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The Role of Epigallocatechin-3-Gallate (EGCG) in Inhibiting Post-Trabeculectomy Fibrosis through the Inhibition of TGF-ß and VEGF

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Abstract
This literature review focuses on the role of epigallocatechin-3-gallate (EGCG), a potent antioxidant found in green tea, in inhibiting post-trabeculectomy fibrosis, particularly through the inhibition of transforming growth factor-beta (TGF-ß) and vascular endothelial growth factor (VEGF). The primary goal of glaucoma treatment is to reduce intraocular pressure (IOP) and prevent optic nerve damage, with trabeculectomy being a common surgical procedure to achieve this. However, the success of this surgery can be compromised by excessive subconjunctival scarring, leading to a failure rate of about 15% within the first few months. EGCG has demonstrated antifibrotic properties, making it a promising therapeutic option for preventing fibrosis after trabeculectomy. The review highlights that Tenon fibroblasts, which are crucial in wound healing and scar formation, can be influenced by EGCG to reduce the risk of fibrosis. The mechanism involves the suppression of myofibroblast differentiation and the modulation of pro-inflammatory cytokines through pathways such as NF-κB and PI3k/Akt. The review also discusses the comparative effectiveness of EGCG against traditional antifibrotic agents like mitomycin C (MMC), which, while effective, can lead to side effects such as ocular toxicity and infection. Furthermore, the review emphasizes the importance of understanding the fibrogenic activity of human Tenon's capsule fibroblasts (HTFs) derived from glaucoma patients, which exhibit a higher propensity for fibrosis compared to those from non-glaucoma patients. This increased fibrogenic activity is linked to elevated expression of pro-fibrotic genes and a higher myofibroblast-to-fibroblast ratio. In conclusion, the findings suggest that EGCG could serve as a valuable adjunct therapy in preventing post-trabeculectomy fibrosis, potentially improving surgical outcomes for glaucoma patients. Further research is warranted to explore the optimal concentrations and mechanisms of action of EGCG in this context.

Keyword: *epigallocatechin-3-gallate, post-trabeculectomy fibrosis, TGF-ß, VEGF*

INTRODUCTION

Reducing or stabilizing intraocular pressure (IOP) is the current goal of glaucoma treatment to prevent additional optic nerve damage [1]. Glaucoma filtration surgery is the most common procedure performed to lower IOP because it creates a filtering bleb for aqueous humor outflow [2]. For surgery to be successful, the filtering role of the bleb needs to be preserved. However, due to severe subconjunctival scarring, 15% of filtering surgeries fail within the first few months [3]. Tenon fibroblasts are the primary effector cells in the filtering bleb, driving fibrotic scar formation and wound healing [4]. Expression of smooth muscle actin (α-SMA) and increased production of extracellular matrix proteins, including type I collagen (Col-I), are markers of the conversion of Tenon fibrocytes to myofibroblasts [2, 4]. According to several studies, suppression of myofibroblast transformation is essential to prevent scar formation.

Anti-fibrotic drugs including 5-fluorouracil (5-FU) and mitomycin C (MMC) have been used surgically to reduce fibrosis of glaucomatous filtration blebs [5]. However, there are side effects such as ocular toxicity, wound leakage, blebitis, dysesthesia, and endophthalmitis associated with these anti-fibrotic drugs [6]. The most common catechin in green tea, epigallocatechin-3-gallate (EGCG), has been shown to be a potent antioxidant and multi-target therapeutic agent [7, 8, 9]. In the past, it has been reported that oral consumption of a good tea extract can help with experimental uveitis and retinal degeneration. In addition, studies on diabetic nephropathy [10], liver fibrosis [11], and pulmonary fibrosis [12]have shown that EGCG has antifibrotic qualities. Here, we will discuss about the role of EGCG in post-trabeculectomy fibrosis through inhibition of TGF-ß and VEGF.

The Role of TGF-ß and VEGF in Post-trabeculectomy Fibrosis

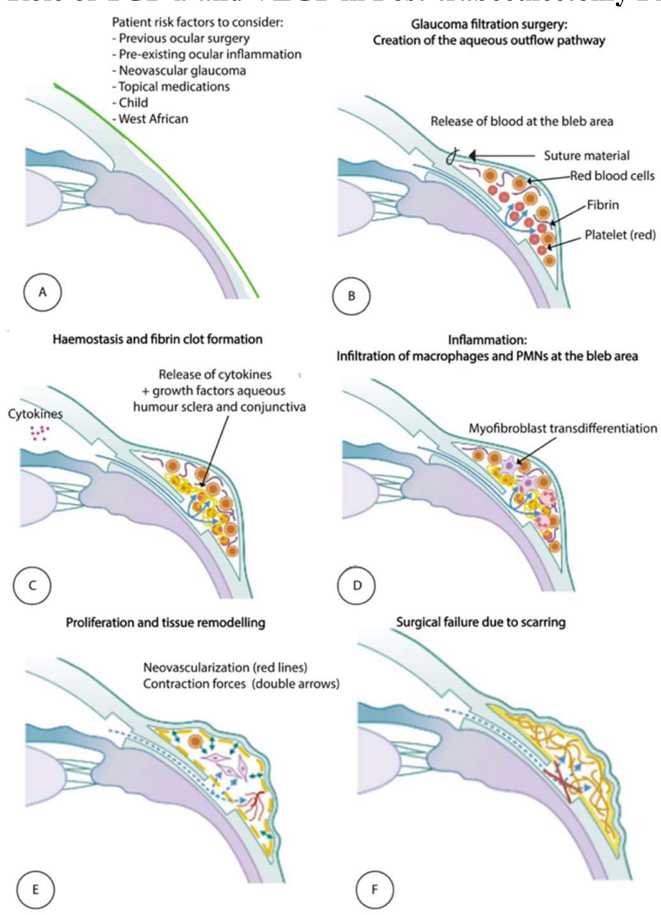

Figure 1. post-trabeculectomy sequence of events [14].

Like all wound healing, conjunctival wound healing begins with blood clotting and the homeostatic phase. During this process, blood cells (platelets, polymorphonuclear neutrophils, and red blood cells) and plasma proteins (plasminogen, fibrinogen, and fibronectin) seep out of the damaged blood vessels. A number of growth factors, including interleukins, transforming growth factor beta (TGF-ß), vascular endothelial growth factor (VEGF), and platelet-derived growth factor, are released by activated platelets. [13, 14].

Blood clotting and fibrin clot formation result from the conversion of fibrinogen to fibrin as shown in (Figure1). The production of the fibrin clot and the release of these proteins cause neutrophils, macrophages, and lymphocytes to migrate and be recruited to the surgical site. These cells are involved in the inflammatory phase of the process. Transforming growth factor beta (TGF-ß), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and connective tissue growth factor are among the genes associated with conjunctival fibrosis. These genes are involved in the control of wound healing. The aqueous humour contains a variety of growth factors, including the transforming growth factor TGF-β, which is a key regulator of fibrosis during wound healing [13, 14].

The proliferation and tissue remodeling phase is the final step of conjunctival fibrosis. Activated fibroblasts and endothelial cells migrate to the site of injury during the proliferation phase, followed by granulation tissue formation and angiogenesis. Neutrophils and monocytes are examples of phagocytic cells that produce proteolytic enzymes to aid in the removal of damaged tissue. Similar to active platelets, activated phagocytes release growth factors like fibroblast growth factor and cytokines like TGF-β that are critical for fibroblast recruitment, activation, and maintenance [15].

Tenon fibroblasts that have been activated multiply and produce extracellular matrix. Scar tissue development occurs due to blood vessel shrinkage and fibroblast transformation to myofibroblast phenotype during tissue turnover. This process promotes cross-linking of collagen and elastin type 1 [14, 15].

The gremlin protein, which GREM1 encodes, has been demonstrated to encourage the development of myofibroblasts from fibroblasts [16]. Gremlin has been demonstrated to directly raise intraocular pressure in glaucoma patients because to its upregulation in trabecular meshwork cells [17]. The findings of a 2007 research by Chaudhary et al., which demonstrated elevated GREM1 mRNA expression in HTCFs given from glaucoma patients, are in line with this [18]. Vascular endothelial growth factor (VEGF) is a key growth factor for fibrosis and blood vessel creation in a process known as angiogenesis [19]. Lastly, although the exact function of VEGF in fibrosis is unknown, anti-VEGF pharmaceuticals are known to have anti-fibrotic effects.

It has been shown that certain integrin genes, such as ITGβ-5, are involved in the activation of latent transforming growth factor-beta 1 (TGFβ1), a significant growth factor that encourages fibrosis [20]. Unknown is the precise mechanism by which circulating and endogenously produced TGFβ1 control HTF-dependent wound healing in people with and without glaucoma. Conversely, latent TGFβ1 can be activated by contracting myofibroblasts, which could explain the increased fibrogenic response observed in the HTF of glaucoma patients [21].

***Human Tenon's capsule fibroblast* (HTF) in glaucoma patients**

According to research on experimental glaucoma surgery and related in vitro studies, human Tenon's capsule fibroblasts, or HTFs, are essential for wound healing after valve-based drainage surgery and may also be involved in surgical failure associated with fibrosis [2, 22]. However, it is still unclear what specific elements of HTFs cause excessive and inadequate wound healing. HTFs are present in the fibrous connective tissue known as the tenon's capsule (TC), which is located under the conjunctiva, joins the sclera anteriorly, and extends posteriorly to the optic nerve meninges [23]. It is crucial for the prognosis of GFS since TC is anatomically located where fibrosis might undermine the therapeutic efficacy of filtration surgery [24]. As a result, more precise modelling of ocular fibrogenesis and TC-dependent wound healing is required. This necessity is growing since fibrosis plays a substantial role in the failure of existing minimally invasive glaucoma surgery (MIGS) [25].

Compared to non-glaucoma patients receiving no medical treatment for their condition, HTFs from glaucoma patients receiving therapy had considerably greater relative mRNA expression of the genes ACTA2, ITGβ-5, VEGFA, COL3A1, and GREM1. Type I collagen rapidly supplanted type III collagen, which is mostly generated during the first three weeks of wound healing and is encoded by COL3A1 [26, 27]. Patients with glaucoma had HTFs that were more likely to synthesize type III collagen. In fact, it is known that scar tissue has a higher ratio of type III to type I collagen [28]. Moreover, glaucoma patients' HTFs revealed increased collagen gene expression, indicating that glaucoma patients are more prone to scarring.

The degree of differentiation into contractile myofibroblasts, which are crucial for wound healing and repair, is a significant predictor of fibroblast activity. Myofibroblasts display αSMA expression during differentiation, and αSMA protein is widely employed in analysing the transition from fibroblasts to myofibroblasts [29]. HTFs derived from glaucoma patients showed a higher myofibroblast-to-fibroblast ratio, which is consistent with higher ACTA2 mRNA expression in HTFs derived from glaucoma patients. Consequently, there is a higher likelihood of myofibroblast differentiation in HTFs derived from glaucoma patients, which may have consequences for scar formation after surgery.

HTFs obtained from individuals with glaucoma exhibit in vitro phenotypes indicating that they have a higher propensity for in vivo fibrogenic activity than HTFs obtained from individuals without glaucoma. A study by Trelford, et al in 2020 evaluated pro-fibrotic behaviors such as increased collagen deposition, remodeling, and contractility [28]. The study's contraction studies demonstrated that HTFs obtained from glaucoma patients contracted collagen constructions more than HTFs acquired from non-glaucoma patients. A potential mediator of the enhanced contractility in glaucoma HTFs might have been the larger myofibroblast-to-fibroblast ratio.

In animal models of glaucoma, collagen remodelling as seen by Sirius red staining has been connected to bleb function [30]. Anti-fibrotic treatments have been shown to inhibit collagen turnover while reducing scarring and improving bleb function [31]. Interestingly, the largest quantity of collagen turnover was seen in the HTFs from glaucoma patients. Consequently, the fact that HTFs derived from glaucoma patients require less stress and/or are predisposed to grow into myofibroblasts may account for the pro-fibrotic phenotype seen. We can conclude from the data that HTFs isolated from patients receiving medical treatment for glaucoma have a higher proportion of myofibroblast differentiation, increased expression of pro-fibrotic genes, and increased collagen contraction and remodelling in comparison to HTFs isolated from patients not receiving treatment for the condition.

Mitomycin C as a gold standard antifibrotic agent in post-trabeculectomy patients

Surgical success rates have improved with greater use of mitomycin C, especially in patients at high risk for failure. Increased rates of bleb leakage, infection, and hypotony have also been reported with the use of this antifibrotic drug; however, these benefits have been associated with longer trabeculectomy survival rates. Antifibrotics can be injected subconjunctivally or administered with a moistened sponge [32].

Mitomycin C (MMC) is a naturally occurring compound that is an antibiotic and antineoplastic agent. MMC is an alkylating chemical that causes DNA to become cross-linked, which prevents DNA replication and induces apoptosis. MMC modulates the fibroproliferative and angiogenic phases of wound healing by being cytotoxic to fibroblasts and vascular endothelial cells. MMC is injected subconjunctivally or applied with a moist sponge. The intraocular pressure (IOP) results from both approaches are comparable, although injection may promote more uniform bleb development [33].

Streptomyces caespitosus is a bacterium that produces the chemical alkaloid mitomycin C (MMC). MMC causes cell death by preventing the production of RNA from DNA. Cultures of human Tenon's fibroblasts have shown evidence of induction of apoptosis after exposure to MMC at concentrations ranging from 0.1 to 1.0 mg/ml for five minutes. The extent of apoptosis varies with the dose administered. In experiments with human Tenon's capsule tissue, MMC virtually stopped fibroblast development. In addition to the dose administered to the tissue, which is concentration dependent, factors include volume, exposure time, method of preparation, administration, and tissue-related variables. Concentration has a significant effect on MMC-induced fibroblast suppression, according to in vitro studies using Tenon's capsule cultures; sponges applied for one minute had the same effect as sponges applied for five minutes [32, 34].

According to Lin et al.'s 2020 report, MMC significantly affected post-trabeculectomy fibrosis. MMC functions by blocking NLRP3, which prevents the activation of the Caspase-3 pathway and inhibits inflammatory conditions. Furthermore, it has been shown that MMC can reduce TGF-ß expression in damaged tissues. Nod-like receptors (NLRs) are a subclass of pattern recognition receptors (PRRs) with nucleotide-binding and oligomerization domains that act as cytoplasmic receptors. NLRs are classified into four subgroups based on their N-terminal domain; the NLRP group has a pyrin domain. The NLRP family consists of fourteen members, including NLRP3, all of which are involved in the inflammasome formation process [34, 35].

Surgical sponges are soaked in MMC solution to deliver MMC during surgery. The sponge is then positioned so that it comes into contact with the sclera at the trabeculectomy site in the subconjunctival space. The concentration is applied for 0.5–5 minutes in the range of 0.1–0.5 mg/mL. Depending on the risk variables associated with trabeculectomy failure, modifications can be made to the concentration or treatment time. To avoid damage to the surrounding tissue, the subconjunctival area is often rinsed with 20 to 50 mL of normal saline after MMC administration [35].

The role of EGCG in inhibiting post-trabeculectomy fibrosis

Among the major catechin components in green tea extract is epigallocatechin-3-gallate (EGCG), which binds proteins and nucleic acids more strongly than other polyphenolic compounds in the extract. Because EGCG is non-toxic and readily soluble in water, urine can effectively remove it. Because of its potential use as an antioxidant, anticancer, anti-inflammatory, and other important bioactivities, this polyphenolic molecule has attracted attention [36].

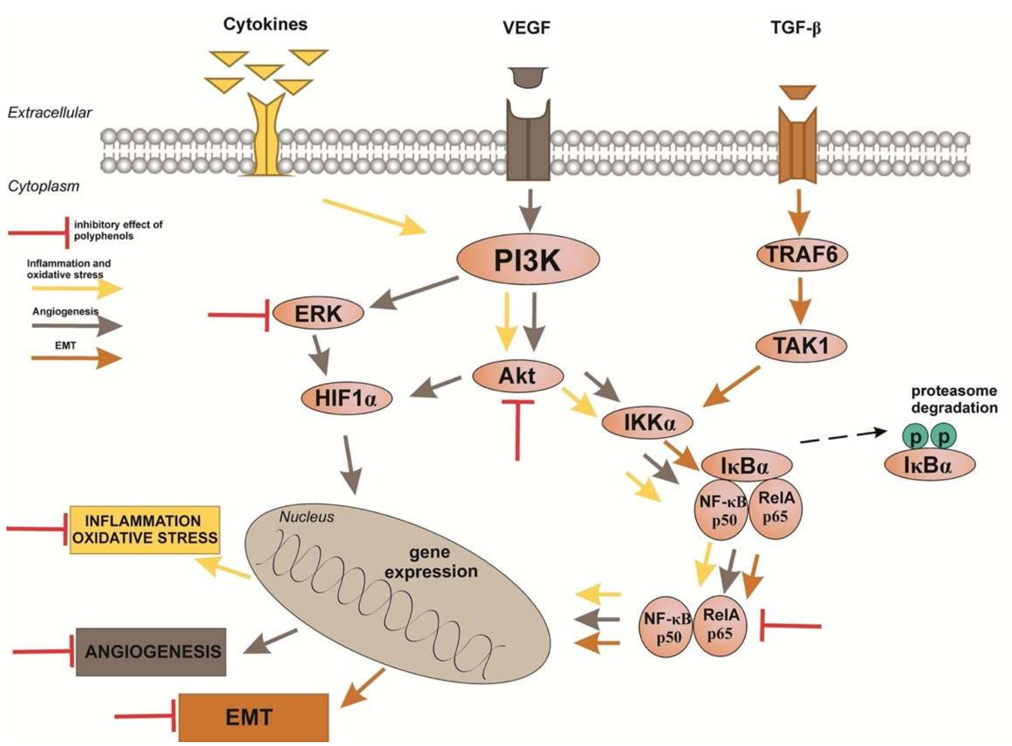

Figure 2. Polyphenol pathway in wound healing [38].

Scar tissue known as post-trabeculectomy fibrosis develops after trabeculectomy surgery as a result of excessive proliferation of fibroblast cells. Because EGCG can prevent UV-B-induced free radical formation, it can also prevent pro-inflammatory cytokines from being activated through the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) pathway as shown in (Figure2). This pathway controls Tumor Necrosis Factor α (TNF-α), an inflammatory mediator that induces cytokines such as interleukin (IL)-1, IL-6, and IL-8. The antioxidants in EGCG can also affect variables that promote angiogenesis by inhibiting HIF1-α in the phosphoinositide-3 kinase phosphorylation pathway (PI3k/Akt), which decreases the production of the growth factor VEGF. Pro-inflammatory enzymes such as cyclooxygenase 2 (COX-2), which is involved in prostaglandin synthesis, can also be suppressed by EGCG. These results imply that EGCG may be a useful additional treatment option to avoid fibrosis after trabeculectomy surgery. [36, 37]. The efficacy and safety of various concentrations of EGCG in inhibiting myofibroblasts in rabbit eyes were studied by Lin et al. in 2020. They found that EGCG concentrations less than or equal to 50 µM (1, 10, 50 µM) showed a good level of safety because at a concentration of 100 µM, the viability of fibroblast cells in Tenon's capsule decreased significantly [38, 39, 40].

CONCLUSION

This literature review presented the potential mechanism of EGCG in inhibiting post-trabeculectomy through the inhibition of TGF-ß and VEGF. Our findings concludes that EGCG is a promising therapeutic modality in preventing post-trabeculectomy in glaucoma patients.

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