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The Effect of PRF Membrane Administration on TGF-β and IL-6 Expression in the Superior Rectus Muscle Post-Strabismus Surgery (An Experimental Study on New Zealand Rabbits): A Literature Review

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ABSTRACT

Strabismus surgery is a common treatment for correcting ocular misalignment. However, postoperative complications, such as fibrosis, often arise and affect recovery and surgical outcomes. Fibrosis is influenced by inflammatory mediators, including Transforming Growth Factor-beta (TGF-β) and Interleukin-6 (IL-6). Platelet-Rich Fibrin (PRF), a platelet concentrate known for its regenerative properties, has been studied for its potential to modulate these inflammatory pathways. This review explores the effect of PRF membranes on TGF-β and IL-6 expression in the superior rectus muscle following strabismus surgery. Findings from experimental studies on New Zealand white rabbits suggest that PRF application can reduce these cytokines' levels, thereby limiting fibrosis and promoting better wound healing. PRF's ability to release growth factors may improve surgical outcomes by supporting tissue repair and reducing inflammation. Although promising evidence from animal studies exists, further clinical research is needed to evaluate PRF's effectiveness and safety in human applications. This review highlights the potential of incorporating PRF into surgical protocols to enhance recovery and minimize complications in strabismus surgery.

Keywords: *Ocular Misalignment, Strabismus Surgery, Fibrosis, Wound Healing, Platelet-Rich Fibrin (PRF), Transforming Growth Factor-beta (TGF-β), Interleukin-6 (IL-6)*

1. INTRODUCTION

Strabismus is a condition of ocular misalignment caused by an imbalance in the extraocular muscles. The global prevalence of strabismus is approximately 1.93%, while in Indonesia, the prevalence is lower at around 0.1%. Severe cases often require surgical intervention to realign the eyes, improving visual function, binocular vision, and cosmetic appearance. However, strabismus surgery carries risks of postoperative complications, particularly fibrosis, characterized by the accumulation of fibrous connective tissue due to dysregulated inflammatory responses.[1]

Fibrosis can disrupt normal tissue function and complicate postoperative recovery. Postoperative fibrosis in strabismus surgery is reported in 20–30% of cases, while in other ocular surgeries, such as cataract or retinal surgeries, the prevalence ranges between 10–15%.[2,3] Fibrosis may lead to complications such as discomfort, blurred vision, overcorrection, recurrence, or even the need for reoperation. Severe fibrosis significantly impacts healthcare costs, causes social distress such as depression, and diminishes patient confidence.[4]

The surgical principles of strabismus correction involve weakening stronger muscles and strengthening weaker ones. Postoperative inflammation can result in fibrotic tissue formation. Key inflammatory mediators, including TGF-β and IL-6, play crucial roles in wound healing, fibrosis, and other tissue repair processes. TGF-β is vital in wound healing, stimulating collagen matrix production by hepatic stellate cells and keloid fibroblasts.[1]

IL-6 is a multifunctional cytokine involved in inflammation, immune response, and hematopoiesis [5]. During wound healing, IL-6 regulates inflammation and fibrosis phases. Uncontrolled IL-6 levels can exacerbate fibrosis.[6] Similarly, TGF-β induces fibroblast-to-myofibroblast transition, contributing to scar formation.[7] Increased TGF-β levels correlate with fibrosis severity across various surgeries.[8,9]

Postoperative inflammatory responses trigger elevated levels of IL-6 (50–100 pg/mL in acute cases) and TGF-β (5–10 ng/mL), persisting for days to weeks depending on patient condition and surgery type.[1,10]

Platelet-Rich Fibrin (PRF), a second-generation platelet concentrate, is rich in growth factors, cytokines, stem cells, and leukocytes, which can accelerate wound healing, reduce inflammation, and minimize fibrosis. Leukocyte-PRF (L-PRF), a PRF variant with higher leukocyte concentration, sustains growth factor and cytokine release, making it particularly effective in modulating inflammatory and fibrotic responses.[11]

PRF's demonstrated efficacy in reducing fibrosis and promoting tissue healing through IL-6 reduction and TGF-β modulation makes it a promising candidate for incorporation into strabismus surgery.[12] However, further research is essential to establish its full potential and optimize its application in reducing postoperative complications.

2. STRABISMUS

Definition

Strabismus is a common ophthalmologic condition characterized by misalignment of the eyes, leading to uncoordinated ocular movements. The terminology for strabismus varies depending on the direction of deviation and its stability. Esotropia refers to inward deviation, exotropia to outward deviation, hypertropia to upward deviation, and hypotropia to downward deviation. Conditions described as "foria" indicate latent strabismus, visible only when binocular fusion is disrupted, while "tropia" refers to manifest misalignment present without disruption. Strabismus may be comitant (consistent deviation in all gaze directions) or incomitant (varying with gaze direction, often associated with paralytic or restrictive strabismus).[13]

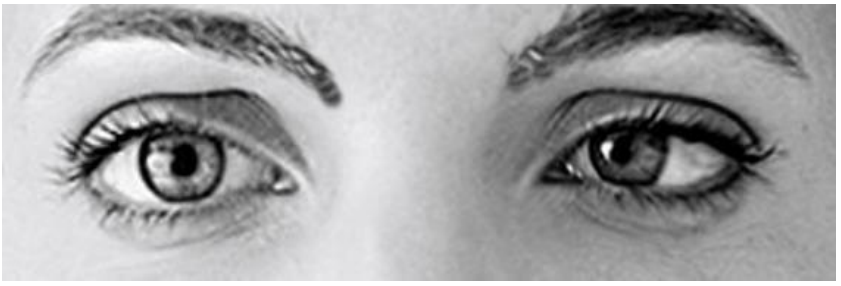

Figure 1: Clinical presentation of strabismus [14]

Function of Extraocular Muscles

Each eye movement results from the coordinated action of six extraocular muscles, responsible for vertical, horizontal, and torsional movements. The medial rectus muscle controls adduction, moving the eye toward the nose, while the lateral rectus controls abduction, moving the eye toward the ear. The superior rectus and inferior oblique muscles facilitate supraduction (upward movement), whereas the inferior rectus and superior oblique control infraduction (downward movement). Additionally, the superior oblique mediates incyclotorsion (inward rotation), and the inferior oblique controls excyclotorsion (outward rotation). These muscles are innervated by different cranial nerves: the superior oblique by cranial nerve IV, the lateral rectus by cranial nerve VI, and the remaining muscles by cranial nerve III.[13]

Two principles govern ocular motility in the context of strabismus. First, Hering's Law of Equal Innervation ensures that agonist muscles in both eyes receive equal stimulation to produce coordinated binocular movements. For example, activation of the lateral rectus muscle in one eye for abduction is matched by activation of the medial rectus in the other eye for adduction. Second, Sherrington's Law of Reciprocal Innervation ensures that agonist-antagonist muscle pairs in each eye receive opposing signals; as one contracts, the other relaxes. For instance, contraction of the medial rectus for adduction results in relaxation of the lateral rectus.[13]

Management of Strabismus

The primary goal of strabismus management is to restore proper eye alignment, with secondary objectives including the treatment of amblyopia, preservation of binocular vision, and elimination of diplopia. Management strategies vary depending on the etiology, type, and severity of the strabismus and individual patient characteristics.[14]

Observation is often the first step for secondary strabismus caused by conditions such as myasthenia gravis, diabetic mononeuropathy, or restrictive strabismus following trauma. Many cases, including neonatal ocular misalignment, resolve

spontaneously as part of normal vergence system development.[14]

Full correction of refractive errors, especially hypermetropia, is a cornerstone of strabismus management. Bifocal lenses or full correction for myopia may be employed for cases like convergence excess esotropia or intermittent exotropia.[15] Refractive correction also successfully addresses amblyopia in nearly one-third of patients.[16]

Amblyopia in strabismus involves reduced visual acuity in one or both eyes due to misalignment, absent other optic pathway abnormalities. Occlusion therapy, the gold standard, involves patching the stronger eye to stimulate use of the weaker eye. This approach is most effective in children under seven years, requiring 2–6 hours of daily patching. Alternatively, atropine 1% drops applied twice daily to the stronger eye achieve similar results.[17,18]

Orthoptic exercises, such as the "pencil push-up" technique, enhance accommodation and strengthen convergence to treat exotropia. This involves holding a pencil at arm's length and slowly moving it toward the nose.[14]

Ophthalmic prisms can shift images closer to the fovea, improving sensory fusion. This method is suitable for deviations less than 20 prism diopters (PD). However, conditions such as amblyopia, suppression, and anomalous retinal correspondence are contraindications for prism therapy.[19]

Medications such as miotics can reduce esotropia by inducing peripheral accommodation. Ecothiopate iodide 0.125% once daily is a short-term treatment for accommodative esotropia, particularly in young children intolerant to glasses.[14] Botulinum toxin type A can induce temporary paralysis of extraocular muscles, aiding strabismus correction, though it may cause transient ptosis or vertical strabismus.[20]

Extraocular Muscle Surgery

Extraocular muscle surgery is considered only when conservative treatments fail to correct deviations. Surgery is indicated for esotropia exceeding 15 PD or exotropia exceeding 20 PD after full optical correction. Accommodative esotropia is not ideal for surgery due to the risk of consecutive esotropia. The optimal age for infantile strabismus surgery is before two years. Postoperative deviations of less than 10 PD yield better binocular vision, while achieving stereopsis requires residual deviations of 4 PD or less. A reduction of 60% of the total deviation or a residual deviation of 10 PD or less six weeks' post-surgery is considered a successful outcome for horizontal strabismus surgery.[14,21]

In Figure 2, the medial rectus muscle is being freed after polyglactin sutures were placed. A Castroviejo locking forceps secures the superior pole of the muscle, while Manson-Aebli scissors are used for cutting. The eyelid is held open using a Cook speculum.[14]

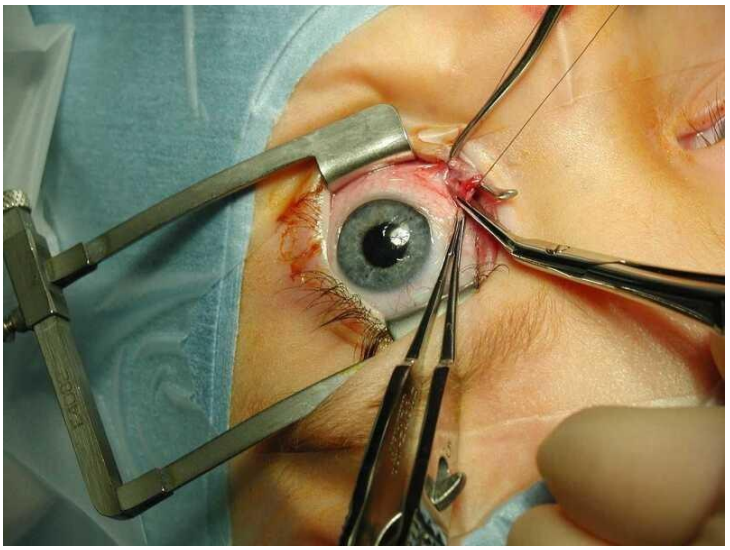

Figure 2: Strabismus surgery [14]

Postoperative Complications in Strabismus Surgery

Postoperative complications from strabismus surgery primarily include infection and fibrosis. Infections range from mild cases, such as conjunctivitis, to moderate conditions like orbital cellulitis, and severe complications such as endophthalmitis. Orbital cellulitis, although rare, can cause vision loss, with an incidence of approximately 1/1,000–1/1,900 cases. Endophthalmitis, which occurs in about 1/30,000–1/185,000 cases, is even rarer but carries a higher risk of blindness. Endophthalmitis is regarded as the most severe complication of strabismus surgery, requiring timely detection and management to prevent significant visual impairment.[22]

Post-surgical scar tissue can form as a response to injury or inflammation. Factors such as fat adherence syndrome, loss of septal elasticity in the extraconal space, shortened conjunctiva, and adhesions between the rectus muscles contribute to scar formation around the eye muscles. These scars may result in stiffness, contracture, or adhesions that hinder proper ocular movement. Such complications can impair visual function and the quality of life of patients undergoing strabismus surgery. Anti-inflammatory medications like steroids can help reduce inflammation and the risk of scarring. Additionally, agents like 5-fluorouracil and mitomycin C have been used intraoperatively to prevent secondary scar formation.[4,22]

Wound Healing in Strabismus Surgery

Wound healing is a complex, integrated process comprising four overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution. These phases must proceed in a specific order, within defined timeframes, and at optimal intensities. Any disruption or prolongation in this process can lead to delayed healing or chronic wounds.[23]

This initial phase, hemostasis, begins immediately after injury with vascular constriction and the formation of a fibrin clot. Platelets within the clot release pro-inflammatory cytokines and growth factors such as TGF-β, PDGF, FGF, and EGF. The next phase is inflammation, where neutrophils infiltrate the wound to clear microbes and cellular debris, releasing proteases and reactive oxygen species (ROS). Macrophages follow, playing dual roles: promoting the inflammatory response by recruiting leukocytes and transitioning to a reparative phenotype to support tissue regeneration. T-lymphocytes migrate later, peaking during the late proliferative or early remodeling phase, contributing to the modulation of wound healing.[23,24]

The proliferation phase involves epithelial proliferation and migration over the wound matrix (re-epithelialization), angiogenesis, collagen synthesis, and ECM production. Fibroblasts and endothelial cells dominate this phase. The final phase, remodeling, involves ECM remodeling and vascular regression, restoring tissue to a near-normal state. Myofibroblasts mediate wound contraction, and the proper alignment and crosslinking of collagen provide tensile strength.[23]

Table 1: Phases of Normal Wound Healing [23]

Phase	Biological and Physiological Events
Hemostasis	Vascular constriction
	Platelet aggregation, degranulation, and fibrin (thrombus) formation
Inflammation	Neutrophil infiltration
	Monocyte infiltration and differentiation into macrophages
	Lymphocyte infiltration
Proliferation	Re-epithelialization
	Angiogenesis
	Collagen synthesis
	ECM formation
Remodeling	Collagen formation
	Vascular maturation and regression

Wound healing follows similar physiological mechanisms across age groups but varies in efficiency. Fetal wounds heal scarlessly due to reduced granulation tissue formation, altered ECM composition, and a modified inflammatory response. In contrast, children's thinner skin and heightened mechanical stress result in more scarring, especially between ages 2 and puberty. Complementary therapies, such as massage, bracing, silicone sheets, and hydrotherapy, can minimize scar formation in children.[25,26]

In regards to the timing of cytokine analysis in experimental studies, day 4 post-surgery is often selected for experimental termination in wound healing studies due to the peak of the acute inflammatory response. During this period, significant increases in pro-inflammatory cytokines such as IL-6 and TGF-β occur, providing an ideal window for analyzing their roles in inflammation and fibrosis.[27,28] Experimental models show that inflammatory responses peak around Day 4–7, with cytokine levels transitioning as the wound environment shifts toward proliferation.[29-31]

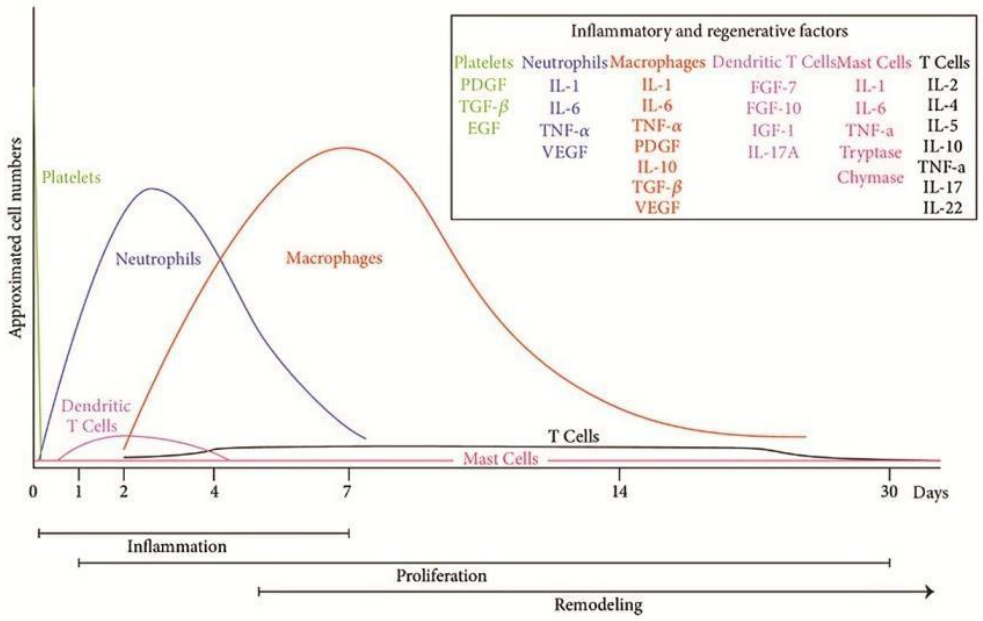

Figure 3: Wound healing process [30]

TGF-B AND IL-6

TGF-β (Transforming Growth Factor-beta) and IL-6 (Interleukin-6) are critical cytokines involved in inflammation and tissue repair, including in the context of strabismus surgery.[28]

The Role of TGF-β in Wound Healing

TGF-β is a multifunctional cytokine crucial for wound healing, produced by keratinocytes, fibroblasts, macrophages, and endothelial cells. During the early wound healing phase, TGF-β attracts neutrophils and macrophages to the injury site, facilitating the removal of cellular debris and bacteria. These immune cells also release additional cytokines and growth factors to promote healing. Following the inflammatory phase, TGF-β stimulates fibroblast proliferation and differentiation. Fibroblasts synthesize collagen, the primary component of scar tissue, which is essential for wound closure. TGF-β also regulates scar remodeling, ensuring that scars are strong yet flexible.[4]

TGF-β plays a vital role in wound healing by affecting several cell types. For example, Saika et al.[32] reported that TGF-β enhances fibroblast proliferation, which is critical for filling tissue defects and producing collagen. Collagen provides structural integrity and support during tissue repair. Additionally, TGF-β has anti-inflammatory properties, suppressing pro-inflammatory cytokine production while promoting anti-inflammatory cytokines. These mechanisms enable TGF-β to regulate the inflammatory response, ensuring an efficient healing process.

Despite its essential role, excessive TGF-β levels can lead to pathological fibrosis in various organs, such as the liver, lungs, and kidneys. In the eye, TGF-β contributes to scar formation following strabismus surgery, as well as in other ocular conditions like corneal opacities, fibrotic conjunctivitis, and diabetic proliferative retinopathy [4]. Researchers are currently exploring therapies to inhibit TGF-β to prevent or reduce fibrosis, showing promising potential for patients with fibrotic disorders.[33]

The Role of IL-6 in Wound Healing

IL-6 is a central mediator of acute inflammation and is critical for timely wound healing. Released early in response to injury, IL-6 induces the production of pro-inflammatory cytokines from macrophages, keratinocytes, endothelial cells, and stromal cells. It also facilitates leukocyte chemotaxis to the wound site.[34] As inflammation progresses, IL-6 signaling mediates the transition to a reparative environment. Proper regulation of IL-6 is essential, as prolonged inflammatory signaling delays healing and increases the risk of infection. Conversely, excessive proliferative signaling can lead to fibrosis, marked by an accumulation of extracellular matrix (ECM) proteins like collagen.[35-36]

Scar formation is the natural endpoint of tissue repair, but excessive scarring can impair normal tissue function. Such pathological fibrosis can also have psychological impacts on patients, often linked to aesthetic concerns and social stigma.[37]

Tissue injury triggers cell necrosis and the release of Damage-Associated Molecular Patterns (DAMPs) such as ATP, DNA fragments, IL-33, and IL-1α. These molecules, normally confined within cells, exert immunomodulatory or inflammatory

effects when released during cell lysis [35]. DAMPs activate pro-inflammatory pathways, including NF-κB and MAPK, stimulating macrophages to release IL-6 as a key regulator of the acute inflammatory response. While IL-6 aids in combating infection and initiating tissue repair, uncontrolled IL-6 production can result in chronic inflammation and excessive fibrosis.[39-41]

Figure 4 illustrates the dual roles of IL-6 in modulating immune cells during inflammation and wound healing. IL-6 enhances the pro-inflammatory activities of Th17 cells, γδ T cells, and M1 macrophages. However, it also promotes anti-inflammatory Th2 cell differentiation and cytokine secretion. Additionally, IL-6 stimulates profibrotic responses in M2 macrophages. Through these mechanisms, TGF-β contributes to IL-6-dependent differentiation of Th17 and γδ T cells.[6]

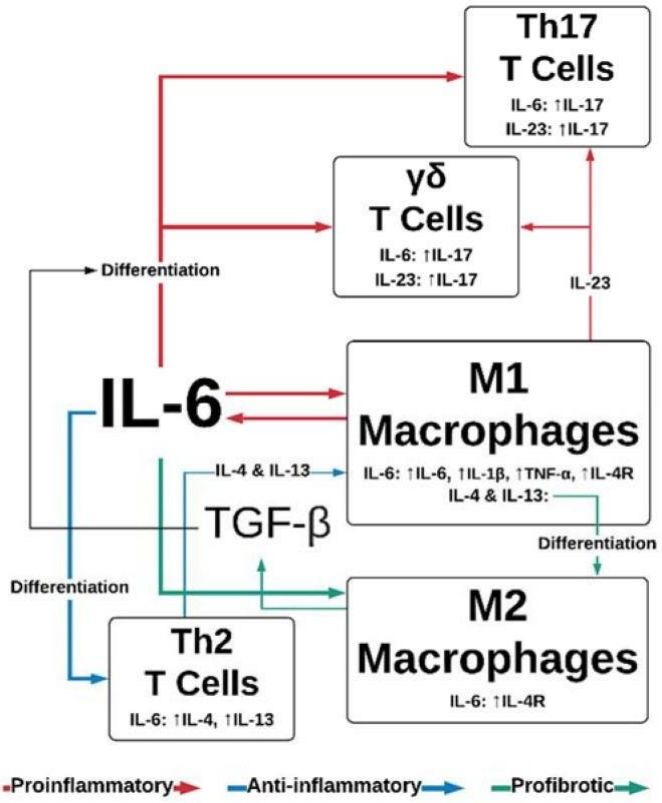

Figure 4: Effects of IL-6 and TGF-β on leukocyte function [6]

IL-6 Trans-Signaling

IL-6 trans-signaling refers to the process where IL-6 binds to its soluble receptor, enabling activation of cells that lack membrane-bound IL-6 receptors. This mechanism allows IL-6 to exert effects on a variety of cell types, including fibroblasts, endothelial cells, and immune cells.[42,43]

IL-6 plays a crucial role in wound healing by attracting fibroblasts to the injury site and stimulating them to produce collagen and fibronectin, essential components for wound closure. It also promotes the formation of new blood vessels at the wound site, ensuring an adequate supply of nutrients and oxygen for cellular repair.[44] However, excessive IL-6 levels can lead to pathological scarring. IL-6 facilitates the differentiation of fibroblasts into myofibroblasts, responsible for wound contraction and collagen production. Additionally, it enhances vascularization, which is beneficial for wound healing but may contribute to fibroproliferative scarring if unregulated.[45,46]

IL-6 can also impair scar remodeling, resulting in rigid and inelastic scar tissue.[47,48] Figure 5 illustrates IL-6-mediated profibrotic interactions among fibroblasts, myofibroblasts, keratinocytes, and endothelial cells. IL-6 works alongside VEGF in endothelial cells to drive neovascularization, perpetuating pathological fibroproliferative scarring. IL-1β, TNF-α, and IL-6 are produced by M1 macrophages at the wound site, while Th17 and γδ T cells produce IL-17.[6,49]

IL-6 also regulates M2 macrophage polarization, which plays a pivotal role in the late stages of wound repair. Additionally, it promotes fibroblast differentiation into myofibroblasts, essential for wound contraction and collagen synthesis.[6]

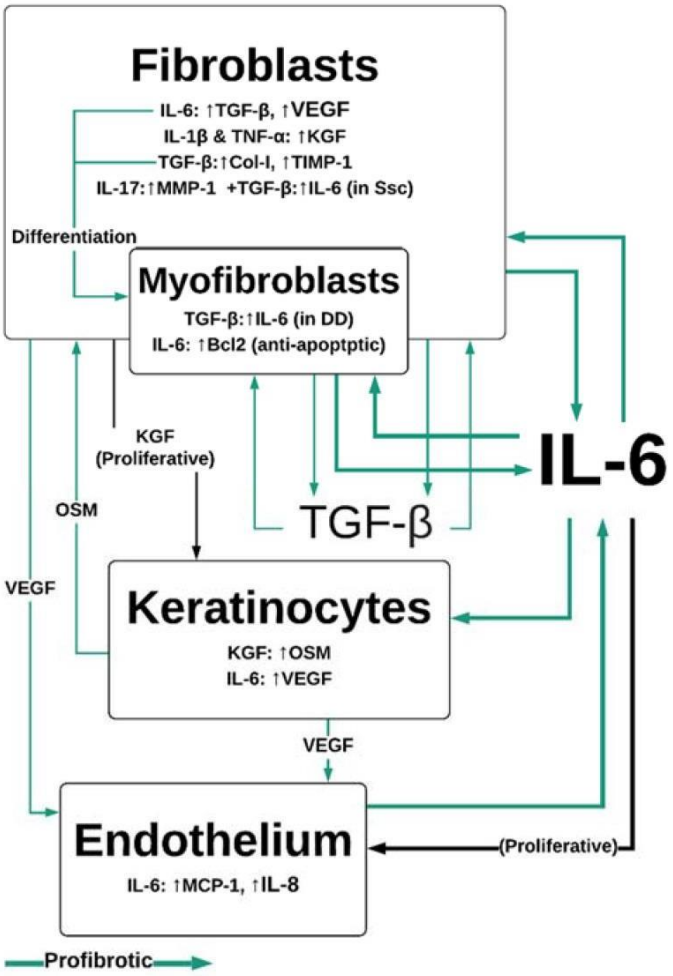

Figure 5: IL-6 and TGF-β mediated interactions [6]

Interaction Between IL-6 and TGF-β

The interaction between IL-6 and TGF-β is central to wound healing and fibrosis. IL-6 stimulates TGF-β production in fibroblasts, keratinocytes, and macrophages, while TGF-β enhances IL-6 receptor expression, increasing cell responsiveness to IL-6.[45]

This interplay is significant in wound healing, as both cytokines accelerate fibroblast proliferation, necessary for filling tissue defects and producing collagen for wound closure. Collagen, the primary component of the extracellular matrix (ECM), provides strength and support to healing tissues. IL-6 and TGF-β also regulate scar remodeling, highlighting the intricate interaction between various factors in the wound healing process. Together, they ensure efficient and effective healing by coordinating different stages of tissue repair.[32]

3. PLATELET-RICH FIBRIN (PRF)

Blood-derived products have been integral to ophthalmologic research since 1946.[50] Platelet-Rich Fibrin (PRF), a second-generation platelet concentrate, has gained attention due to its applications in wound healing. PRF is prepared through centrifugation of autologous blood, yielding a fibrin membrane rich in platelets and bioactive agents. These platelets contain growth factors, adhesion molecules, cytokines, and hemostatic factors that accelerate healing by enhancing cell adhesion, proliferation, and epithelial regeneration. PRF also exhibits anti-inflammatory, antifibrotic, and antimicrobial properties, all critical for effective wound healing.[51-53]

While PRF has been widely adopted in fields such as dentistry, orthopedics, plastic surgery, and otorhinolaryngology, its use in ophthalmology is relatively novel. Nonetheless, PRF has shown promise in managing corneal and ocular surface pathologies.[53-55]

A randomized controlled trial evaluating PRF membranes for donor palatal free gingival grafts found no significant difference compared to commercial collagen dressings.[56] However, PRF membranes were more user-friendly and cost-

effective.[57] The success of PRF applications depends heavily on precise centrifugation protocols, as variations can significantly affect the biological properties of the fibrin matrix.[58]

In the context of platelet concentrates such as PRP (Platelet-Rich Plasma) and PRF, understanding their specific characteristics is vital for optimizing wound healing outcomes. Dohan et al.[59] proposed a classification of platelet concentrates into four types based on preparation methods, composition, and fibrin matrix properties: Pure PRP (PPP/P-PRP), Leucocyte and PRP (L-PRP), Pure PRF (P-PRF), and Leucocyte and PRF (L-PRF). Each type possesses unique characteristics suitable for specific wound healing applications.

4. CONCLUSION

Research on the use of Platelet-Rich Fibrin (PRF) in wound healing following strabismus surgery remains limited. However, existing evidence suggests that PRF effectively accelerates wound healing and reduces fibrosis. PRF has been shown to modulate inflammatory and fibrotic responses by lowering IL-6 levels and regulating TGF-β activity, thereby potentially reducing scar formation and enhancing the quality of wound healing.[11,60,61] Despite these promising findings, further studies are needed to explore the role of PRF in improving wound healing and minimizing fibrosis in the context of strabismus surgery. This study aims to analyze the effects of PRF membrane application on TGF-β and IL-6 expression following strabismus surgery, contributing to a deeper understanding of its therapeutic potential.

5. RECOMMENDATIONS

To maximize the potential of Platelet-Rich Fibrin (PRF) in wound healing and fibrosis reduction, future research should focus on large-scale, randomized controlled trials to validate its efficacy and safety in strabismus surgery, while optimizing preparation protocols and application techniques. Clinically, PRF should be considered for integration into postoperative protocols, especially in cases with a high risk of fibrosis, supported by standardized guidelines for its use in ophthalmology. Additionally, interdisciplinary collaboration among researchers, clinicians, and material scientists is essential to refine PRF formulations and explore adjunctive therapies that could further enhance its therapeutic benefits.

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