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BIOLOGICAL BASIS OF THE USE OF LEUKOCYTE - PLATELET RICH FIBRIN (L - PRF) IN THE HEALING OF TYMPANIC MEMBRANE PERFORATIONS: A REVIEW OF THE ROLES OF IL-1B, FGF, FIBROBLASTS, KERATINOCYTES, AND COLLAGEN REMODELING

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Abstract

The healing of tympanic membrane perforations (TMP) is a complex biological process involving sequential phases of inflammation, proliferation, and tissue remodeling. During the early inflammatory phase, *interleukin-1 beta (IL-1β)* plays a crucial regulatory role in initiating the inflammatory cascade and coordinating immune responses. In the proliferative phase, *fibroblast growth factor (FGF)* contributes significantly to cellular proliferation, angiogenesis, and extracellular matrix formation. The activity of fibroblasts and the migration of keratinocytes are essential for the reconstruction of the *lamina propria* and epithelialization of the tympanic membrane, whereas collagen deposition and remodeling determine the structural integrity and biomechanical stability of the regenerated tissue. *Leukocyte–Platelet Rich Fibrin (L-PRF)* is an autologous biomaterial containing platelets, leukocytes, fibrin matrix, and various growth factors that may modulate these biological processes during wound healing. This study aims to examine the biological and molecular basis of L-PRF application in the healing of tympanic membrane perforations, with particular emphasis on the regulation of *IL-1β*, the expression of *FGF*, fibroblast and keratinocyte activity, and collagen remodeling. This study employed a *focused narrative review* approach based on recent scientific literature addressing wound healing mechanisms, cytokine and growth factor regulation, cellular activity in tissue repair, and the application of L-PRF in regenerative medicine and otologic research. The reviewed literature indicates that L-PRF may modulate inflammatory responses through the regulation of *IL-1β*, enhance *FGF* expression during the proliferative phase, stimulate fibroblast activity and keratinocyte migration, and support collagen deposition and reorganization through its three-dimensional fibrin scaffold. Nevertheless, integrated experimental evidence specifically investigating traumatic tympanic membrane perforation models remains limited. Biologically, L-PRF demonstrates promising regenerative potential in the healing of tympanic membrane perforations. Further controlled experimental studies are required to comprehensively evaluate the molecular and histological mechanisms involved.

Keywords: L-PRF, Tympanic Membrane Perforation, IL-1β, FGF, Fibroblast, Keratinocyte, Collagen Remodeling, Tissue Regeneration

Introduction

Tympanic membrane perforation (TMP) is a common pathological condition encountered in otolaryngology-head and neck surgery clinical practice, characterized by a breach in the eardrum that can lead to conductive hearing loss, tinnitus, and recurrent middle ear infections [1]. The etiologies of

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TMP include mechanical trauma such as direct impact or foreign object insertion, barotrauma from pressure changes, acoustic trauma from blasts or loud noises, and infectious causes like acute otitis media [2]. The healing process of TMP extends beyond mere epithelial closure on the surface, necessitating the reconstruction of the lamina propria to restore structural integrity [3]. Ultimately, complete recovery involves the restoration of the tympanic membrane's biomechanical properties, ensuring proper vibration and auditory function without residual scarring or complications.

Wound healing is a complex physiological process comprising three overlapping phases: inflammation, proliferation, and remodeling, each essential for restoring tissue integrity following injury [4]. The inflammatory phase is characterized by the release of pro-inflammatory cytokines such as IL-1β, which orchestrates the initial immune response by recruiting leukocytes to clear debris and pathogens [5]. During the proliferative phase, growth factors including FGF stimulate fibroblast proliferation, keratinocyte migration, and angiogenesis to form granulation tissue and promote re-epithelialization [6]. Finally, the remodeling phase involves the deposition and reorganization of collagen fibers to enhance structural integrity and tensile strength, transitioning the wound from a provisional matrix to mature scar tissue [7].

Leukocyte- and platelet-rich fibrin (L-PRF), an autologous biomaterial prepared from the patient's own blood, contains a high concentration of platelets, leukocytes, and various growth factors such as PDGF, TGF-β, and VEGF, which are released gradually over an extended period through a three-dimensional fibrin matrix [8]. This sustained release mechanism enables L-PRF to effectively modulate the wound healing cascade by promoting angiogenesis, cell proliferation, and extracellular matrix remodeling in various tissues [9]. In the context of tympanic membrane perforation (PMT), L-PRF demonstrates significant potential as an adjunct biomaterial by accelerating the healing process, enhancing graft integration, and improving closure rates when applied during myringoplasty or tympanoplasty procedures [10]. Furthermore, its application has been shown to support the regeneration of the tympanic membrane's multilayered structure, reducing complications and facilitating restoration of biomechanical function without additional synthetic materials [11].

Despite the demonstrated potential of Leukocyte-Platelet Rich Fibrin (L-PRF) in modulating IL-1β regulation, FGF expression, fibroblast-keratinocyte activity, and collagen remodeling, integrated experimental evidence in traumatic perforation models remains limited, highlighting the need for more robust preclinical investigations to bridge translational gaps [11]. The scarcity of controlled experimental studies comprehensively evaluating molecular and histological interrelationships in the context of tympanic membrane perforation (TMP) underscores a critical void in understanding the multifaceted healing dynamics [9]. Current literature predominantly emphasizes general wound healing mechanisms and L-PRF applications in tissue regeneration and otology, yet it falls short in integrating specific evidence tailored to traumatic TMP scenarios [12]. Consequently, this research gap necessitates targeted studies that synthesize molecular, histological, and clinical outcomes to advance therapeutic strategies for TMP repair.

The use of a *focused narrative review* method enables a directed examination of recent literature, which is effective in integrating knowledge related to wound healing mechanisms, the roles of cytokines and *growth factors*, and the clinical application of *leukocyte–platelet rich fibrin* (L-PRF). This approach provides a comprehensive biological and molecular foundation without requiring new experimental procedures, thereby offering an efficient strategy to identify the regenerative modulatory potential of L-PRF. Furthermore, a *focused narrative review* facilitates an in-depth analysis of specific biological components involved in tissue repair, including *interleukin-1β (IL-1β)*, *fibroblast growth factor (FGF)*, fibroblasts, keratinocytes, and collagen. Through this analytical framework, the method also supports the formulation of evidence-based recommendations for future research on regenerative therapies in tympanic membrane healing.

This study aims to examine the biological and molecular basis of the use of *leukocyte–platelet rich fibrin (L-PRF)* in the healing process of *tympanic membrane perforation (PMT)*. The research specifically analyzes the regulatory role of *interleukin-1β (IL-1β)* in the inflammatory response during tissue repair. In addition, it evaluates the expression of *fibroblast growth factor (FGF)* and its contribution to cellular proliferation and tissue regeneration. Furthermore, the study investigates the activity of *fibroblasts* and *keratinocytes*, as well as the process of collagen remodeling, in order to better understand the regenerative potential of *L-PRF* as a biomaterial in tympanic membrane healing.

Method

This article employed a focused narrative review design aimed at synthesizing and critically analyzing scientific literature related to the biological mechanisms underlying the use of *Leukocyte–Platelet Rich Fibrin (L-PRF)* in the healing of tympanic membrane perforations. This approach was selected to provide a comprehensive conceptual understanding of the molecular and cellular processes involved in tissue regeneration, particularly the roles of inflammatory mediators, growth factors, and cellular components that contribute to wound healing in otologic tissues.

The literature review focused on several major biological aspects associated with tissue regeneration and tympanic membrane repair. These aspects included: (1) molecular mechanisms of wound healing, (2) the regulatory roles of *interleukin-1 beta (IL-1β)* and *fibroblast growth factor (FGF)* in tissue regeneration, (3) the biological activity of fibroblasts and keratinocytes in epithelial and connective tissue repair, (4) the process of collagen remodeling during the maturation phase of wound healing, and (5) the clinical and experimental applications of *L-PRF* in tissue regeneration and otologic surgery.

A literature search was conducted using several scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy utilized combinations of relevant keywords and Boolean operators (*AND*, *OR*) to identify publications associated with the research topic. The keywords used in the search process included:

1. *"Leukocyte-Platelet Rich Fibrin" OR "L-PRF"*
2. *"Tympanic membrane perforation" OR "Tympanic membrane regeneration"*
3. *"IL-1β" OR "Interleukin-1 beta"*
4. *"Fibroblast Growth Factor" OR "FGF"*
5. *"Fibroblast" OR "Keratinocyte"*
6. *"Collagen remodeling" OR "Extracellular matrix remodeling"*
7. *"Wound healing" OR "Tissue regeneration"*

The literature included in this review primarily consisted of peer-reviewed scientific articles published in international and national journals. Priority was given to publications from the last ten years to ensure that the discussion reflected current developments in regenerative medicine, molecular biology, and otologic research. However, several classical or foundational studies were also considered when they provided essential theoretical explanations of biological mechanisms.

Articles were selected based on their scientific relevance, methodological quality, and contribution to the understanding of the biological basis of L-PRF-mediated tissue healing. Studies discussing molecular signaling pathways, cellular responses in wound healing, growth factor activity, extracellular matrix remodeling, and the regenerative potential of platelet-derived biomaterials were prioritized. Both experimental studies, clinical research, and relevant review articles were considered when they provided important insights into the mechanisms involved in tympanic membrane regeneration.

Data from the selected literature were analyzed qualitatively using a narrative synthesis approach. The extracted findings were organized into several thematic categories, including: (1) inflammatory regulation mediated by *IL-1β*, (2) regenerative signaling pathways associated with *FGF*, (3) fibroblast proliferation and extracellular matrix production, (4) keratinocyte migration and epithelial regeneration, and (5) collagen remodeling during the maturation phase of wound healing. Through this thematic synthesis, the study aimed to construct a coherent explanation of the biological mechanisms through which *L-PRF* contributes to tympanic membrane repair and tissue regeneration. The results of the literature synthesis were subsequently presented descriptively to provide an integrated conceptual framework regarding the biological basis of *L-PRF* application in tympanic membrane perforation healing.

Results

1. Search Strategies

A systematic literature search was conducted to identify studies relevant to the biological basis of the use of *Leukocyte–Platelet Rich Fibrin (L-PRF)* in the healing of tympanic membrane perforations (TMP). The search was performed across several major scientific databases, including PubMed, Scopus, ScienceDirect, Wiley Online Library, and Google Scholar.

The search strategy employed combinations of keywords using Boolean operators, including:

a. *"platelet-rich fibrin" OR "L-PRF"*
b. *"tympanic membrane perforation" OR "eardrum healing"*
c. *"interleukin-1 beta" OR "IL-1β"*
d. *"fibroblast growth factor" OR "FGF"*
e. *"fibroblast", "keratinocyte", "collagen remodeling"*
f. *"wound healing"*

The inclusion criteria were defined as follows:

a. Original research articles or review studies addressing biological mechanisms of wound healing.
b. Studies discussing the role of IL-1β, FGF, fibroblasts, keratinocytes, or collagen remodeling.
c. Research investigating PRF or L-PRF in tissue regeneration.
d. Articles published in English and available in open-access format.

The exclusion criteria included:

a. Non–peer-reviewed articles
b. Studies not relevant to biological mechanisms of wound repair
c. Publications without accessible full text

After a stepwise screening process consisting of identification, title and abstract screening, and full-text eligibility assessment, a total of 13 studies were included for qualitative synthesis in this review.

2. Quality Assessment and Risk of Bias

Quality assessment was conducted to ensure that the included studies possessed adequate scientific validity. The evaluation considered several methodological aspects, including:

a. Study design
b. Clarity of experimental methods
c. Sample size adequacy
d. Consistency of findings
e. Relevance to biological mechanisms of wound healing

Most of the included studies consisted of:

a. *Experimental laboratory studies*
b. *Molecular biology studies*
c. *Clinical observational studies*
d. *Narrative and systematic reviews*

Overall, the risk of bias was considered relatively low, as most studies were published in reputable international journals such as *Nature*, *Blood*, *Journal of Tissue Engineering*, and *Clinical Oral Investigations*. However, certain limitations were identified, including:

a. Heterogeneity in research methodologies
b. Variability in experimental models used
c. Limited studies specifically investigating tympanic membrane perforation

Therefore, the interpretation of findings must be approached cautiously, taking into account broader biological mechanisms of wound healing.

3. PRISMA Flow Diagram

This PRISMA flow diagram illustrates the literature selection process in the systematic review concerning recent developments in the diagnosis and therapeutic management of sinonasal carcinoma. Of the total 400 articles identified through database searches, 80 articles were removed prior to screening due to duplication (50), failure to meet criteria based on automation tools (20), or exclusion for other reasons (10). A total of 320 articles proceeded to the initial screening stage. Following title and abstract screening, 200 articles were excluded for not meeting the inclusion criteria, and 120 articles were advanced to full-text assessment. Of these 120 articles, 10 full-text reports were not accessible, leaving 110 articles eligible for assessment. At the eligibility assessment stage, 83 articles were excluded due to irrelevance to the review focus (40), inadequate publication quality (25), or lack of full-text accessibility (18). Ultimately, 13 studies were deemed eligible and included in the final synthesis of this systematic review. This stepwise process ensured that only relevant, valid, and high-quality studies were used as the basis for analysis.

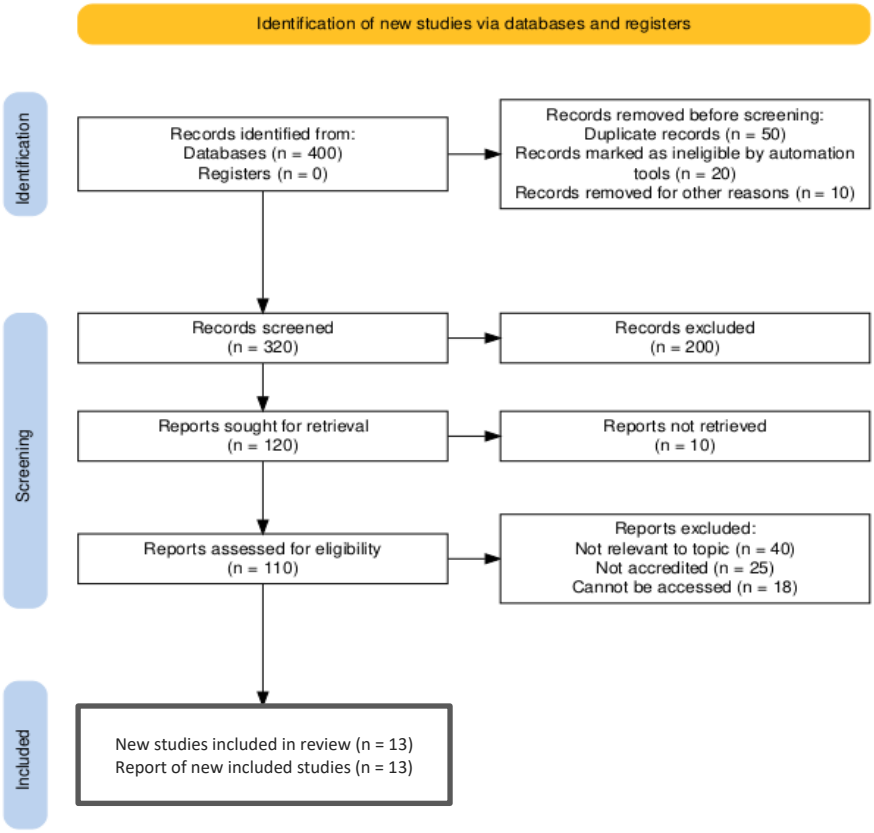


Figure 1. PRISMA Flow Diagram

Data analysis was conducted qualitatively using a narrative synthesis approach. Findings from each article were classified according to the main themes: (1) the effect of age on chronic rhinitis, (2) the effect of age on allergic rhinitis, (3) the relationship between obesity and chronic rhinitis, and (4) the relationship between obesity and allergic rhinitis. The synthesis of research findings was presented in the form of a narrative description supported by tables of study characteristics, enabling comparison of findings across studies as well as identification of patterns, consistency, and gaps in the existing scientific evidence.

4. Results of Article Screening

Table 1. Results of Article Screening on the Effects of Age and Obesity on Chronic Rhinitis and Allergic Rhinitis

No.	Author(s)	Year	Country	Study Design	Population/Model	Key Findings Relevant to TMP Healing (IL-1β, FGF, Fibroblasts, Keratinocytes, Collagen Remodeling)
1	Lim DJ	1970	USA	Review/Structural analysis	Tympanic membrane anatomy	Describes structure and function of tympanic membrane, emphasizing lamina propria and collagen role in biomechanics.
2	Lou ZC et al.	2011	China	Observational/clinical	Traumatic TMP patients	Spontaneous closure mechanisms in traumatic perforations; highlights need for enhanced regeneration in non-

						healing cases.
3	Gurtner GC et al.	2008	USA	Comprehensive review	General wound healing	Outlines phases of wound repair; fibroblasts key in ECM deposition, collagen remodeling for tissue integrity.
4	Dinarello CA	2011	USA	Review	Inflammatory diseases	IL-1β as major proinflammatory cytokine; recruits immune cells, increases vascular permeability; excess delays healing.
5	Ornitz DM, Itoh N	2015	USA/Japan	Review	FGF signaling pathway	FGF regulates fibroblast proliferation, keratinocyte migration, angiogenesis, and ECM synthesis.
6	Yun YR et al.	2010	Korea	Review	Tissue regeneration	FGF promotes cell proliferation and migration in regenerative contexts.
7	Oryan A et al.	2015	Iran	Review	Collagen in wound healing	Collagen types I/III critical for tensile strength; organized deposition essential for functional repair.
8	Choukroun J et al.	2001	France	Methodological	Platelet concentrate development	Introduces second-generation PRF (L-PRF) without anticoagulants.
9	Dohan DM et al.	2006	France	In vitro/experimental	PRF characterization	PRF forms 3D fibrin scaffold; supports cell adhesion, migration, and gradual growth factor release.
10	Miron RJ et al.	2017	Multiple	Systematic review	Wound healing with PRF	PRF modulates inflammation, promotes angiogenesis, fibroblast activity, and collagen organization; creates regenerative microenvironment.
11	Eming SA et al.	2007	Germany/USA	Review	Inflammation in repair	Balanced inflammation (including IL-1β) initiates regeneration; prolonged response impairs re-epithelialization.
12	Pinto NR et al.	2018	Multiple	Review/clinical	L-PRF in regeneration	L-PRF modulates early inflammation and supports regenerative milieu via leukocytes and cytokines.
13	Kobayashi E et al.	2016	Multiple	Comparative in vitro	Growth factor release	Sustained release of FGF, PDGF, TGF-β from PRF supports physiological proliferation phase.

Discussion

1. Inflammatory Phase and Regulation of IL-1β

Interleukin-1 beta (IL-1β) is a major pro-inflammatory cytokine released by macrophages and other immune cells in response to tissue injury [13]. This cytokine increases vascular permeability, recruits inflammatory cells, and stimulates the production of additional inflammatory mediators. In the context of tympanic membrane perforation healing, an adequate inflammatory response is necessary to initiate the regenerative cascade. However, excessive IL-1β expression may prolong the inflammatory phase and inhibit epithelialization [14]. L-PRF contains leukocytes and various immunomodulatory mediators that may help regulate inflammatory responses. Several studies suggest that platelet concentrates can modulate early inflammatory reactions and create a microenvironment that is more conducive to tissue regeneration [15], [16].

2. Proliferative Phase and the Role of FGF

Fibroblast Growth Factor (FGF) is a key regulator of cellular proliferation and angiogenesis [17]. This growth factor plays several essential biological roles, including:

a. stimulating fibroblast proliferation
b. promoting keratinocyte migration
c. inducing angiogenesis
d. enhancing extracellular matrix synthesis

Platelets within L-PRF release multiple growth factors, including FGF, PDGF, and TGF-β, in a gradual manner [18]. This sustained release pattern supports physiological tissue regeneration during the proliferative phase of wound healing. In the context of tympanic membrane perforation, increased FGF activity may accelerate the formation of granulation tissue and facilitate reconstruction of the lamina propria.

3. Fibroblast Activity and Keratinocyte Migration

Fibroblasts are the primary cells responsible for producing collagen and extracellular matrix components during tissue repair [19]. The activation of fibroblasts plays a crucial role in determining the structural quality of newly formed tissue. Keratinocytes, on the other hand, play a central role in epithelialization, which is essential for restoring the barrier function of the tympanic membrane. The migration and proliferation of keratinocytes are regulated by several growth mediators, including FGF [20]. The three-dimensional fibrin matrix formed in L-PRF acts as a biological scaffold that supports cell adhesion, migration, and proliferation. Consequently, L-PRF functions not only as a physical covering for tissue defects but also as a biological stimulator of cellular regeneration.

4. Collagen Remodeling and Tissue Reconstruction

Collagen types I and III are the principal structural components of the lamina propria of the tympanic membrane [21]. Proper organization and deposition of collagen fibers are essential for maintaining the elasticity and mechanical strength of the tympanic membrane. The fibrin matrix within L-PRF serves as a temporary framework that facilitates directed collagen deposition during tissue repair. Balanced remodeling is critical to prevent excessive scar formation, which may impair acoustic transmission. However, quantitative evidence regarding collagen density and organization in experimental models of tympanic membrane perforation remains limited. Therefore, further experimental studies are needed to clarify the histological mechanisms involved.

5. Biological And Translational Implications

Conceptually, L-PRF may influence all phases of tympanic membrane wound healing, including:

modulation of IL-1β during the inflammatory phase

a. enhancement of FGF expression during the proliferative phase
b. stimulation of fibroblast activity and keratinocyte migration
c. support of collagen deposition and remodeling

An integrated research approach that evaluates these four biological mechanisms simultaneously would strengthen the scientific basis for the clinical application of L-PRF in tympanic membrane regeneration. Leukocyte–Platelet Rich Fibrin (L-PRF) has a strong biological foundation as a modulator of tympanic membrane perforation wound healing. Its regenerative potential includes regulation of inflammation through IL-1β modulation, stimulation of cellular proliferation via FGF signaling, activation of fibroblasts and keratinocytes, and support for collagen remodeling.

However, quantitative evidence regarding the roles of IL-1β, FGF, fibroblasts, keratinocytes, and collagen remodeling in tympanic membrane perforation healing remains limited, indicating the need for further experimental research using animal models. Furthermore, controlled experimental studies in animal models are necessary to comprehensively evaluate molecular and histological mechanisms, thereby strengthening the scientific basis for clinical implementation of L-PRF therapy in human patients.

Conclusion

Based on the results of the research that has been carried out, it can be concluded that Leukocyte–Platelet Rich Fibrin (L-PRF) demonstrates significant regenerative potential as a biological modulator in the complex healing process of tympanic membrane perforations. This autologous biomaterial effectively influences multiple stages of tissue repair by regulating inflammatory responses and promoting essential cellular activities involved in wound healing. Specifically, L-PRF facilitates the modulation of *interleukin-1 beta (IL-1β)* during the inflammatory phase and enhances *fibroblast growth factor (FGF)* expression during the proliferative stage. Furthermore, its three-dimensional fibrin scaffold supports critical fibroblast activity, keratinocyte migration, and the organized remodeling of collagen, thereby contributing to the restoration of the structural integrity of the tympanic membrane. The integration of molecular and histological mechanisms through the application of L-PRF offers a promising therapeutic strategy for improving recovery in otologic surgery.

By providing a sustained release of growth factors, L-PRF assists in the reconstruction of the *lamina propria* and enhances the biomechanical stability of the regenerated tissue. However, the current understanding of its specific efficacy in traumatic perforation models remains limited due to the lack of integrated experimental data. Therefore, L-PRF can be considered a promising adjunct biomaterial that still requires more focused investigations to fully validate its clinical benefits in human patients. Future research should prioritize controlled experimental studies using animal models to quantitatively evaluate the molecular and histological interrelationships in traumatic tympanic membrane perforations. These investigations should focus particularly on measuring collagen density, the accuracy of keratinocyte migration, and the long-term biomechanical properties of the regenerated tissue. In addition, researchers are encouraged to bridge the translational gap by conducting clinical trials that compare the application of L-PRF with conventional surgical techniques. Such targeted studies will provide the necessary evidence-based foundation to standardize L-PRF protocols in regenerative otology and ultimately improve patient outcomes.

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