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Review

Conjunctival fibrosis following filtering glaucoma surgery

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ABSTRACT

Despite advances in surgical technique and postoperative care, fibrosis remains the major impediment to a marked reduction of intraocular pressure without the need of additional medication (complete success) following filtering glaucoma surgery. Several aspects specific to filtering surgery may contribute to enhanced fibrosis. Changes in conjunctival tissue structure and composition due to preceding treatments as well as alterations in interstitial fluid flow and content due to aqueous humor efflux may act as important drivers of fibrosis. In light of these pathophysiological considerations, current and possible future strategies to control fibrosis following filtering glaucoma surgery are discussed.

1. Introduction

Filtering glaucoma surgery (trabeculectomy in particular) prevails as the most effective strategy to achieve sustained intraocular pressure reduction in glaucoma patients and serves as a reference in clinical studies. Despite continuous improvement of technical surgical details, the primary goal to achieve target pressure without need for additional topical medication (complete success) is missed in 35–43% of the patients (Khaw et al., 2007; Klink et al., 2009; Landers et al., 2012) and postoperative scarring remains the major impediment to higher success rates (Fig. 1). Therefore, we will discuss the peculiar aspects of filtering glaucoma surgery as they pertain to driving scar formation.

In general, filtering procedures such as trabeculectomy or placement of subconjunctival drainage implants aim at allowing aqueous humor to leave the anterior chamber through a novel transscleral route towards the subconjunctival space. The extraocular aqueous humor forms a subconjunctival bleb and fluid is absorbed by the conjunctival vasculature.

There is a high propensity of subconjunctival fibrous tissue formation during postsurgical healing which may seal off the transscleral and subconjunctival flow of aqueous, thus resulting in inadequate IOP reduction. Risk factors for scar-related failure are previous surgical procedures breaching the conjunctiva, a long history of topical conjunctival medication, conjunctival inflammation and younger age. Currently, antiinflammatory medication and antimetabolites are used to reduce the conjunctival scarring response, but further improvements to achieve better control of fibrosis appear highly desirable.

2. Wound healing and scarring

Surgery inevitably induces tissue trauma with at least some release of blood cells and plasma proteins which will trigger a localized inflammatory response and provide a short-term structural support. The inflammatory phase is characterized by the activation of the innate immune system and the release of inflammatory cytokines. It is targeted by drugs such as steroids to limit subsequent events. During this early inflammatory phase, platelet activation provides a rich source of mediators such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF-A) and transforming growth factor beta-1 (TGF-β1). These factors enhance recruitment of polymorphonuclear cells and macrophages which serve to remove debris and prevent infection with lymphocytes subsequently entering the site (Chang et al., 2000; Wynn and Ramalingam, 2012). One to three days following surgery, the proliferative phase of wound healing ensues with

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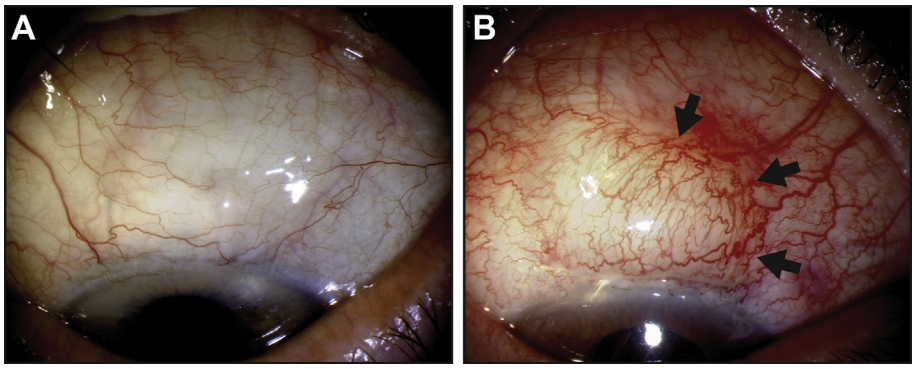

Fig. 1. Clinical presentation of filtering blebs. (A) Unscarred diffuse filtering bleb 12 months following trabeculectomy. (B) Scarring filtering bleb with beginning encapsulation (arrows) and enhanced vascularity, 6 weeks following trabeculectomy.

propagation of resident and invading fibroblasts driven by mitogens such as PDGF (Pierce et al., 1989). The growth factor TGF-β serves a key role in wound healing as it induces the transdifferentiation of fibroblasts to highly contractile myofibroblasts characterized by expression of alpha-smooth muscle actin (α-SMA) (Desmouliere et al., 1993) and enhanced expression of extracellular matrix proteins (fibronectin, tenascins, collagens), which these cells actively assemble to strengthen the extracellular matrix (ECM) scaffold. Thus, myofibroblasts are at the core of tissue restoration as they provide both, the extracellular matrix material and the mechanical strength to allow for wound closure.

Excessive scar formation or fibrosis is characterized by the persisting presence of myofibroblasts (Gabbiani, 2003), which otherwise disband in apoptosis (Desmouliere et al., 1995) when a provisional tissue repair is achieved. Thus, in a simplistic manner, scar formation might be seen as an overreaching wound healing process. Inflammation, increased mechanical load or distinct growth factors may drive scarring and fibrosis by prolonged or enhanced myofibroblast stimulation (Gabbiani, 2003; Wynn and Ramalingam, 2012). Fibrosis occurs in various pathophysiological settings which likely differ in the relative contribution of these driving forces.

3. Fibrosis-promoting aspects of filtering glaucoma surgery

3.1. Conjunctival sutures

Sutures induce a mild inflammatory response which may be maintained throughout their presence. In line with a fibrosis-promoting role of inflammation, clinical evidence suggests that early suture removal improves the success rate of filtering glaucoma surgery and reduces conjunctival fibrosis (Klink et al., 2009). However, appropriate timing of early suture removal deserves clinical experience and cautious consideration.

3.2. Conjunctival predisposition

Current glaucoma therapy typically rests on initial use of topical medication to lower intraocular pressure. This topical treatment is frequently associated with conjunctival inflammation due to toxic or allergic responses to preservatives (Baudouin et al., 2004; Stalmans et al., 2013) as well as to distinct drugs (Krupin et al., 2011). A correlation of precedent topical medication, tear levels of the cytokine monocyte chemoattractant protein-1 (MCP-1) and conjunctival scarring following trabeculectomy has been reported (Chong et al., 2010). Dry eye disease and related aberrations in inflammatory signaling and tear composition can also contribute to conjunctival scarring (Lee et al., 2013). Earlier studies had demonstrated increased amounts of conjunctival lymphocytes and fibroblasts following long-term treatment with preserved topical medication (Broadway et al., 1993; Sherwood et al., 1989). In general, chronic inflammation is an established risk factor for fibrosis due to the release of mediators such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) which lead to increased tissue levels of TGF-β (Kolb et al., 2001; Wynn and Ramalingam, 2012). A chronic Th2-mediated allergic response may also induce fibrosis in an IL-13-dependent manner (Liu et al., 2011). It is thus conceivable, that glaucoma surgery would induce an enhanced wound healing response in a conjunctival tissue pre-inflamed due to long-term topical treatment. Along these lines, a preventive topical treatment with non-steroidal antiinflammatory drugs or steroids preceding glaucoma surgery has proven beneficial (Breusegem et al., 2010; Broadway et al., 1996) and toxic preservatives should be avoided.

Previous conjunctival surgery also increases the risk of fibrosis as it inflicts long-term changes with increased presence of fibroblasts and macrophages (Broadway et al., 1998). Furthermore, several growth factors such as VEGF-A, EGF, TGF-β are embedded in the ECM (Saika et al., 2001) and will be released by localized enzyme activity (Mott and Werb, 2004) or mechanical stress (Wipff et al., 2007) as they occur following surgery (Fig. 2). The composition of the ECM conveys further important information as distinct ECM molecules drive certain biological functions (Klingberg et al., 2013). For example, the ED-A splice variant of fibronectin is crucial for myofibroblast transdifferentiation (Serini et al., 1998) and is present in scarred conjunctival tissue (Meyer-ter-Vehn et al., 2008a). Matricellular proteins such as CTGF or SPARC are expressed in wound healing, modulate cell–matrix interactions and can enhance fibrosis (Daniels et al., 2003; Fuchshofer et al., 2011; Seher et al., 2011; Wallace et al., 2014). A recent report found a correlation of preoperative conjunctival levels of TGF-β, the fibrosis-related crosslinking enzyme lysyl-oxidase-like 2 (LOXL-2) and post-surgical fibrosis (Park et al., 2014). Thus it appears that tissue harbors a multifaceted “structural memory”, which will shape subsequent responses and predispose to enhanced fibrosis after repeat surgery.

3.3. Aqueous humor

Following filtering glaucoma surgery, the anterior chamber drains to the subconjunctival space and aqueous humor percolates conjunctival tissue. Therefore, components of aqueous humor may