Primary 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 IOP resulting from increased resistance to aqueous humor outflow 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). 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 juxtaocular microvascular connective tissue (JCT) has been reported in eyes with POAG (Figure 1C and 1D), whether or not they are undergoing medical treatment. This change is associated with increasing severity of optic nerve damage, but morphometric studies of such specimens have been unable to account for the greater outflow resistance in POAG. Numerous studies...
have demonstrated that transforming growth factor-β2 (TGF-β2) is elevated in the aqueous humor of patients with POAG.9-13 High levels of TGF-β2 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 pores20,21 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...
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.33

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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