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Short Communication

Harvesting the biochemical potential of L-PRF with their growth factors and cytokines

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ABSTRACT

Leukocyte platelet-rich fibrin (L-PRF) is an autologous biomaterial used in regenerative medicine and tissue healing. This review emphasizes the role of growth factors and cytokines in L-PRF, which contribute significantly to the healing process in various clinical scenarios. The analysis focuses on the controlled release of Platelet-derived growth factors (PDGF), Fibroblast growth factors (FGF), and Vascular endothelial growth factors (VEGF), demonstrating a propensity to promote angiogenesis and stimulate the migration and proliferation of cells necessary for tissue regeneration. The review also examines the roles of anti-inflammatory and pro-inflammatory cytokines, including Interleukins (IL-1, IL-4, IL-10, IL-6) and Tumor necrosis factor-alpha (TNF-α), and Interferon-gamma (IFN-γ), in modulating the inflammatory response during tissue healing. The goal of this comprehensive review is to enhance the understanding of L-PRF and its constituent factors, opening avenues for harnessing its potential in regenerative medicine. The bioactive components within L-PRF stimulate tissue healing and repair, creating an optimal environment for tissue regeneration.

1. Introduction

Leukocyte platelet-rich fibrin (L-PRF) is an autologous biomaterial used in regenerative medicine and tissue healing. It is obtained by centrifuging one's blood samples, producing a fibrin matrix with high concentrations of platelets, leukocytes, growth factors, and cytokines.[1] These substances are crucial for the healing process, making L-PRF a natural scaffold that supports tissue healing and regeneration in various clinical scenarios.[2]

The positive clinical results of platelet-rich fibrin can be attributed to the controlled release of platelet-derived growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor. These growth factors aid in the regeneration process by promoting angiogenesis and stimulating the migration and proliferation of osteoblasts, fibroblasts, and mesenchymal cells.[1,3–5] Furthermore, leukocytes present in the L-PRF membranes can also produce both pro- and anti-inflammatory cytokines, which can impact the outcome of treatments positively or negatively.[3] However, the debate surrounding the effects of these mediators continues in the scientific community.[3–6]

This short review will highlight the role of the main growth factors and cytokines present in L-PRF for tissue healing.

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2. Growth Factors

2.1. Platelet-derived growth factors (PDGF)

In L-PRF, PDGF is a growth factor released by activated platelets. They are essential in tissue healing since they stimulate cell proliferation and act during chemotaxis for different cells. PDGF promotes fibroblast proliferation, which is responsible for collagen production and structural support of the extracellular matrix in tissues.[3] This also helps to increase collagen synthesis and deposition, facilitating tissue repair and wound closure. PDGF plays an important role in angiogenesis by attracting endothelial cells, which promotes the formation of new vessels. This process helps in promoting tissue viability and regeneration.[3,4]

2.2. Fibroblast growth factors (FGF)

FGF is a group of growth factors for tissue healing, especially in soft tissue. As a part of this group, there is the basic fibroblast growth factor, also known as FGFb or FGF-2. FGFb plays an important role in stimulating the growth, development, and movement of different cell types, especially fibroblasts. This phenomenon leads to the production and deposition of collagen, which allows for wound healing. FGFb also helps in the growth of endothelial cells, which support angiogenesis.[7] FGFb further enhances the recruitment and activation of immune cells (e.g., lymphocytes, macrophages, and neutrophils), creating an environment for tissue repair.[3–5]

2.3. Vascular endothelial growth factors (VEGF)

VEGF is a group of growth factors that play a role in angiogenesis. They are essential for tissue healing because they help rebuild the blood supply to damaged tissues, providing them with oxygen and nutrients needed for recovery. VEGF boosts the growth and movement of endothelial cells, which are important in building blood vessels. It also modifies existing blood vessels, ensuring an effective vascular network in healing tissues. By promoting angiogenesis, VEGF improves the transfer of oxygen, nutrients, and immune cells to the injury site, which helps advance tissue regeneration and repair. Additionally, VEGF contributes to vascular permeability, making it easier for immune cells to be recruited to the injury site, initiating the necessary inflammatory response and tissue remodeling for healing.[3–5]

3. Anti-inflammatory Cytokines

3.1. Interleukin-1 (IL-1)

During tissue healing, IL-1 plays a dual role. In the early stages of tissue injury, it promotes the inflammatory response and then initiates the resolution phase. By recruiting immune cells to the injury site and stimulating the production of other cytokines that promote inflammation, IL-1 is important for debris removal, pathogen clearance, and reparative processes. Additionally, IL-1 promotes the production of anti-inflammatory cytokines such as IL-4 and IL-10, which counterbalance the pro-inflammatory effects and help the transition to the resolution phase.[8]

IL-1β is a type of cytokine that supports the body's inflammatory response when healing damaged tissue. It works by attracting immune cells to the injured location and triggering the production of other cytokines. Moreover, it encourages vascular permeability and stimulates the growth of fibroblasts, collagen synthesis, and the restructuring of the extracellular matrix. Matrix metalloproteinases are helpful in tissue remodeling and wound closure.[4,9] An excessive amount of IL-1β can lead to tissue damage, but according to previous studies, the quantity of IL-1β is low and not harmful to human tissues.[3]

3.2. Interleukin-4 (IL-4)

IL-4 has an impact on multiple cell types that contribute to tissue healing. It reduces the production of pro-inflammatory cytokines, which aids in balancing the levels of pro-inflammatory and anti-inflammatory signals. IL-4 encourages the development of immune cells that have an anti-inflammatory phenotype, such as M1 and M2 macrophages. These macrophages are responsible for tissue repair and remodeling by releasing substances that assist in angiogenesis, collagen synthesis, and extracellular matrix remodeling, which ultimately facilitate the healing process.[8–10]

3.3. Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine that helps regulate the immune response and control excessive inflammation during tissue healing. Its main function is to inhibit the production of pro-inflammatory cytokines and reduce the activation of immune cells that contribute to inflammation. Additionally, IL-10 promotes tissue repair by stimulating collagen synthesis, angiogenesis, and fibroblast proliferation. By suppressing immune cell activation and encouraging an anti-inflammatory phenotype, it also helps resolve inflammation. Ultimately, IL-10 plays an essential role in reducing inflammation and promoting tissue healing.[11]

4. Pro-inflammatory Cytokines

4.1. Interleukin-6 (IL-6)

During tissue healing, IL-6 promotes inflammation and serves multiple roles. It causes the production of acute-phase proteins, which are important during the early stages of the immune response. IL-6 also enhances the recruitment

and activation of immune cells to the damaged area, which are responsible for phagocytosis, tissue debris clearance, and the release of pro-inflammatory mediators necessary for tissue repair.[9] Additionally, IL-6 affects various cell types that are involved in tissue healing, promoting fibroblast proliferation, collagen synthesis, extracellular matrix remodeling, and angiogenesis.[3,4]

4.2. Tumor necrosis factor-alpha (TNF-α)

TNF-α plays a role in increasing the inflammatory response by attracting immune cells, such as neutrophils and monocytes, to the injured area. It also stimulates the production of other pro-inflammatory cytokines, which increases the inflammatory process. Additionally, TNF-α promotes fibroblast proliferation, collagen synthesis, and extracellular matrix remodeling, which are essential for tissue repair and scar formation. However, excessive production of TNF-α can harm tissues, causing cell death, disrupting the extracellular matrix, and impeding angiogenesis. It is important to note that the amount of TNF-α in L-PRF is not enough to be harmful to human tissues.[3,4,9]

4.3. Interferon-gamma (IFN-γ)

During tissue healing, the immune response is regulated by IFN-γ. This protein boosts the abilities of macrophages to destroy microbes and remove debris, promoting the production of pro-inflammatory cytokines and chemokines.[12] Antigen presentation is increased, allowing for the cytotoxic T lymphocytes to kill cells. IFN-γ also affects fibroblast function by controlling the production of collagen and the remodeling of the extracellular matrix.[13] This impacts tissue repair and the formation of scars.

5. Prospective Research Directions

Researchers contemplating studies employing L-PRF or similar blood concentrates should consider analyzing these proteins using immunoassay techniques, such as the Enzyme-Linked Immunosorbent Assay (ELISA) – an enzyme-mediated colorimetric substrate amplification method – or fluorescence-based approaches like LUMINEX. The rationale behind this suggestion arises from the diverse methodologies available for producing autologous blood concentrates,[1–5] each considering different parameters, such as the Relative Centrifugal Force (RCF), radius, and rotor angulation. As these parameters may alter the protein release within the biological medium, thereby influencing their quantification, their modification could directly affect the stages under discussion (e.g., tissue healing, inflammation modulation, and angiogenesis). Therefore, it is critical that research protocols, in experimental or clinical studies, at the very least specify the centrifuge model (brand and rotor), speed, and maximum RCF (computed based on maximum radius).[14–16] This data will foster the method's reproducibility, thereby circumventing potential errors in future investigations.

6. Conclusion

L-PRF is a potent blend of growth factors and cytokines that are essential in the recovery process. These substances promote cell growth, the creation of fresh blood vessels, and the reconstruction of tissues. Anti-inflammatory cytokines decrease inflammation, making a favorable setting for tissue mending, while pro-inflammatory cytokines start and manage inflammation, attracting immune cells and activating fibroblast function. It is important to comprehend the roles of these factors to make the most of L-PRF in regenerative medicine.

7. Source of Funding

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8. Conflict of Interest

None.

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