 mm Hg in Figure 2B was reversed; only deformation of the TM was seen facing the CC ostium region. SC was wider in this eye (C) than in the one perfused continually at 45 mm Hg (Figure 1B). When a healthy eye was fixed at 0 mm Hg, SC was open, and the herniation was not visible at the CC ostium (D). In comparison, when an eye with POAG was fixed at 0 mm Hg, a collapse of SC adjacent to both sides of the CC ostium with focal adhesions between the inner and outer walls of SC and herniations of the inner wall and JCT into the CC ostia was observed. Scale bar = 25 μ m.

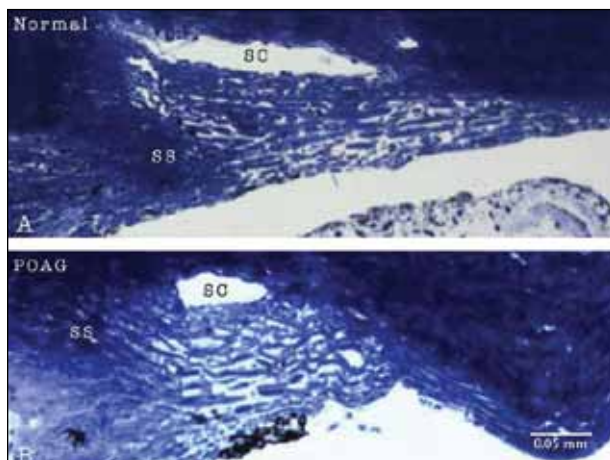


Figure 3. Compared to healthy eyes (A), the scleral spur (SS) is shorter in POAG eyes (B). The dimensions of SC are significantly smaller in POAG eyes than in healthy eyes.

a critical distance posteriorly, causing the TM to bow inward and holding the SC open in healthy eyes. The scleral spur in eyes with POAG may be too short to hold SC open.³⁵

No. 7. A REDUCTION IN ACTIVE OUTFLOW AREA

Outflow is segmental in healthy eyes. The active outflow area decreases in eyes with POAG compared to age-matched normal eyes. More continuous and thicker basement membranes observed along the inner wall of SC, increased ECM deposition in the JCT, and obstruction of the CC ostia by herniations might contribute to the reduction in active outflow areas and outflow facility in POAG.³⁶

CONCLUSION

This short article summarizes the histopathological findings in the trabecular outflow pathway of eyes with POAG. Some of the changes are secondary to the elevation in IOP, but all of them are likely to contribute to the pathogenesis of POAG to some extent. ■

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