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Antiscarring in Glaucoma Surgery

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Abstract

Purpose: To provide an overview of the antifibrotic strategies that are currently in use or under evaluation for the enhancement of filtering surgery. ***Methods:*** A literature research was done and the available evidence was summarized. ***Results:*** A summary of the available antiscarring agents is provided, going from the well-established antimitotic agents [mitomycin C (MMC) and 5-fluorouracil], over anti-inflammatory agents (steroids and non-steroidal anti-inflammatory agents), growth factor inhibitors (inhibitors of transforming growth factor-β, vascular endothelial growth factor, and placental growth factor) to ρ-kinase inhibitors. ***Conclusion:*** Although MMC is widely used, its safety and efficacy profile is not entirely satisfactory. Alternative antifibrotic strategies have been studied extensively, which has led to the identification of a number of promising molecules. However, further clinical trials are needed to establish their optimal dosing and potential complementary effects with the existing compounds.

Introduction

Filtering surgery is the most effective treatment to lower intraocular pressure (IOP) in glaucoma patients. Trabeculectomy is the reference procedure. However, this surgical technique is associated with a postoperative wound healing reaction, which leads to scarring and surgical failure in a considerable proportion of cases. Considerable efforts have therefore been made in the past decennia in an attempt to improve the surgical success. Pharmacological enhancement of trabeculectomy using different antiscarring agents was found to significantly improve surgical outcome.

Antimitotics

Mitomycin C (MMC) and 5-fluorouracil (5-FU) have been found to be effective in inhibiting postoperative scarring and are currently known as the gold standards in clinical practice [1].

MMC cross-links DNA and inhibits DNA replication. It can interfere with any phase in the cell cycle and inhibits mitosis as well as synthesis of proteins. MMC has been shown in the early 1980s to significantly improve the success rate of trabeculectomy by fibroblast and endothelial cell proliferation, but at the price of potentially vision-threatening side effects (especially when used at high concentrations), such as corneal toxicity, thin-walled avascular blebs, blebitis, endo-

phthalmitis, and hypotony due to their nonspecific mechanism of action. The efficacy (and side effects) are dependent on the dose, exposure time, and surface area [2–4]. With lower levels of exposure, bleb-related complications are less common, but the incidence of bleb fibrosis increases, which illustrates the trade-off between efficacy and safety.

5-FU interferes in thymidine nucleotide synthesis, resulting in DNA synthesis inhibition and ultimately cell death. In the 1990s, 5-FU was shown to inhibit fibroblast growth. Compared to MMC, 5-FU has a lower risk of serious ocular complications. However, at high levels, it is toxic to all actively replicating tissues, such as corneal epithelium. Comparative studies have consistently shown that MMC is more effective as an antiscarring agent after filtering surgery than 5-FU. Therefore, MMC is nowadays more widely used than 5-FU [5].

Of note, although these antimitotic agents have been used for decades now to enhance filtering surgery, their use for this indication is still off-label in Europe. MMC has only recently been approved for ocular use in the US.

Anti-Inflammatory Agents

Corticosteroids suppress leukocyte concentration and function, as well as vascular permeability, resulting in a diminished fibroblast activity and wound healing reaction. Therefore, steroids are routinely used after filtration surgery.

Theoretically, the use of corticosteroids carries a risk of IOP elevation due to steroid responses. However, although steroid responses are more frequent in glaucoma patients than in the general population, an IOP elevation due to steroid responses is less frequent after filtering surgery, probably because the aqueous humor bypasses the affected trabeculum via the created channel. Non-steroidal anti-inflammatory drugs also suppress the wound healing process but are less potent than steroids.

Inhibition of Growth Factors

It has been demonstrated that a large number of growth factors involved in the wound healing process is upregulated in the aqueous of glaucoma patients, and that this growth factor-loaded aqueous can increase the proliferation of Tenon's fibroblasts by 60% compared to the aqueous from patients without glaucoma. Therefore, these upregulated profibrotic growth factors have been investigated as potential targets for new antiscarring strategies.

Transforming Growth Factor-β Inhibition

Transforming growth factor (TGF)-β is a key cytokine in the wound healing process and has been demonstrated to be present at significantly higher levels in the aqueous of glaucoma patients compared to normal individuals. This growth factor has been shown to stimulate proliferation of human Tenon's fibroblasts and enhance collagen contraction in in vitro models [5].

Extensive research has been performed to investigate the antiscarring potency of TGF-β inhibition. CAT-152 (Cambridge Antibody Technology, Cambridge, UK), a recombinant human monoclonal antibody against TGF-β, was studied by Sir Peng Khaw et al. [5]. In a rabbit model, repeated subconjunctival injections (0.1 mg/ml) on postoperative days 0, 1, 3, and 7 significantly improved the surgical outcome compared to placebo-injected eyes. Histological analysis confirmed that there was less collagen deposition and improved bleb formation without side effects. A multicenter prospective randomized clinical trial was subsequently set up, but, unfortunately, this trial was prematurely discontinued due to lack of efficacy at the used dose (which was identical to the dose used in the rabbit study). It is up to date unclear whether a dosing problem caused the lack of efficacy in the human trial.

Other TGF-β inhibitors have been explored in preclinical studies, but no clinical trials demonstrating a relevant benefit in patients are available until now.

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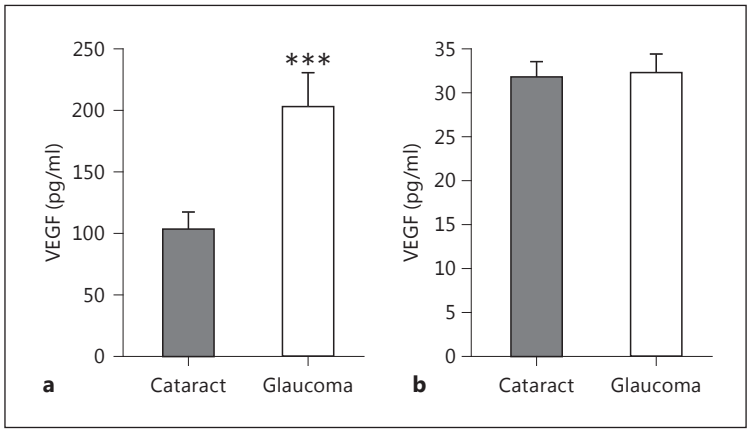

Fig. 1. VEGF expression in aqueous (**a**; n = 20; *** $p < 0.001$ vs. cataract) and plasma (**b**; n = 10–17; $p > 0.05$) samples from glaucoma and cataract patients. Reprinted from Li et al. [6, p. 5218] with permission.

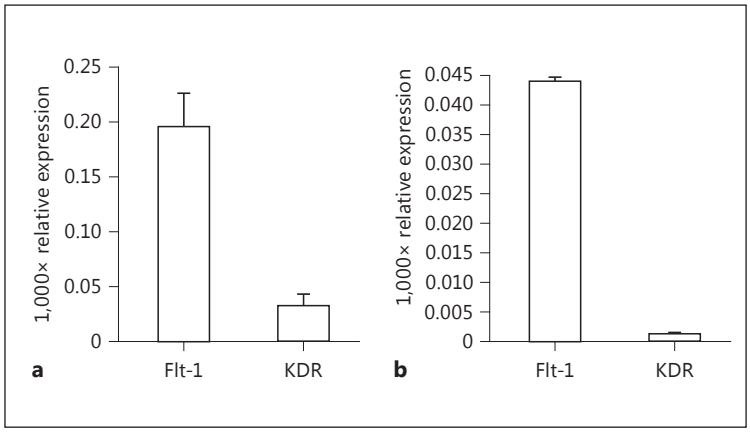

Fig. 2. VEGF receptor expression on human (**a**) and rabbit (**b**) Tenon's fibroblasts. Reprinted from Li et al. [6, p. 5219] with permission.

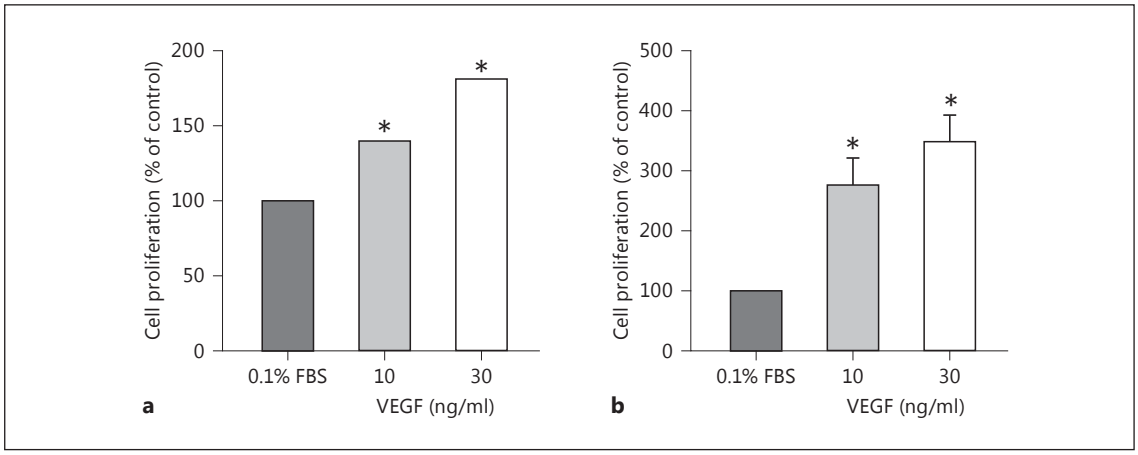

Fig. 3. Dose-dependent stimulation of human (**a**) and rabbit (**b**) Tenon's fibroblast proliferation by recombinant VEGF. * $p < 0.05$ vs. 0.1% FBS. Reprinted from Li et al. [6, p. 5220] with permission.

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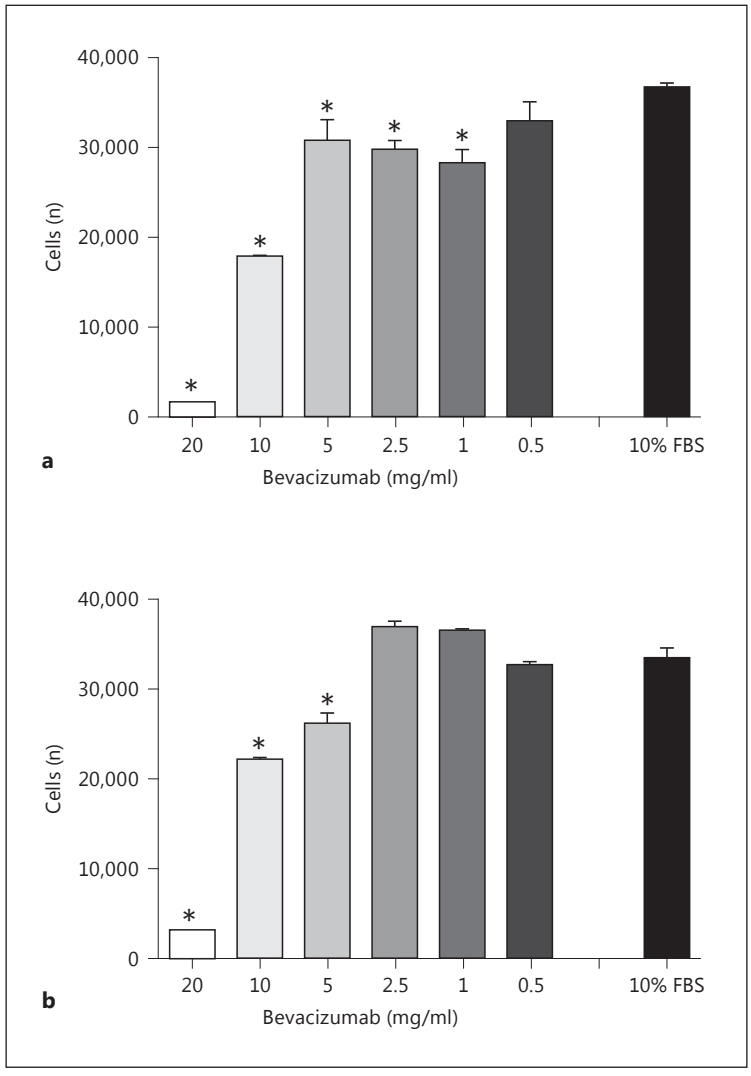

Fig. 4. Dose-dependent inhibition of human (**a**) and rabbit (**b**) Tenon's fibroblast proliferation with bevacizumab. * $p < 0.05$ vs. 10% FBS. Reprinted from Li et al. [6, p. 5220] with permission.

Vascular Endothelial Growth Factor Inhibition

Vascular endothelial growth factor (VEGF) has been shown to be implemented in various processes involved in wound healing, such as inflammation, angiogenesis, and fibrosis. Therefore, the potential of VEGF inhibition to reduce postoperative scarring was investigated [6]. VEGF was shown to be upregulated in the aqueous humor taken from glaucoma patients compared to nonglaucomatous patients undergoing cataract surgery (fig. 1).

Further, cultured rabbit as well as human Tenon's fibroblasts and endothelial cells were shown to express VEGF receptors (fig. 2). In these fibroblast cultures, it was then shown that recombinant VEGF could stimulate proliferation in a dose-dependent manner (fig. 3).

Finally, a dose-dependent inhibition of human and rabbit Tenon's fibroblasts was observed by bevacizumab, a monoclonal humanized anti-VEGF antibody (fig. 4).

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