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Inhibition of the Post-Trabeculectomy Wound Healing Process by Epigallocatechin-3-Gallate (EGCG) through Regulation of Matrix Metalloproteinase-3 (MMP-3) Expression and Fibroblast Migration in Human Tenon Fibroblasts

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Abstract

This review investigates the role of Epigallocatechin-3-gallate (EGCG) in inhibiting wound healing through the regulation of matrix metalloproteinase-3 (MMP-3) expression and fibroblast migration in human Tenon fibroblasts. Glaucoma, a chronic optic neuropathy characterized by optic nerve degeneration, often necessitates surgical interventions such as glaucoma filtration surgery (GFS) due to persistent vision loss despite initial treatments aimed at reducing intraocular pressure (IOP). However, excessive wound healing and fibrosis significantly contribute to a surgical failure rate of 35-43%. This review highlights that excessive fibrosis in the subconjunctival bleb region is a primary cause of post-trabeculectomy failure, with failure rates ranging from 24% to 74% within four years post-surgery. The findings suggest that EGCG may play a crucial role in modulating the wound healing process by influencing the behavior of Tenon fibroblast cells, which are essential for wound healing and fibrotic tissue formation. By regulating MMP-3 expression and fibroblast migration, EGCG presents a potential therapeutic avenue to mitigate fibrosis and improve surgical outcomes in glaucoma treatment. In conclusion, this review underscores the importance of understanding the mechanisms by which EGCG affects wound healing, potentially leading to more effective strategies for managing fibrosis in glaucoma surgeries

Keywords: Epigallocatechin-3-gallate, wound healing, matrix metalloproteinase-3, glaucoma, fibrosis.

INTRODUCTION

Glaucoma is a category of chronic optic neuropathies marked by progressive degeneration of the optic nerve and cells in higher brain areas defined as visual cortex [1]. There are several types of glaucoma, with primary open angle glaucoma (POAG) being the type with the highest prevalence [2]. POAG is related with functional problems in the drainage system located in trabecular meshwork, which is positioned at the intersection of the cornea and iris [3, 4]. The dysfunction in aqueous humour outflow causes high intraocular pressure (IOP), a significant risk factor for the development and progressivity of glaucoma[1].

Glaucoma patients are treated with antiglaucoma agents aimed at reducing intraocular pressure (IOP) as initial therapy to inhibit further thinning of retinal ganglion cell layers [1, 2]. However, some patients continue

to experience progressive vision loss despite pharmacological intervention and may require surgical drainage procedures such as trabeculectomy, which is the most commonly performed filtration surgical procedure. Since the advent of trabeculectomy, excessive healing response and fibrotic tissue formation have emerged as significant risk factors, contributing to a surgical failure rate ranging from 35% to 43% [5]. Surgical failures define as an IOP exceeding or falling below the established upper or lower IOP thresholds, resulting in glaucoma-related vision loss or necessitating additional surgical intervention [4]. Moreover, perioperative administration of anti-glaucoma medications has been shown to augment the likelihood of poor surgical outcomes by increasing the count of inflammatory mediators and facilitating fibrosis. [6, 7]. Additionally, preservatives commonly found in antiglaucoma agents, such as benzalkonium chloride (BAK), have been demonstrated to disrupt cell membrane integrity and increase the concentration of pro-inflammatory mediators within subconjunctival tissues [8].

Excessive fibrosis in the subconjunctival bleb region is the most common cause of post-trabeculectomy failure. Until recently, there has been no optimal treatment that can modify wound healing and avoid subconjunctival fibrosis following trabeculectomy. Tenon fibroblast cells are essential for the beginning and mediation of wound healing, as well as the creation of fibrotic tissue following trabeculectomy. Several techniques have been developed to modulate wound healing with the goal of preventing post-trabeculectomy fibrosis, including the use of steroids, antimetabolites, and antivascular endothelial growth factor (anti-VEGF) [9, 10].

Bleb fibrosis can cause failure with a rate ranging from 24% to 74% in the four years following surgery. The failure rate of trabeculectomy with mitomycin C (MMC) is between 23% to 51% after 5 years. The antimetabolite MMC has been shown to improve trabeculectomy success rates, but it is also linked with a higher risk of significant consequences including as hypotony, bleb leaking, infection, and endophthalmitis [9, 10].

Multiple stages of wound healing have a major impact on the long-term outcome of trabeculectomy treatments. While the remodelling phase is mostly responsible for deciding the result of wound closure through the creation of extracellular matrix, the coagulation phase is crucial in controlling the proliferative and inflammatory phases. A low degree of wound contractility, which indicates the correct ratio of fibroblast activity to collagen deposition and degradation—collagen being the major extracellular matrix component—is indicative of the remodelling phase's effectiveness [11, 12].

The migration of human Tenon fibroblasts (HTF), which play a critical role in the wound healing process, can be stimulated by post-trabeculectomy wounds. Fibroblast migration may be monitored in vitro by tracking the direction of fibroblast migration towards the site of the wound. Matrix metalloproteinase-3 (MMP-3), an endopeptide enzyme capable of breaking down all components of the extracellular membrane (ECM) in connective tissue and cell surface molecules, will also be released during surgical wound healing. MMP is expressed at high levels in fibroblasts. MMP-3 has a significant role in cell motility, proteolysis, and angiogenesis because it activates pro-MMPs such MMP-1, MMP-9, and MMP-13 and causes angiostatin. Within 48 hours, MMP expression in cells is visible [13].

Although it frequently has major adverse effects, adjuvant treatment to employ antimetabolites to stop the fibrosis process has demonstrated substantial success. Even at a typical dose of 0.4 mg/mL, problems in the form of scleral ulceration, iritis, and corneal dellen occurred in 5%–19% of patients, according to a research looking at the adverse effects of MMC at different concentrations. As an alternative in adjuvant therapy following surgery, a variety of different antimetabolites are being investigated, given the notable number of problems linked to the use of MMC (Martins, Costa, Alves, Chammas, & Schor, 2016; Cui, Zhang, Zhang, Li, & Li, 2024; Kavitha, Tejaswini, Venkatesh, & Zebardast, 2024).

With little side effects, novel treatment alternatives that may stop the fibrosis process have been discovered in a number of past trials. Research on the possible anti-inflammatory and antifibrotic properties of epigallocatechin-3-gallate (EGCG) on different tissue types has started. According to a research on human pterygium fibroblasts following excision, EGCG can dramatically lower fibrosis and recurrence. This has

potential implications in reducing surgical failure. EGCG, in contrast to traditional medications, may therefore be a promising novel therapeutic approach with the potential for low adverse effects to avoid post-trabeculectomy fibrosis. (Lin et al., 2020; Safitri et. al., 2022). Consequently, we examine the mechanisms by which epigallocatechin-3-gallate (EGCG) prevents the wound healing process by inhibiting matrix metalloproteinase-3 (MMP-3) and fibroblast migration.

Human tenon fibroblast (HTF) in post-trabeculectomy patients

The thin connective tissue called the Tenon capsule is the source of human Tenon fibroblasts, a particular kind of fibroblast cell. The capsule surrounds the eyeball. The Tenon capsule supports the eye structurally and acts as a mechanical shield. This tissue's fibroblasts are crucial for scar formation and wound healing. Tenon fibroblasts (HTF) are cells that produce collagen and other extracellular matrix constituents that influence the tissue's elastic and mechanical strengths [17].

The HTFs from eyes with and without glaucoma differ from one another [4]. HTF often maintains a more physiological condition and does not experience significant phenotypic alterations in eyes without glaucoma. There is less chance of excessive scar tissue development in eyes without glaucoma because the synthesis of collagen and extracellular matrix components is more balanced and in line with normal tissue demands. Pathological alterations in HTF can happen in glaucoma-affected eyes, which aids in the disease's development [4]. Exposure to long-term glaucoma medications has been linked to increased inflammation and fibrogenesis, two factors that lead to surgical failure [18]. Patients with glaucoma may exhibit increased susceptibility to post-surgical fibrosis due to elevated levels of pro-fibrotic factors within the trabecular meshwork, as well as the effects of ongoing glaucoma medication treatment.

Bleb function has been linked to collagen remodelling in glaucoma animal models [19]. It has been demonstrated that anti-fibrotic therapies limit collagen turnover while minimising scarring and enhancing bleb function [20]. Interestingly, the largest quantity of collagen turnover was seen in the HTFs from glaucoma patients. Therefore, the fact that HTFs derived from glaucoma patients require less stress and/or are predisposed to grow into myofibroblasts may account for the shown pro-fibrotic character. Compared to HTFs derived from patients not receiving antiglaucoma medications, we can conclude from the data presented that HTFs isolated from patients receiving medical treatment for the condition have a higher proportion of myofibroblast differentiation, upregulation of profibrotic genes, and elevated collagen contraction and remodelling [20].

A glimpse of matrix metalloproteinase

Collagen and elastic fibres are scattered over a substrate made up of glycosaminoglycans, proteoglycans, and glycoproteins found in connective tissue to form the extracellular matrix. Numerous studies have demonstrated that the extracellular matrix can affect wound healing in two ways: directly, by modifying crucial aspects of cell behaviour like adhesion, migration, proliferation, or survival; or indirectly, by affecting extracellular protease secretion, activation, and activity, or by modifying growth factor activity. More specifically, growth factors can be released by the extracellular matrix and their impact on cells engaged in wound healing can be altered or their duration of action prolonged [21, 22].

The ability of MMPs to degrade proteins found in the extracellular matrix and their requirement for iron ions (zinc) to function is known as matrix metalloproteinase. MMPs are created during normal wound healing by wounded cells including fibroblasts, vascular endothelial cells, and activated inflammatory cells like neutrophils and macrophages [23, 24].

MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 are a few of the known human MMPs that have been the subject of in-depth research on wound healing. The majority of MMPs are secreted in the extracellular matrix, however membrane-type MMPs (MT-MMPs) are those that are still attached to the cell membrane. It is believed that this group plays a significant role in pro-MMP and pro-TNF activation [25, 26].

MMPs break down the extracellular matrix damaged by trauma, allowing the creation of new matrix components such as collagen, fibronectin, and proteoglycans by wounded cells to merge with the intact matrix in the afflicted area. Furthermore, MMPs aid in the reduction of biofilms, which are matrix structures made by bacteria to fend off the immune system. The inflammatory cells' produced MMPs function to disrupt the bacterial biofilm's adherence to the wound region. Myofibroblast-secreted MMPs are necessary for the freshly formed scar matrix to contract. At first, an uneven scar matrix is created as a result of wound healing. After scar development, the uneven matrix is eventually removed and replaced with a more regular structure, although cells still release low quantities of MMPs [25, 26].

Fibroblast cells migration in wound healing

Fibroblasts move both in vivo and in vitro over wounds. The average velocity of fibroblasts is less than 1 μm/min. Single cell migration and collective migration are the two primary forms of cell movement. Individual cells move when there is single cell migration. Cell protrusion and adhesion formation at the leading margin, the creation of contractile forces between the leading and trailing edges, and the release of trailing adhesions are typical processes in this kind of migration. Groups or aggregates of cells migrate together during the course of development, wound healing, and some types of cancer metastasis. This process is known as collective cell migration. Compared to single cell migration, this kind of migration is frequently quicker and more organised [13, 27].

Fibroblasts are cells that are present in connective tissue and are in charge of synthesising collagen and fibronectin, two components of the extracellular matrix. Fibroblasts have been studied extensively and are easily cultured in vitro. Fibroblasts that have been cultured have a spreading shape and many extension mechanisms. Growth factors that are expressed in the wound serve as chemotactic and mitogenous agents that promote fibroblast migration. The steps in the fibroblast migration cycle include adhesion creation, cell protrusion, contractile force buildup, and trailing adhesion release, which results in cell retraction. Growth factors have the ability to roughly triple the pace of fibroblast migration [13, 27].

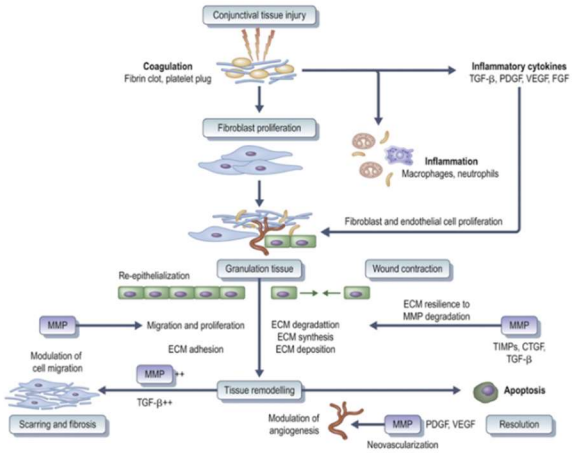

Figure 1 The role of MMP in modulation of cell migration leads to fibrosis wound healing process [27]

Epigalocatechin-3-Gallate (EGCG)

Within the Theaceae family, tea (Camellia sinensis) ranks among the most widely consumed beverages

globally. It has long been accepted that green tea offers therapeutic benefits for both the prevention and treatment of several illnesses. Current scientific research is expanding our understanding of the biological and pharmacological characteristics of green tea, which provides anti-inflammatory and antioxidant benefits. The biological benefits of tea that are attributed to its active ingredients are called catechins, or polyphenols. The primary constituent of catechin compounds and the most potent version of all catechins is epigallocatechin-3-gallate, or EGCG. Significant biological effects of EGCG include anti-microbial, anti-cancer, antioxidant, anti-inflammatory, and anti-fibrotic properties [28, 29, 30].

Role of EGCG in inhibiting wound healing and fibrosis

Research has demonstrated that in models of eye diseases, EGCG has anti-inflammatory, antioxidant, and antiangiogenic properties. Additionally, it has been demonstrated that EGCG causes cell death, inhibits cell development, and prevents numerous cancer cell types from metastasising [31]. One further advantage of EGCG that has been documented is its ability to trigger autophagy. It has been demonstrated that EGCG regulates autophagy to provide anti-inflammatory, anti-proliferative, neuroprotective, and anti-fibrosis effects. EGCG has the ability to boost autophagic flow, lysosomal acidification, and LC3-II production. EGCG has been shown to promote autophagy, which has been linked to antioxidant, anticancer, antidiabetic, and antiobesity benefits as well as neuroprotection, improved metabolism, and tissue repair in a variety of disorders [32, 33, 34].

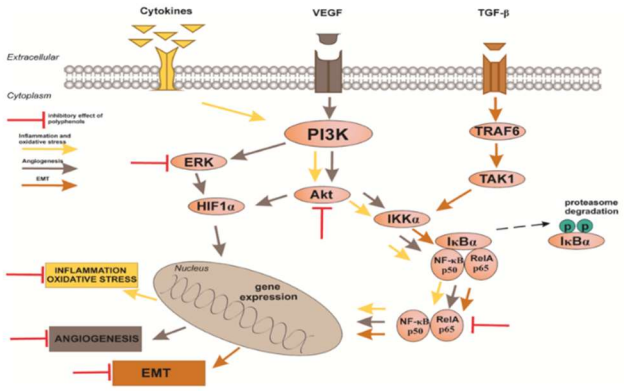

Figure 2 EGCG in modulation of extracellular and intracellular inflammation signals [32]

Using experimental animal models and cell cultures, a number of prior research in the field of ophthalmology have investigated the effects and distribution of green tea catechins on eye tissue. EGCG is primarily present in a range of ocular tissues. Furthermore, studies have demonstrated that green tea extracts, such as epigallocatechin-3-gallate (EGCG), possess antioxidant properties that mitigate oxidative damage to retinal photoreceptors in animal models of age-related macular degeneration (AMD). They also exhibit anti-inflammatory effects that reduce the inflammatory response in autoimmune uveitis, preserve visual function by decelerating photoreceptor degeneration in retinitis pigmentosa, and protect the retinal pigment epithelium from glycation, thereby preventing the onset of diabetic retinopathy. Moreover, by decreasing the production of TNF-α and other interleukins (IL) including IL-1β, IL-6, IL-17, C-C motif ligand 2 (CCL2), and matrix metalloproteinases (MMPs), such as in corneal ulcers and dry eye syndrome, green tea catechins also help to reduce inflammation on the ocular surface. Green tea extract has also been demonstrated to inhibit apoptosis, oxidative stress, and inflammation in retinal ganglion cells, which is relevant to the area of glaucoma [33, 34].

Many therapeutic properties, including anti-oxidative [35], anti-inflammatory [36], and anti-fibrotic

actions [37], are displayed by EGCG. It might influence epigenetic modifications including DNA methylation and histone acetylation, as well as cell signalling pathways like NF-κB, AMP-activated protein kinase (AMPK), and mitogen-activated protein kinase (MAPK) [38]. Renowned for its ability to target mitochondria, EGCG has the potential to control several aspects of mitochondrial metabolism, including biogenesis and bioenergetics. Additionally, it may modulate the cell cycle and programmed cell death through pathways mediated by the mitochondria [39,40].

The persistent activation of NF-κB, along with excessive production of pro-inflammatory cytokines and proteolytic enzymes, depletion of the Nrf2 antioxidant system, activation of growth factors, and heightened expression of fibrogenic and angiogenic factors, results in increased levels of matrix metalloproteinases (MMPs), smooth muscle actin (SMA), collagen, and associated components, all of which play a role in the development of lung fibrotizing diseases. Epigallocatechin-3-gallate (EGCG) has been shown to be beneficial in the treatment of these conditions [39, 40,41]. EGCG treatment has been shown to prevent a reduction in body weight, lower markers of inflammation such as TNF-α and IL-1β levels, and inhibit the activities of NF-κB and myeloperoxidase (MPO). Additionally, it reduces lipid peroxidation markers, increases antioxidant levels that enhance Nrf2 activity, and decreases the content of hydroxyproline, a collagen degradation product associated with the downregulation of MMP-2, MMP-3, TGF-β1, and α-SMA [42,43,44,45,46].

CONCLUSION

In order to effectively treat fibrosis after trabeculectomy, it is critical to comprehend the mechanisms by which EGCG influences wound healing processes. In order to increase surgical intervention success rates and boost patient outcomes, future research should concentrate on the therapeutic use of EGCG.

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