

# The Impact of Wound Healing on Glaucoma Therapy

These processes and the ophthalmologist's ability to control them ultimately determine the long-term success of all glaucoma surgery.

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The processes involved in wound healing and tissue repair ultimately determine the outcome of glaucoma filtration surgery. In the long term, scarring is the main cause of failure with all drainage procedures, whether they use trabeculectomy, nonpenetrating surgery, traditional setons, or new minimally invasive devices (Figure 1). Surgical function may be prolonged through the use of the nonspecific anticancer agents mitomycin C and 5-fluorouracil but with an increased risk of side effects. Bleb leaks, hypotony, and endophthalmitis are more common after the use of antimetabolites<sup>1</sup> with associated vision loss. The search continues for efficacious treatments that are selective for the cellular processes instrumental in wound healing but without toxic side effects.

## WOUND-HEALING PROCESSES

Surgical trauma to tissue layers incites three main processes that are aimed at repair: (1) hemostasis and inflammatory cell activation, (2) fibroplasia and deposition of granulation tissue, and (3) wound remodelling. These processes overlap temporally and are closely interlinked, with one dictating the course of the others. Initial triggers are the damaged cells themselves and the aggregation of platelets, which result in the release of growth factors and cytokines. Monocytes become activated to macrophages, which, together with neutrophils, phagocytose debris. The macrophages also release multiple growth factors, including platelet-derived growth factor, vascular endothelial growth factor (VEGF), transforming growth factor  $\beta$  (TGF- $\beta$ ), and fibroblast growth factor. They recruit and activate fibroblasts to myofibroblasts, with the laying down of collagen and tissue matrix. Over

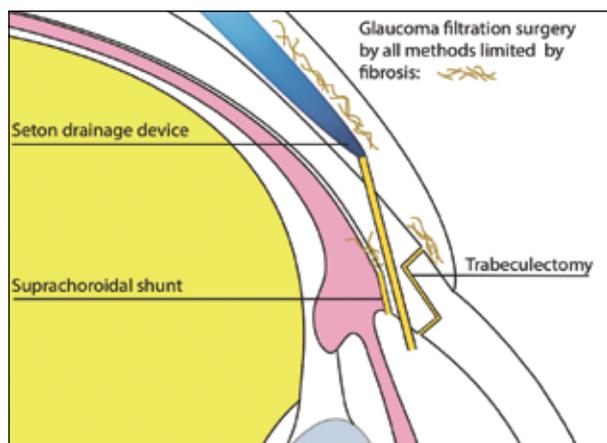


Figure 1. Different procedures for glaucoma filtration surgery. Scarring is the main cause of failure.

time, tissue remodelling occurs via the action of matrix metalloproteinases in conjunction with the development of new blood vessels (angiogenesis).

## SCARRING OR RESTORATION

What determines whether a tissue becomes scarred or resumes its normal histological architecture? Prior tissue and cellular activation (which occurs with long-term topical therapy, particularly using drugs associated with inflammation) or a greater degree and duration of tissue insult increase fibroplasia and reduce the likelihood of resolution without scarring. The phenotype of macrophages changes with time and the extent to which cell corpses are engulfed (efferocytosis).<sup>2</sup> Early on, M1-type macrophages predominate and instigate inflammation.

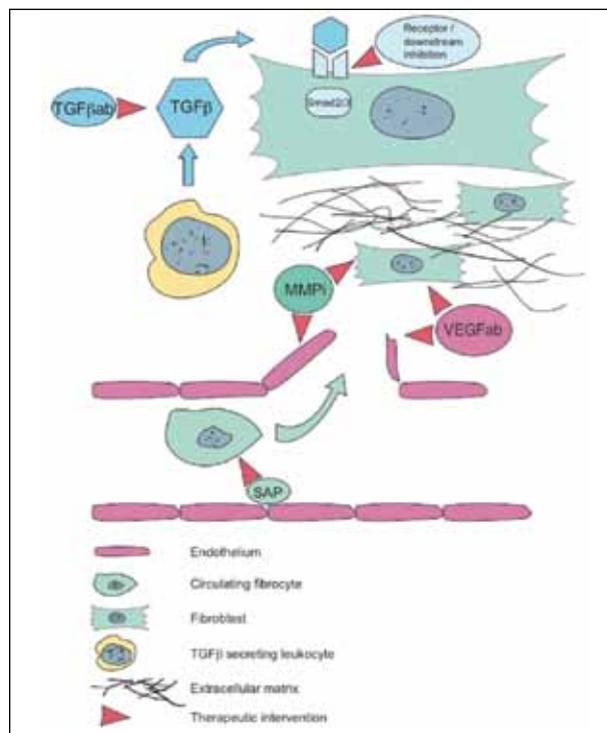
As efferocytosis begins, a switch in phenotype occurs to the M2-type macrophage, which dampens inflammation but is also involved in fibrosis, accompanied by TGF- $\beta$  production. How disorganized the tissue is will govern its fate. It is therefore not surprising that minimal disturbance of tissue with less hemorrhaging produces better surgical outcomes. Chronic, persistent inflammation is a very poor prognostic factor in glaucoma surgery, with a high grading of redness at 6 weeks using the Moorfields bleb grading system ([www.blebs.net](http://www.blebs.net)) being associated with a sixfold higher relative risk of surgical failure.

The balance between the resolution of inflammation and fibrosis is evident in patients with dysregulated immune systems.<sup>3</sup> The inability to resolve inflammation in patients with rheumatoid arthritis, systemic lupus erythematosus, and scleroderma leads to extensive fibrosis. Individuals with ocular inflammatory disease, which may or may not be associated with systemic manifestations, are at far greater risk of bleb failure. Identifying these patients and taking appropriate precautions pre- and postoperatively are crucial to achieving therapeutic success. Despite the routine use of steroids to dampen inflammation in the postoperative period, there is evidence that the preoperative administration of these agents might improve outcomes.<sup>4</sup> This finding is particularly pertinent for uveitic patients.

## DIRECTING HEALING WITH ANTIMETABOLITES

Ophthalmic surgeons commonly use antimetabolites to reduce fibrosis. Care is required, however, because the excessive or incorrect application of these agents leads to tissue necrosis, resulting in bleb leakage and hypotony. When ophthalmologists first began using mitomycin C, they regarded cystic, avascular blebs as inevitable and normal. We postulated that the formation of a ring of scar tissue (the so-called ring of steel), together with aqueous drainage directed anteriorly at the limbus, led to cystic blebs.

Laboratory work has demonstrated that treated fibroblasts can influence the activity of other untreated cells.<sup>5</sup> Furthermore, the focal application of antimetabolites may influence resultant residual fibroblast activity at the edge of the treated area, with the potential for encapsulation. We proposed widening the area of antimetabolite application, which considerably reduced the risk of encapsulation and subsequent cystic avascular blebs.<sup>6,7</sup> The dose is titrated according to each patient's scarring potential. In the postoperative period, tight control is maintained over aqueous flow through the use of adjustable and/or releasable sutures.<sup>8</sup> This approach is critical but labor intensive, because many clinical assessments are required. Too little flow may result in closure and failure of the fistula; too much may result in hypotony and vision loss. A subcon-



**Figure 2.** Possible points of therapeutic intervention for the modulation of wound healing. Cell modulators (eg, serum amyloid P [SAP]) prevent the activation of circulating monocytes to fibroblasts. Specific inhibitors of cytokine pathway signalling (eg, TGF- $\beta$ ) affect fibroblast activation. Antibodies to vascular endothelial growth factor (VEGF ab) reduce angiogenesis and fibroplasia. Matrix metalloproteinase inhibitors (MMPi) affect multiple types of cells, including fibroblasts and endothelial cells. Adapted from Lockwood A, Brocchini S, Khaw PT. New developments in the pharmacologic modulation of wound healing after glaucoma filtration surgery. *Curr Opin Pharmacol.* 2013;13(1):65-71.

junctival injection of antimetabolite is performed if the surgeon deems a bleb to be at risk of scarring.

## NEW WOUND-MODULATING AGENTS AND COMBINATIONS

A key goal of research is to develop treatments that are more selective for the cells and processes responsible for scarring, with the aim of improving surgical efficacy without toxic side effects. Showing significant promise are experimental models with growth factor antagonists such as inhibitors of TGF- $\beta$ , VEGF, or matrix metalloproteinases and analogues of serum amyloid P (Figure 2). Translating these to clinical use is more challenging, and the current efficacy in humans of single, highly specific antagonists such as VEGF antibodies appears to be limited.<sup>9</sup> This may in part be due to current drug delivery

systems and pharmacokinetics, which need improvement and are the subject of much investigation.<sup>10</sup>

Pluripotency and redundancy of many signalling pathways also exist, with differential expression over time during the wound-healing process. It is likely that a combination of treatments is required to achieve therapeutic success, as has been the case with cancer treatments. Undoubtedly, a greater understanding of the involved mechanisms and an improved ability to deliver treatments via new routes, such as genetic manipulation with viral vectors, will augment surgeons' control of the wound-healing process. It will then be possible to tailor treatment to the individual and achieve consistent long-term IOP control.

Ultimately, the impact of wound healing on glaucoma therapy is potentially profound. The ability to fully control the long-term wound-healing response in all patients coupled with appropriate "flow technology" would allow long-term IOP control at around 10 mm Hg for the patient's lifetime without any other therapy. That outcome would enhance quality of life and minimize disease progression in the majority of patients. It would also revolutionize the management of glaucoma worldwide. ■

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