

PREVENTING POSTOPERATIVE FIBROSIS

A look at different approaches to managing postoperative fibrosis after glaucoma surgery.



BY IAN PITHA, MD, PhD

Fibrosis is an impediment to any glaucoma surgery that aims to lower IOP by diverting aqueous fluid from the anterior chamber to the subconjunctival or supra-Tenon space. We surgeons who treat glaucoma attempt to control this process with a meticulous surgical technique, by applying antifibrotic medications at the time of surgery, and by controlling inflammation during the postoperative period. Despite these efforts and significant advances in our understanding of the molecular mechanisms of fibrosis, we are not yet able to control conjunctival fibrosis adequately and must deal with the complications of inadequate wound healing and excessive fibrosis.

Fibrosis results from an overly vigorous and unchecked healing response that is influenced by external and internal factors. Healing occurs in stages, and it begins the instant a surgical incision is made. The acute stages of coagulation and inflammation occur over minutes to days, whereas the proliferative and remodeling stages occur over days to weeks or longer. Although various cell types are involved in fibrosis, the workhorse of wound remodeling and collagen deposition is the fibroblast, which plays an important role in creating and remodeling extracellular tissue.

Glaucoma filtration surgery produces several unique stimuli to fibroblast activation and fibrosis. Aqueous humor in the postoperative period, and especially the aqueous humor of glaucoma patients, contains factors such as transforming growth factor beta that promote fibrosis. Additionally, seminal work by Wilcox and Kadri¹ showed that bleb capsular thickness is directly related to the radius of curvature of a given bleb, suggesting that wall tension and biomechanical factors directly influence bleb fibrosis.

Our job as glaucoma doctors who perform filtration surgery has been to combat these fibrotic stimuli in order to create a functional outlet for pressure reduction. Although we have tools to help us, including mitomycin C (MMC), 5-fluorouracil (5-FU), and steroids, they are inadequate

to promote healing while avoiding the complications associated with impaired healing, such as bleb leaks and endophthalmitis. This article discusses several strategies that may alter our approach to fibrosis prevention and management.

BRINGING PRECISION MEDICINE TO FILTRATION SURGERY

Risk for fibrosis is multifactorial, but we recognize that certain patients are at higher risk of scarring than others. Different patient characteristics such as age, sex, race, history of glaucoma eye drop use, overall health, and glaucoma all factor into our internal assessment of a patient's *a priori* risk for fibrosis after glaucoma surgery.

AT A GLANCE

- ▶ Fibrosis results from an overly vigorous and unchecked healing response that is influenced by external and internal factors.
- ▶ Fibrosis is an impediment to any glaucoma surgery that aims to lower IOP by diverting aqueous fluid from the anterior chamber to the subconjunctival or supra-Tenon space.
- ▶ A number of promising approaches have been explored to control fibrosis while allowing the necessary process of wound healing to occur, although many have yet to achieve widespread clinical use.



"AS OUR UNDERSTANDING OF CONJUNCTIVAL FIBROSIS AND THE POTENTIAL APPROACHES TO CONTROL THIS PROCESS DEVELOP, WE CAN START TO ENVISION A FUTURE WHEN WE WILL BE ABLE TO ACCURATELY RISK STRATIFY OUR PATIENTS FOR POSTOPERATIVE FIBROSIS AND TAILOR THERAPY TO PREVENT POSTOPERATIVE SCARRING AND OPTIMIZE PATIENT OUTCOMES."

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But what if we had a better way to risk stratify our patients? Yu-Wai-Man et al² approached this question by comparing the molecular gene expression signatures of conjunctival fibroblasts isolated from patients with scarred trabeculectomy blebs versus those of patients with functional blebs. The investigators uncovered a set of genes that were selectively upregulated and downregulated in fibrotic versus nonfibrotic conjunctivas. These findings give insight into the molecular processes that underlie conjunctival fibrosis and prompt the question of whether we can use genetic markers to risk stratify patients for conjunctival fibrosis, which could ultimately inform surgical and post-surgical strategies.³

RADIATION EXPOSURE

It has long been known that radiation exposure inhibits the inflammatory and proliferative phases of wound healing. In many cases, impaired wound healing is a complication of radiation exposure, but there is an opportunity to use this activity to our advantage in glaucoma filtration surgery.

Specific sources of beta-irradiation have long half-lives and permit delivery of focal irradiation with minimal tissue penetration. Strontium-90 has been used to prevent pterygium recurrence because of the isotope's minimal tissue penetration, which reduces the likelihood of damaging untargeted ocular structures.⁴ Beta-irradiation exposure has been associated with complications such as scleral thinning, malacia, and ulceration. In glaucoma surgery, beta-irradiation has several potential advantages compared with antimetabolite use: (1) beta-irradiation allows focal delivery of a radiation dose over the conjunctiva without any potential leakage and (2) a given probe can be reused

many times without the need for recalibration (the half-life of strontium-90 is 28 years).

Promising results in rabbit studies led to clinical studies, including a Cochrane review that was published in 2012.⁵ Those authors concluded that beta-irradiation showed promise over trabeculectomy alone but should be compared with current antimetabolites. To date, there have been several such comparisons, but no long-term, randomized studies are available to guide the clinical adoption of beta-irradiation.

SUSTAINED DELIVERY OF ANTIFIBROTICS

MMC is delivered in a pulsed manner but has a sustained effect. In 1993, Khaw et al⁶ demonstrated that 5 minutes of intraoperative MMC treatment (0.4 mg/mL) reduced local conjunctival fibroblast proliferation for at least 30 days. This study was performed in rabbits, but it highlights the potent antiproliferative activity of this drug.

There are several potential advantages to pursuing sustained antifibrotic delivery over pulsed MMC application. Different antifibrotics could require sustained delivery in order to reduce fibrosis. It is also possible that delivery of 5-FU and MMC at lower peak dosages would preserve their antifibrotic effect while reducing the risk for medication resistance and toxicity.

A number of potential approaches to sustained delivery of antifibrotic agents, such as paclitaxel, sirolimus, and bevacizumab, have appeared promising in preclinical studies. More recently, sustained-delivery films that release 5-FU and MMC at low doses for 7 to 30 days after trabeculectomy in rabbit models showed promise for reducing drug toxicity while preventing fibrosis and preserving bleb function and architecture.⁷

Lastly, there is significant interest in optimizing sustained delivery of antifibrotic agents in a number of different organ systems. One of these formulations could potentially prove effective in controlling conjunctival fibrosis after filtration surgery as well.

GENETIC MANIPULATION OF FIBROTIC BLEBS

For many years, direct genetic manipulation of tissues has been considered an elegant yet mostly unattainable therapy. In 2004, Heatley et al⁸ used a recombinant adenovirus to deliver the p21 gene to conjunctival tissue. They showed that fibrosis in a monkey model of glaucoma surgery was prevented without any complications associated with MMC injection. More recently, local delivery of siRNA meant to knockdown profibrotic factors in the conjunctiva specifically was accomplished using layer-by-layer nanoparticles and liposomal delivery.^{9,10}

CONCLUSION

Fibrosis continues to be a substantial limiting factor in many glaucoma surgeries. A number of promising approaches have been explored over the years to control fibrosis while allowing the necessary process of wound healing to occur. Many of these approaches have yet to achieve widespread clinical use. Nonetheless, as our understanding of conjunctival fibrosis and the potential approaches

to control this process develop, we can start to envision a future when we will be able to accurately risk stratify our patients for postoperative fibrosis and tailor therapy to prevent postoperative scarring and optimize outcomes. ■

1. Wilcox M, Kadri OA. Force and geometry determine structure and function of glaucoma filtration capsules. *Ophthalmologica*. 2007;221(4):238-243.
2. Yu-Wai-Man C, Owen N, Lees J, et al. Genome-wide RNA-sequencing analysis identifies a distinct fibrosis gene signature in the conjunctiva after glaucoma surgery. *Sci Rep*. 2017;7(1):5644.
3. Yu-Wai-Man C, Khaw PT. Personalized medicine in ocular fibrosis: myth or future biomarkers. *Adv Wound Care (New Rochelle)*. 2016;5(9):390-402.
4. Simsek T, Gunalp I, Atilla H. Comparative efficacy of beta-irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol*. 2001;11(2):126-132.
5. Kirwan JF, Rennie C, Evans JR. Beta radiation for glaucoma surgery. *Cochrane Database Syst Rev*. 2012(6):CD003433.
6. Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz G, McGorray S. Prolonged localized tissue effects from 5-minute exposures to fluorouracil and mitomycin C. *Arch Ophthalmol*. 1993;111(2):263-267.
7. Swann FB, Singh S, Blake D, et al. Effect of two novel sustained-release drug release systems on bleb fibrosis: an in vivo trabeculectomy study in a rabbit model [published online February 21, 2019]. *J Glaucoma*. doi:10.1097/IJC.0000000000001215.
8. Heatley G, Kiland J, Faha B, et al. Gene therapy using p21WAF-1/Cip-1 to modulate wound healing after glaucoma trabeculectomy surgery in a primate model of ocular hypertension. *Gene Ther*. 2004;11(12):949-955.
9. Yu-Wai-Man C, Tagalakis AD, Manunta MD, Hart SL, Khaw PT. Receptor-targeted liposome-peptide-siRNA nanoparticles represent an efficient delivery system for MRTF silencing in conjunctival fibrosis. *Sci Rep*. 2016;6:21881.
10. Seet LF, Tan YF, Toh LZ, et al. Targeted therapy for the post-operative conjunctiva: SPARC silencing reduces collagen deposition. *Br J Ophthalmol*. 2018;102(10):1460-1470.

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