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KEY ASPECTS OF THE PATHOGENESIS OF THE SCARRING PROCESS (LITERATURE REVIEW)

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ABSTRACT

. This literature review examines key pathogenetic aspects of the surgical wound scarring process. Understanding these processes is essential for developing strategies to manage wound healing after glaucoma surgery, as this can optimize surgical outcomes and prevent potential complications. Targeting the different stages of scarring is an important approach in the correction of wound healing not only in glaucoma surgery but also in other medical fields. The development of methods aimed at regulating inflammation, stimulating tissue regeneration and controlling scar formation improves surgical outcomes and accelerates healing. Research in the fields of molecular biology, polymer chemistry and physics, and pharmacology is helping to identify new target molecules and pathways that can be used to optimize the healing process. This opens up new possibilities for creating innovative treatments and preventing complications after surgery. Thus, molecularly targeted intervention on different stages of scarring represents a promising strategy that can significantly improve surgical outcomes and improve the quality of life of patients.

Key words: surgical wound; scarring; pathogenetic aspects.

INTRODUCTION

With any injury, whether surgical or traumatic, the body triggers an important wound healing process. Cellular damage triggers a series of events and initiates the healing process, which can occur by regeneration (complete tissue repair) and repair (partial repair of tissue structures) [9]. The main priorities of this process include stopping bleeding, preventing infection, and restoring tissue integrity and function [2, 4, 5]. In glaucoma surgery, unlike most other surgeries, the desired outcome is incomplete scarring of the surgical wound to allow filtration of intraocular fluid from the anterior chamber of the eye into the subconjunctival space. This process plays a key role in the successful outcome of surgery. Excessive scarring, on the other hand, can lead to ineffective hypotensive surgery [5,6,7,10].

Most patients who are scheduled for glaucoma surgery take hypotensive medications for a long period of time [20, 22]. These drugs and the preservatives they contain can cause changes on the ocular surface such as decreased tear production, epithelial damage, and chronic inflammation [1, 11, 12, 14, 22]. As a result, there is an increase in the number of epithelial layers and changes in the density of bocaloid cells in the conjunctiva, as well as an accumulation of collagen and cellular elements in the subepithelial layers. Increased expression of proinflammatory cytokines (interferon-gamma (IFN-γ), -alpha (IFN-α), tumor necrosis factor (TNF), interleukins (IL) IL-1, IL-6, IL-8, IL-10, IL-12) is detected in the lacrimal and intraocular fluid [8, 12, 13, 19].

The excessive presence of proinflammatory cytokines and growth factors can increase inflammation, which negatively affects the results of glaucoma surgery. This can lead to a shorter duration of filtering bleb function, decreased filtration area, and contribute to an earlier postoperative increase in intraocular pressure [3, 15, 20, 22].

The wound healing processes of the conjunctiva, tenon capsule, and sclera involve fibrosis formation and go through several stages: traumatic inflammation, connective tissue neogenesis, and scar formation. These processes can be divided into several overlapping phases, including phases of coagulation (hemostasis), inflammation, proliferation, and remodeling. According to morphologic classification, leukocytic, macrophage, and fibroblastic phases are distinguished based on the predominant cell types in each phase. The management of these processes requires a thorough understanding of the pathophysiologic mechanisms of wound healing [4, 16, 18, 25].

The process of acute wound healing is a complex sequence of stages, including hemostasis (stopping bleeding), inflammation, proliferation (cell

multiplication and migration) and remodeling. (see Figure 1) [9]. These stages are dynamic, interrelated, and regulated by various factors.

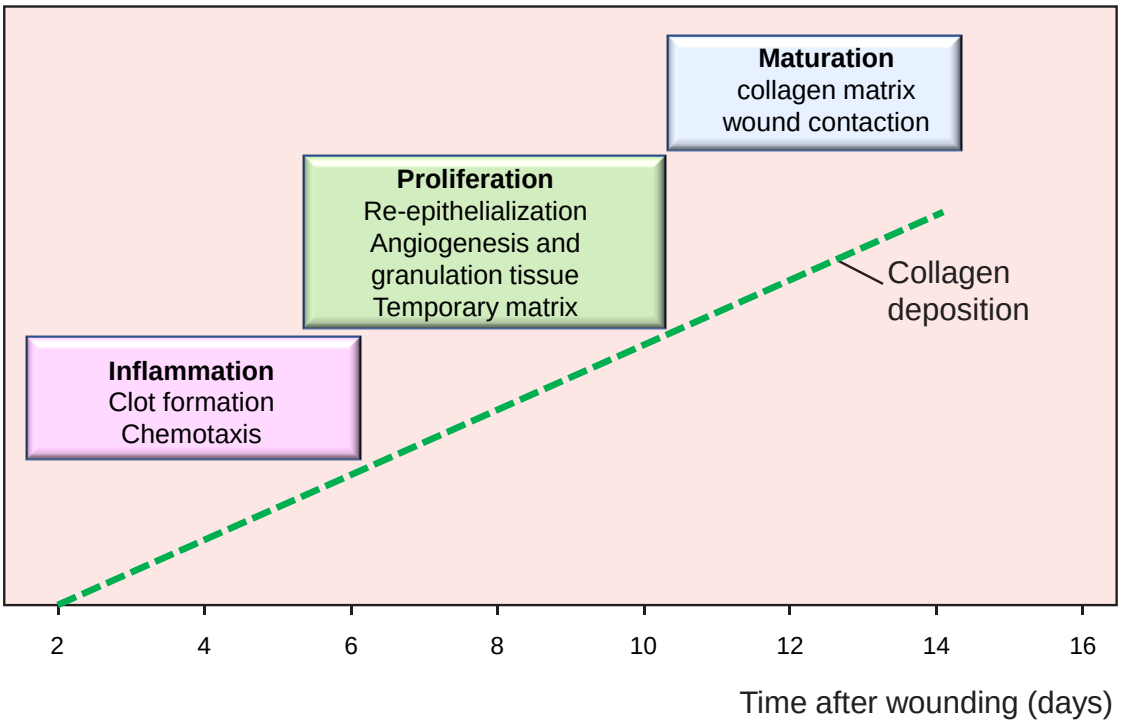

Figure 1. Phases of wound healing [9].

Coagulation phase (hemostasis): When tissue damage occurs, microvessels are injured, causing blood to escape into the wound. To prevent blood loss, the body responds quickly by constricting blood vessels and activating blood clotting, which leads to clot formation and platelet aggregation. This clot, composed of various proteins, serves as the basis for cell migration. Platelets in the clot play an important role in hemostasis and inflammatory response. When activated, they release various substances and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β; transforming growth factor-β, TGF-β), basic fibroblast growth factor (bFGF; basic fibroblast growth factor, bFGF), epidermal growth factor (EGF; epidermal growth factor, EGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), connective tissue growth factor (CTGF) and others. These proteins stimulate wound healing by attracting and activating fibroblasts, endothelial cells, and macrophages [10, 13, 14, 15].

Inflammatory phase: The inflammatory phase lasts for the first five days after the injury, and during this phase neutrophils, immunocompetent cells that perform the function of phagocytosis of bacteria and foreign materials, appear. The number of neutrophils peaks after 24-48 hours and then gradually decreases. However, their presence is not necessary for wound healing, and in the absence of

infection their function is performed by macrophages. In the early stage of inflammation, the complement system and the classical molecular cascade are activated, leading to the entry of granulocytes (neutrophils) and polymorphonuclear leukocytes (PMNL) into the wound area. These cells migrate into the wound tissue, phagocytize bacteria and tissue degradation products, preventing infection, but do not directly affect the healing process [8, 14, 20].

Macrophages actively appear in the wound 48-96 hours after injury, reaching their peak at 72 hours, and remain in the wound throughout the healing process, albeit in smaller numbers. They perform important functions such as phagocytosis of dead tissue and pathogens, and produce various growth factors and cytokines that promote extracellular matrix formation. Unlike neutrophils, macrophages play an integral role in the wound healing process. The intensity of stimulation of new vessels and collagen formation by macrophages directly depends on their number [12, 14, 21, 22, 23].

In the final stage of inflammation, approximately 48-72 hours after the injury, the number of PMNL begins to decrease and monocytes migrate into the wound area. Monocytes transform into macrophages and acquire the appropriate phenotype. Monocyte migration is influenced by various chemoattractants present in the wound area. These may include proteins of the complement and coagulation system, fragments of immunoglobulin G (IgG), collagen and elastin breakdown products, and various cytokines such as TGF β, PDGF, and leukotriene B4. These chemoattractants create a concentration gradient that directs the movement of monocytes toward the wound. Upon reaching the wound, monocytes transform into activated macrophages, which perform various functions related to cleansing tissues of dead cells, bacteria, and breakdown products. They also release cytokines and growth factors that promote wound healing and tissue remodeling [6, 13, 22].

Macrophages play a key role in the inflammation phase (see Figure 2) [9]. In addition to their bactericidal function, they produce cytokines and growth factors necessary for the proliferative phase of healing. They can also release enzymes, such as collagenases, which help to cleanse tissues. If the number of monocytes and macrophages in the body decreases, this can lead to impaired wound healing, delayed fibroblast proliferation, impaired angiogenesis, and the development of fibrosis. Polymorphonuclear leukocytes and macrophages also secrete additional growth factors such as TGF α, heparin-binding EGF-like growth factor (HS-EGF), and FGF-2, which additionally stimulate the inflammatory response [4, 6, 21, 22].

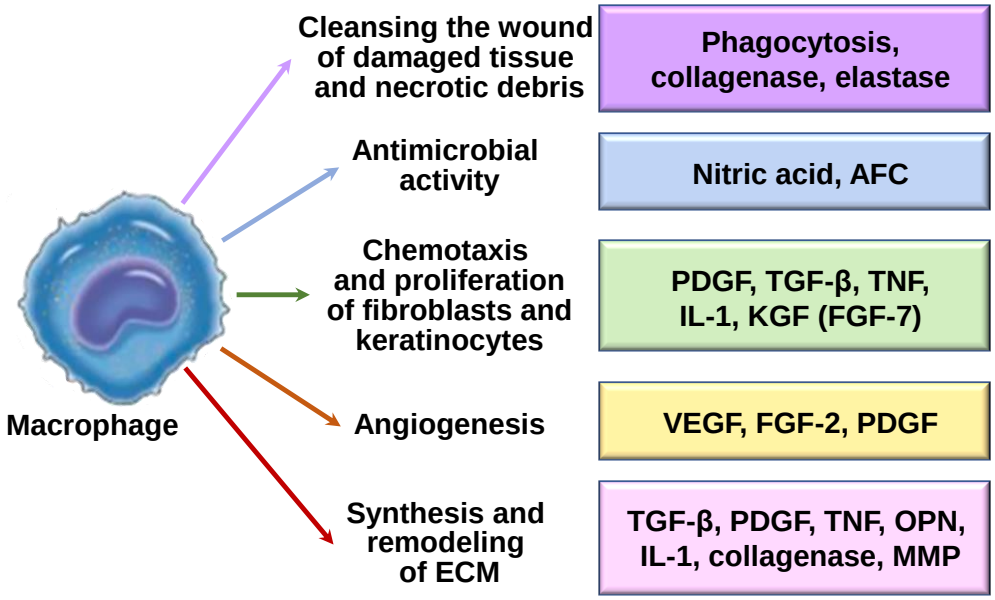

Figure 2. Different effects of macrophages in wound healing [9].

Seventy-two hours after the onset of inflammation, lymphocytes appear in the wound and can be attracted by IL-1 and immunoglobulin G (IgG). IL-1 is considered a key factor in the regulation of collagenase activity, indicating that lymphocytes are involved in the process of collagen and extracellular matrix (ECM) remodeling [11, 13, 21].

Lymphocytes begin to appear in the wound on the first day after injury, but their number increases significantly from day 5 to day 7. Most lymphocytes remain in the wound until day 14, after which their numbers gradually decrease over a period of 4 months. Lymphocytes play a key role in the specific immune response to trauma and infection. T-lymphocytes are activated by contact with antigens presented by macrophages and cause proliferation of antigen-specific cells. The cytokines released by them stimulate other immunocompetent cells such as macrophages and fibroblasts. Experimental evidence supports the necessity of T-lymphocytes for effective wound healing [10, 17, 18]. In the early stages of healing (days 5-14), CD4+ T-lymphocytes predominate and later give way to CD8+ cells. T-lymphocytes stimulate fibroblasts in the initial stages of healing, but then begin to play a regulatory role, limiting the repair process and switching to an inhibitory effect later on [16]. Although the role of lymphocytes in wound healing is still not fully understood, they are thought to play a significant role in chronic inflammation [8, 10, 12, 17, 23].

Thus, the inflammation phase of an acute wound includes activation of the complement system, migration of granulocytes and polymorphonuclear leukocytes, subsequent migration of monocytes and their transformation into macrophages, and the appearance of lymphocytes. All of these cells fulfill their functions in

fighting infection and cleansing tissues, as well as supporting healing and remodeling processes.

Proliferative phase. In the proliferative phase (days 3-14) there is active formation of granulation tissue. During this period, there is a rapid growth of cellular elements, mainly fibroblasts, which show increased activity. The main processes of this phase, such as angiogenesis (formation of new vessels) and fibrogenesis (formation of connective tissue), are controlled by growth factors VEGF, PDGF and TGF- β. These factors are synthesized by both fibroblasts and other immunocompetent cells such as macrophages and lymphocytes. Under the influence of TGF-β, fibroblasts are transformed into myofibroblasts, which promote contraction and wound healing [11, 14, 18, 20, 21].

In this phase, replacement of the original fibrin/fibronectin matrix by newly formed granulation tissue occurs. Within 2-4 days after wound formation, fibroblasts and myofibroblasts migrate into the wound. The fibroblasts begin to synthesize ECM including types I and III collagen, elastin, laminin-1, nidogen, and glycosaminoglycans such as chondroitin sulfate, hyaluronic acid, and dermatansulfate. These components attract large amounts of water and sodium. Fibroblasts also secrete cytokines and growth factors that affect both the fibroblasts themselves and surrounding cells. This process is enabled by the secretion of a number of growth factors, including fibroblast growth factor binding protein (FGFBP). FGFBP stimulates collagen synthesis and fibroblast proliferation [5, 7, 18].

Fibroblasts, the cells responsible for wound healing, produce various cytokines and growth factors that affect neighboring cells. For example, they secrete FGFBP, epidermal growth factor (EGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), FGF-10, and others [8, 14, 16]. Fibroblasts also interact with keratinocytes, skin epithelial cells. They stimulate keratinocytes to synthesize basal membrane components such as types IV and VII collagen, laminin-5, and perlycan [15, 20, 23]. In response, keratinocytes produce cytokine IL-1, which in turn stimulates fibroblasts to synthesize KGF-7 (keratinocyte growth factor) [14, 24, 25].

Thus, there is an interaction between fibroblasts and keratinocytes that promotes the synthesis and remodeling of the basal membrane. These interactions form a complex system of positive feedback, where fibroblasts and keratinocytes mutually stimulate each other, contributing to the wound healing process.

The formation of newly formed vessels occurs at all stages of the healing process. The growth factors such as TNF-β and PDGF released by platelets during the hemostasis phase attract macrophages and granulocytes, stimulating the

process of angiogenesis. Macrophages play a key role in this process by secreting TNF-α and FGF-2. Capillary sprouts infiltrate the fibrin/fibronectin wound clot and form a branched microvascular network in the granulation tissue within days. As collagen accumulates in the granulation tissue, the density of blood vessels decreases. An imbalance in the process of angiogenesis and new blood vessel formation can lead to delayed wound healing. It is important to maintain a balance in these processes for effective tissue regeneration and wound healing [14, 24].

Granulation tissue consists of actively dividing fibroblasts, capillaries, and tissue macrophages in a matrix composed of collagen, glycosaminoglycans, hyaluronan, fibronectin, and tenascin. Granulation tissue formation begins in the wound about 48 hours after injury, and by 96 hours, fibroblasts become the major cell type in this tissue. Approximately 48 hours after injury, granulation tissue formation begins in the wound, and by 96 hours, fibroblasts become the major cell type in this tissue [24].

Keratinocytes play an important role in the process of epithelialization and also regulate the formation of new blood vessels by expressing VEGF. The growth of capillaries within the tissue supplies oxygen and nutrients to fibroblasts, promotes cell proliferation, and supports the formation of the structural matrix of the wound. Exudation and edema gradually decrease, and granulation tissue fills the entire wound surface [12, 17, 18].

The remodeling phase, which begins with the development of granulation tissue, is the longest and represents a key stage in the wound healing process. In this phase, there is a gradual strengthening and restructuring of the tissue, which leads to an increase in wound strength. Newly formed collagen fibers reach approximately 80% of the strength of intact skin, which means that complete regeneration and restoration of tissue structure takes some time after healing [15, 22, 25].

The remodeling phase is a balance between tissue formation and destruction, which is controlled by the activities of enzymes such as matrix metalloproteinases (MMP),), and their natural tissue inhibitors (TIMP) [9]. MMPs are a family of enzymes including more than 20 zinc-dependent proteins. MMPs include: collagenases-1, -2, and -3 (MMP-1, -8, and -13), which disintegrate fibrillar collagen types I, II, and III; gelatinases (MMP-2 and -9), which degrade both basal membrane collagen and fibronectin; stromelysins (MMP-3, -10, and -11), which affect various components of the ECM, including proteoglycans, laminin, fibronectin, and amorphous collagens; and the ADAM family of membrane-bound metalloproteinases. MMPs are produced by fibroblasts, macrophages, neutrophils, synovial and some epithelial cells as precursors. Their secretion is induced by

PDGF, FGF, IL-1, TNF, phagocytosis in macrophages and inhibited by TGF-β and steroids. MMPs are activated by free radicals and proteinases (plasmin). Their half-life is short and they are rapidly inhibited by tissue inhibitors of metalloproteinases (TIMP) produced by mesenchymal cells. Collagenases and their inhibitors are important in the sanitation of injury foci and the remodeling of connective tissue necessary for recovery.

Normally, the ratio of collagen types I and III is approximately 4:1. In the initial stage of wound healing, collagen is deposited without a definite structure, but subsequent wound contraction occurs due to the interaction between fibroblasts and the extracellular matrix, which is probably influenced by various extracellular factors, including TPR-β, TGF, and FGF [14, 18]. Wound healing promotes fiber organization and imparts toughness to the tissue. Initially randomly distributed collagen fibers undergo cross-linking and form bundles that gradually give the tissue elasticity and tensile strength. Under the action of plasminogen activators and MMPs, the extracellular matrix is degraded, resulting in the destruction of hyaluronic acid and fibronectin. As noted by the authors, active remodeling of the scar occurs up to 1 year after injury and continues throughout life very slowly. Over time, the number of macrophages and fibroblasts decreases due to apoptosis, which occurs for unknown reasons [19, 21].

According to the authors [6, 11, 19] the release of cytokines and re-epithelialization factors can contribute to the activation of apoptosis, which helps to remove damaged cells and prepare the tissue for healing. The subsequent remodeling process involves stopping capillary growth, which promotes the formation of a scar without cells or vessels. This final step in the acute wound healing process helps to close the wound and restore tissue integrity [17, 18].

Thus, understanding scarring processes is important in developing strategies to manage wound healing after glaucoma surgery, as it can optimize surgical outcomes and prevent potential complications. Targeting the different stages of the scarring process is a key focus in correcting surgical wound healing not only in glaucoma surgery but also in other fields of medicine. Development of methods aimed at regulation of inflammation, stimulation of tissue regeneration and control of scar formation will improve the results of surgical interventions and accelerate the healing process. Research in molecular biology, polymer chemistry and physics, and pharmacology is identifying new target molecules and pathways that can be used to optimize the healing process. This opens up new possibilities for creating innovative treatments and preventing complications after surgery. Consequently, molecularly targeting different stages of the scarring process is a

promising strategy that can significantly improve surgical outcomes and enhance the quality of life of patients.

REFERENCES

1. Alekseeva NT. Morfologicheskie osobennosti ranevogo processa v kozhe pri regional'nom lechebnom vozdejstvii [dissertation]. Voronezh: 2014. 327 p.

2. Germanova VN, Karlova EV, Korigodskij AR. Metodika nasyshcheniya biorezorbiruemogo drenazha ciklosporinom A v profilaktike posleoperacionnogo rubcevaniya v hirurgii glaukomy. Zhurnal nauchnyh statej. Zdorov'e i obrazovanie v XXI veke. 2018;1(20):29-33.

3. Germanova VN. Nasyshchenie antiglaukomatoznyh drenazhej ciklosporinom A kak sposob prolongirovaniya dejstviya preparata v bor'be s posleoperacionnym rubcevaniem. Prakticheskaya medicina. 2018;4(16):92-96.

4. Germanova VN, Karlova EV, Zolotarev AV. Medikamentoznaya profilaktika posleoperacionnogo rubcevaniya v hirurgicheskom lechenii glaukomy. Vestnik oftal'mologii. 2020;4(136):130-137.

5. Zajceva EL, Tokmakova AYu. Rol' faktorov rosta i citokinov v reparativnyh processah v myagkih tkanyah u bol'nyh saharnym diabetom. Saharnyj diabet. 2014;17(1):59-70.

6. Lucevich OE, Tolstyh PI, Tamrazova OB, et al. Sovremennyj vzglyad na patofiziologiyu i lechenie gnojnyh ran. Hirurgiya. 2011;5:72-77.

7. Maksimova NV, Lyundup AV, Lyubimov RO, et al. Patofiziologicheskie aspekty processa zazhivleniya ran v norme i pri sindrome diabeticheskoj stopy. Vestnik Rossijskoj akademii medicinskih nauk. 2014;11-12(69):110-117.

8. Obolenskij VN. Hronicheskaya rana: obzor sovremennyh metodov lecheniya. RMZH. 2013;5:282-289.

9. Osnovi patologii zabolevaniy po Robbinsu and Kotranu. Kumar V, Abbas AK, Fausto N, Aster JK, editors. E.A. Kogan, translator. M: Logosphere; 2014. Vol. 1, Chapter 3. p. 88-120.

10. Petrov SYu, Safonova DM. Sovremennaya koncepciya izbytochnogo rubcevaniya v hirurgii glaukomy. Oftal'mologiya. 2015;12(4):9-17.

11. Rossinskaya VV, Boltovskaya VV, Germanova VN, Karlova EV, Kulagina LN. Vliyanie ciklosporina A na fibroblasty tenonovoj kapsuly cheloveka: issledovanie in vitro. Morfologicheskie vedomosti. 2021;2:58-66.

12. Barbul A, Breslin JP, Woodyard RJ, et al. The effect of in vivo T helper and T suppressor lymphocyte depletion on wound healing. Annals of surgery. 1989;209(4):479-483.

13. Blomme EA, Sugimoto Y, Lin YC, Capen CC, Rosol TJ. Parathyroid hormone-related protein is a positive regulator of keratinocyte growth factor expression by normal dermal fibroblasts. Mol Cell Endocrinol. 1999;152(1-2):189-197.

14. Chang L, Crowston JG, Cordeiro MF, et al. The role of the immune system in conjunctival wound healing after glaucoma surgery. Surv Ophthalmol. 2000;45(1):49-68.

15. Clark RAF, Henson PM. The molecular and cellular biology of wound repair. 2nd ed. New York: Plenum Press; 1996. 611 p.

16. Csosz E, Deak E, Tóth N, et al. Comparative analysis of cytokine profiles of glaucomatous tears and aqueous humour reveals potential biomarkers for trabeculectomy complications. FEBS Open Bio. 2019;9(5):1020-1028. https://doi.org/10.1002/2211-5463.12637

17. Csosz E, Tóth N, Deak E, et al. Wound-Healing Markers Revealed by Proximity Extension Assay in Tears of Patients following Glaucoma Surgery. Int J Mol Sci. 2018;19(12):4096. https://doi.org/10.3390/ijms19124096

18. Cvenkel B, Kopitar AN, Ihan A. Inflammatory molecules in aqueous humour and on ocular surface and glaucoma surgery outcome. Mediators of inflammation. 2010;Article ID 939602. https://doi.org/10.1155/2010/939602

19. de Faria N, Russ H, Rose P, et al. Conjunctival changes and inflammatory aspects in rabbits' conjunctivas induced by fixed combinations of prostaglandin analogues and timolol maleate. J Ophthalmic Inflamm Infect. 2013;3(1):22. https://doi.org/10.1186/1869-5760-3-22

20. Doersch K, DelloStritto D, Newell-Rogers M. The contribution of interleukin-2 to effective wound healing. Experimental Biology and Medicine. 2016;242(4):384-396. https://doi.org/10.1177/1535370216675773

21. Eming S, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. Sci Transl Med. 2014;6(265):265. https://doi.org/10.1126/scitranslmed.3009337

22. Holló G. Wound Healing and Glaucoma Surgery: Modulating the Scarring Process with Conventional Antimetabolites and New Molecules. Glaucoma Surgery. 2017;59:80-89. https://doi.org/10.1159/000458488

23. Schreml S, Szeimies RM, Prantl L, Landthaler M, Babilas P. Wound healing in the 21st century. J Am Acad Dermatol. 2010;63(5):866-881. https://doi.org/10.1016/j.jaad.2009.10.048

24. Yamanaka O, Kitano-Izutani A, Tomoyose K, et al. Pathobiology of wound healing after glaucoma filtration surgery. BMC Ophthalmology. 2015;15(Suppl 1):19-27. https://doi.org/10.1186/s12886-015-0134-8

25. Zada M, Pattamatta U, White A. Modulation of Fibroblasts in Conjunctival Wound Healing. Ophthalmology. 2018;125(2):179-192. https://doi.org/10.1016/j.ophtha.2017.08.028