Power System Technology
ISSN:1000-3673

Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Release of Growth Factors and Scaffold Properties of Platelet-Rich Fibrin in Periodontal and Peri-Implant Healing: Mechanism and Clinical Impact

Mesfer Saeed Alalyani[(1)], Raed Abdullah Almalki[(2)], Khaled Saad Alqahtani[(2)], Abdulkarim Abdullah Alabdulkarim[(3)], Hashem Saad Alghamdi[(4)], Saad Abdulqader Alshamrani[(3)], Hamed Mohammed Tashery[(3)], Ziyad Hussain Alharbi[(5)], Mohammed Nasser Alamri[(3)], Ziyad Hamad Alharbi[(3)]

[1] Periodontist, Eastern Riyadh Dental Centre, Riyadh Second Health Cluster, Riyadh

[2] Dental Hygienist, Eastern Riyadh Dental Centre, Riyadh Second Health Cluster, Riyadh

[3] General Dentist, Eastern Riyadh Dental Centre, Riyadh Second Health Cluster, Riyad

[4] Advanced General Dentistry, Eastern Riyadh Dental Centre, Riyadh Second Health Cluster, Riyadh

[5] Dental Hygienist, Dental Services Administration, Riyadh Second Health Cluster, Riyadh

Abstract:

Platelet-rich fibrin (PRF) has shown great potential in periodontal and peri-implant tissues as a biomaterial, for its favourable characteristics of growth factor delivery and bio-scaffold. This review traces the concept of PRF in an assessment of its potential for tissue regeneration, its ability to deliver pertinent growth factors including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β) and vascular endothelial growth factor (VEGF). These factors help in the process of stimulating cell division, development of new blood vessels and eventually collagen synthesis. Besides, PRF's fibrin framework allows cell mobility and tissue incorporation, which also favoured the healing events. This review highlights the fact that PRF enhances clinical efficacy in periodontal and peri-implant therapy concerning tissue regeneration and decrease in inflammation.

Keywords: Platelet-Rich Fibrin, Growth Factors, Scaffold Properties, Periodontal Regeneration, Peri-implant healing

1. Introduction:

Periodontal diseases are disease processes involving the periodontium, a term used to describe the supportive apparatus surrounding a tooth, which includes the gingival tissue, alveolar bone, cementum, and periodontal ligament [1].

Clinically it presents as loss of clinical attachment in relation to the cemento-enamel junction (CEJ) and is associated with an inflammatory reaction in the gingiva clinically detectable as

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

erythema, swelling, and bleeding on probing (BoP). It may also include signs like formation of periodontal pockets, recessions of the gingival margins, involvement of furcation areas, and, eventually, radiographic alveolar bone loss. There might be some reported symptoms like increased mobility, tooth migration, and tilting may also be part of the diagnostic process [2].

The clinical counterpart of periodontal disease in an implant is a vague explanation of peri-implantitis. Peri-implantitis is a progressive and irreversible disease of the hard and soft tissues surrounding the implant and it is accompanied with bone resorption, decreased osseointegration, increased pocket formation and purulence, bleeding on probing, bone loss and deep probing depths [3].

The management of Periodontal disease and its particularly hostile expression as peri-implantitis remains one of the challenges in dentistry.

With the advent of newer methods, the management of periodontal and peri-implant diseases has become a broader scope of research. One such modality for its management is the use of Platelet Rich Fibrin (PRF).

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate that is emerging as a promising biomaterial in regenerative dentistry. It comes with an array of uses in dentistry and specifically in Periodontics. Unlike other platelet concentrates, PRF provides a natural scaffold and releases a variety of growth factors critical for tissue repair.

Platelets contain biologically active proteins that can adhere on to a growing fibrin mesh or on to the ECM. The proteins thus create a chemotactic gradient that will be used in recruiting stem cells. Such stem cells differ and rejuvenate the body since they bring about the healing process through regeneration. Therefore, we can claim that the application of autologous platelet concentrates provides a new perspective in the management of periodontal regeneration, in particular for the treatment of the clinical cases that require a fast-healing process [4].

2. PRF: Preparation of PRF:

PRF is a platelet and growth factor concentrate derived from a small volume of whole blood without anticoagulant that is centrifuged in a closed system to form a fibrin matrix. Since there are no chemical anticoagulants or biochemical additives used in the preparation of PRF, it retains the most natural state of the growth factors as well as the cellular fragments present in PRF, which is also the case with that of PRP.

The classical technique for preparation of PRF was initially introduced by Dr. Choukroun in 2000[5]. The technique involves collection of blood samples from the patient without anticoagulants in 10 ml tubes. The collected sample is immediately centrifuged at a rate of 3000 RPM for 10 min. As soon as the blood touches the test tube walls, during centrifugation, the coagulation cascade is initiated post activation of the platelets.

The outcome consists of the following three layers:

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

● Top-most layer consisting of acellular platelet poor plasma.

● PRF clot in the middle.

● Red corpuscle base at the bottom

3. Types of PRF used in Dentistry [6]:

There was a need for modification of the conventional PRF technique in order to fulfil the various requirements of the treatment modalities and hence some variations were proposed.

PRF can be of six varieties based on their preparation methods and equipment:

a. Leukocyte and platelet-rich fibrin (L-PRF) -Second-generation platelet concentrate, no anticoagulant required for preparation.

b. Advanced platelet-rich fibrin (A-PRF) - Lower rotational speed than L-PRF, more PDGF, VEGF, TGF-β, IGF, more platelets

c. Advanced platelet-rich fibrin plus (A-PRF+) -The centrifugation time is shorter than A-PRF, and there are more TGF, VEGF, PDGF, EGF, and IGF than A-PRF

d. Injectable platelet-rich fibrin (I-PRF) -The preparation time is short, the liquid preparation makes the fibroblast migrate faster and contains more PDGF, TGF-β and collagen I

e. Titanium platelet-rich fibrin (T-PRF)-Titanium induces platelet activation, denser fibrin reticular structure, prolonged growth factor release time and higher concentrations of VEGF, PDGF, TGF, IGF-I and hepatic growth factor (HGF)

f. Horizontal platelet-rich fibrin (H-PRF) -Higher production and more platelets and white blood cells, more cells were evenly distributed in the PRF clot.

An additional category of PRF is the Concentrated platelet rich fibrin (C-PRF) [7]; The liquid PRF that is directly collected from the buffy-coat layer following L-PRF protocols is referred to as concentrated PRF (C-PRF).

These categories of PRF (b-e) are collated under the umbrella of Third generation platelet concentrates.

Each of these PRF have their own set of advantages and disadvantages.

4. Composition of PRF

Platelet-rich fibrin (PRF) is made up of the following components [8,9]:

a. Platelets: The main component of PRF, platelets are responsible for its biological activity.

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

b. Leukocytes: Play a role in growth factor release, anti-infectious activities, immune regulation, and matrix remodelling.

c. Fibrin: A clot that is enriched with platelets and leukocytes.

d. Growth factors: Includes platelet-derived growth factor (PDGF), transforming growth factor (TGF β1), and vascular endothelial growth factor (VEGF).

e. Cytokines: Includes immune cytokines, such as IL-1β and IL-6.

f. Glycoproteins: Includes thrombospondin-1.

In this review article we will concentrate on the Growth factors present in PRF, its properties and mechanism of action.

4.1 Growth Factors:

In general, growth factors are considered to be a small group of proteins that induce a cellular response following the binding to cell receptors. Growth factors are natural biological mediators that regulate those crucial cellular events which are associated with tissue repair and regeneration. Being a distinctive release system of growth factors, platelet-rich fibrin has gained a wonderful position in regenerative medicine. Following is the specific discussion on certain growth factors present in PRF, their release mode, and action on healing of periodontal and peri-implant tissues.

4.1.1 Composition of Growth Factors in PRF

Platelet Rich Fibrin (PRF) is an autologous blood-derived biomaterial with high platelets and leukocyte count, and encapsulated within the fibrin matrix besides a variety of growth factors. It makes a natural scaffold for healing and regeneration of the tissues, thus making PRF a pivotal tool in multiple applications of medicine and dentistry. The growth factors available in PRF include PDGF, TGF-β, VEGF, EGF, IGF1, and FGF. These are key factors which are involved in proliferation, angiogenesis, and the formation of extracellular matrix; the latter three are inter-related but perform different functions that maintain the process of tissue repair [10, 11].

Platelet-Derived Growth Factor (PDGF):

Platelet-derived growth factors (PDGFs) are a family of four cystine-knot-type growth factors: PDGF-A, -B, -C, and -D. The PDGFs are mainly secreted by damaged platelets, fibroblasts, and vascular endothelial cells [12]. PDGF has a great role in the recruitment and activation of fibroblasts responsible for synthesizing collagen and making the extracellular matrix. Their synthesis and secretion increase during the process of wound formation causing neutrophils, macrophages, fibroblasts, and smooth muscle cells to migrate towards the wound area starting the inflammation process. It also has a role in differentiation and maturation morphology by redistributing actin filaments [13]. It also induces migration and proliferation of

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

mesenchymatous cell lineage; it facilitates angiogenesis, macrophages chemotaxis, and activation; it induces the secretion of TGF-β from macrophages [9].

Biological Functions of PDGF

1. **Recruitment and Stimulation of Fibroblasts**: The two major roles of PDGF include recruitment and activation of fibroblasts, which are necessary for collagen synthesis as well as the development of ECM. PDGF stimulates proliferation and differentiation of fibroblasts; therefore, increased collagen synthesis and deposition of ECM enhance tissue repair.

2. **Increase in Production During Wound Healing**: PDGF activity increases dramatically during the healing process of the wound. Up-regulation is important for the recruitment of various cell types, such as neutrophils, macrophages, and smooth muscle cells to the site of the injury. This eventually leads to the induction of inflammation, setting a stage for further healing.

3. **Initiation of Inflammatory Response**: It brings immune cells, such as neutrophils and macrophages, to the site of injury. These responses orchestrate the inflammatory phase, which involves cleaning up debris, fighting infections, and preparing the tissue for repair.

4. **Regulation of Cell Morphology and Differentiation**: PDGF contributes to cell differentiation and morphology through the remodelling of the actin filaments in the cell. The reorganization of these actin filaments is required for the proper functioning of cells, like migrating and holding their structure together; hence, it is easy to have cells move into areas that need repair.

5. **Promotion of Mesenchymal Cell Migration and Proliferation**: It promotes the migration and proliferation of mesenchymal cell lineages, which include fibroblasts, smooth muscle cells, and other tissue repair cells, thus ensuring adequate provision of tissues for repair.

6. **Angiogenesis**: Besides these roles in fibroblast activity, PDGF is also thought to play a role in angiogenesis or the process of creating new blood vessels. It stimulates the proliferation and movement of endothelial cells that are essential for new capillary networks providing nutrients and oxygen for newly regenerating tissues.

7. **Macrophage Chemotaxis and Activation**: PDGF is also a chemotactic agent that attracts macrophages to the wound site. When the macrophages have arrived, they may keep releasing a host of other growth factors, including TGF-β, to continue advancing the repair of tissues. It increases overall effectiveness in healing through the PDGF and macrophage synergism.

Transforming Growth Factor (TGF-β):

TGF-β is a family of isoforms namely: TGF-β1, TGF-β2, TGF-β3. The major function of the TGF-β family is cell proliferation, differentiation, and migration, in all tissues of the human body. Transforming growth factor (TGF) β1 is an activator that helps the tissue repair process

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

and is highly abundant in the bone matrix [13]. Also, it involves the formation of collagen and ECM accumulation. It would modulate the inflammatory response thereby allowing a shift of inflammation to the phase of tissue repair. TGF-β may further promote angiogenesis, collagen synthesis, and release of collagenase as well as modulate osteoblastic cell division [14] thereby promoting the process of tissue regeneration and repair.

Biological Functions of TGF-β

1. **Cell Proliferation and Differentiation:** TGF-β also controls cell proliferation and differentiation. Depending on the cell context, TGF-β can either act pro-growth or anti-growth. For instance, it promotes the differentiation of mesenchymal stem cells towards more specific cell types like osteoblasts and chondrocytes, which are necessary for bone and cartilage formation, respectively.

2. **Extracellular Matrix (ECM) Production:** It also stimulates the production and assembly of the extracellular matrix. TGF-β, primarily through stimulating fibroblast activity, elevates the amount of collagen produced so that tissue shape and function are preserved. This is the basis of why TGF-β is an essential factor in wound healing and regeneration of damaged tissues.

3. **Modulation of Inflammatory Responses:** One of its very important roles attributed to TGF-β has been its role in the modulation of inflammation. It promotes a transition from the inflammatory phase of wound healing to the tissue repair phase. In this phase, the immune cell activity is also regulated so that an over inflammatory state, which may cause harm, is avoided.

4. **Promotion of Angiogenesis**: TGF-β causes the formation of new blood vessels by encouraging the secretion of a number of factors that stimulate proliferation and migration of endothelial cells. This should ease the process of developing new vasculature; indeed, in healing processes, an adequate blood supply is very important for the delivery of nutrition and oxygen to regenerating tissues.

5. **Collagenase Secretion:** TGF-β regulates synthesis, the enzymes responsible for degrading collagen. Secretion of collagenases is one of the ways that regulate remodelling of the ECM in the healing process. Thus, TGF-β maintains the balance between synthesis and degradation of collagen in ensuring the normal architecture of tissues.

6. **Modulation of Osteoblastic Activity:** TGF-β has a strong impact on bone metabolism because of the regulation of osteoblastic activity. The agent is known to enhance the proliferation and differentiation of osteoblasts and modulate activity in response to mechanical stress and numerous signals. This modulation will be important for the maintenance of bone health and the facilitation of repair after injury.

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Vascular Endothelial Growth Factor (VEGF):

Vascular endothelial growth factors (VEGFs) are crucial angiogenic catalysts that are released following exposure to the soluble modulators, such as cytokines and growth factors. The significant functions of the VEGF signalling pathway include the formation of blood vessels, proliferation and migration of endothelial cells, survival of cells, regulation of vascular permeability, and bone homeostasis and repair. It regulates the differentiation and function of osteoblasts and osteoclasts [15]. It incorporates VEGF, one of the key elements involved in the process of wound and injury healing, significantly helping in the angiogenesis process. Increased neovascularization by VEGF increases nutrition and oxygen supply for regenerating tissues and accelerates the periodontal defect-healing process and improves success rate in dental implants.

Biological Functions of VEGF

1. **Angiogenesis**: VEGF is the primary angiogenesis regulator. It promotes the development of new vessels from existing vessels, a phenomenon critical during wound healing and tissue repair. Of particular relevance in areas, including healing from trauma or surgery, that need an enhanced blood supply.

2. **Endothelial Cell Proliferation and Migration**: It facilitates proliferation and motion of endothelial cells-the layer of cells forming the inner lining of blood vessels, thereby promoting the process of angiogenesis.

3. **Cell Survival**: VEGF is a survival factor for endothelial cells. VEGF inhibits apoptosis and maintains the structure and architecture of blood vessels by phosphorylating specific intracellular signalling pathways.

4. **Regulation of Vascular Permeability**: VEGF increases vascular permeability, allowing plasma proteins and other substances to pass through the blood vessel walls. This feature is particularly useful during an inflammatory response; it enables the delivery of immune cells and other critical components to injuries or infections.

5. **Bone Homeostasis and Repair**: VEGF plays the most important role not only in vascularization but also significantly affects bone health. It directly impacts osteoblast, a cell responsible for bone formation during differentiation and function, and osteoclasts which are responsible for bone resorption. Thus, through its regulation of these two primary cellular activities, VEGF plays an integral role in bone homeostasis and bone repair.

6. **Enhanced Nutrient and Oxygen Supply**: The neovascularization induced by VEGF enhances the substantial delivery of nutrients and oxygen to the regenerating tissue. Blood supply plays a crucial role in healing as it ensures tissues obtain necessary resources on their path to recovery and regeneration.

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

7. **Role in Periodontal Healing**: VEGF, especially in the context of periodontal disease, has an important role in healing of periodontal defects. Acceleration of healing is offered due to VEGF-induced angiogenesis necessary for regaining integrity to periodontal tissues. Better blood flow facilitates the supply of the much-needed nutrients and oxygen, thus contributing to the regeneration of structures of periodontal nature.

8. **Impact on Dental Implants**: The success rate of dental implants largely depends upon the quality of vascularization in the adjacent tissues around the implantation site. VEGF-enhanced neovascularization is currently used for the enhancement of integration of dental implants with the surrounding bone, resulting in better outcomes. It assures proper blood supply to the implant site, thus ensuring enough oxygenation and nutrient availability and, therefore, facilitates healing at the site.

Epidermal Growth Factor (EGF):

EGF is a small polypeptide growth factor controlling the growth and differentiation of epithelial periodontal tissues. It is released by platelets, macrophages, and fibroblasts. EGF increases the proliferation of epithelial cells and fibroblasts. In addition to this, it has been identified in considerable amount in saliva after performing periodontal surgery. It also enhances collagen synthesis and exerts chemotactic activity on vascular endothelial cells and fibroblasts [16]. It also stimulates angiogenesis; activates proliferation and differentiation of epithelial cells; increase cytokine secretion in epithelial and mesenchymal cells [9].

Biological Functions of EGF

1. **Epithelial Cell Proliferation and Differentiation:** It is the EGF that is especially known for amplifying the proliferation of epithelial cells; when it binds with specific receptors, it activates signalling pathways, affecting cell division and differentiation. Such an action is important in repairing epithelial tissues after surgery or injuries.

2. **Fibroblast Activation**: In addition to promoting epithelial cell proliferation, EGF stimulates the proliferation of fibroblasts. Fibroblasts are vitally important cells within wound healing as they have the function of producing collagen and other components of the extracellular matrix. Thus, through influencing fibroblast activity, EGF supports integrity and functional recovery of damaged tissues.

3. **Presence in Saliva**: EGF has been detected in higher concentrations in saliva after periodontal surgery, thus indicating its involvement in post-surgical repair. Presence of EGF in saliva also suggests that it may function as a local signalling molecule which facilitates the healing responses of periodontal tissues following surgical interventions.

4. **Collagen Construction**: EGF performs its action in promoting collagen construction, which is absolutely crucial for tissue repair. The same indirectly ensures that the synthesized

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

and deposited collagen within the matrix allows the repaired tissues to regain their structural strength and integrity through improved activity of fibroblasts.

5. **Chemotactic Effects**: EGF can have chemotactic effects to attract different types of cells towards the injury site or site of surgical repair, such as vascular endothelial cells and fibroblasts. This promotes healing by allowing cells to migrate to the site to carry out tissue repair and regeneration.

6. **Promotion of Angiogenesis**: EGF promotes angiogenesis, which is the formation of new blood vessels. It increases the proliferation and migration of endothelial cells to promote angiogenesis and thus promote the creation of new capillaries that supply fresh oxygen and nourishment to healing tissues. For periodontal healing, this function can significantly enhance tissue recovery.

7. **Cytokine Secretion**: It has been proved that EGF is involved in the secretion of cytokines by epithelial and mesenchymal cells. Cytokines are signalling molecules that mediate and regulate various immune reactions, inflammation, and cell communication. The EGF facilitates the secretion of cytokines as part of its coordinating role in the complex tissue repair processes.

Insulin like Growth Factor-1 (IGF1):

IGF is a polypeptide hormone and are growth factors that are isolated from serum and that share some structural and biological properties with insulin. They are massively present in blood circulation but can also be released during platelet degranulation [17]. It stimulates differentiation and mitogenesis of mesenchymal cells [17] and induces survival signals to protect cells from various apoptotic stimuli.

It comes in two forms: IGF 1 and IGF 2.

IGF1, or somatomedin C, is a peptide factor which has been known to exhibit mitogenic and metabolic effects and has mostly been attributed to growth, survival, and differentiation of various cell types and tissues. The IGF system, highly complex, plays a role in odontogenesis, growth, periodontal homeostasis, proliferation, and carcinogenesis within the oral and dentofacial tissues [18]. It also promotes chemotaxis and osteoblast and bone formation activation; it also causes differentiation and mitogenesis of mesenchymal cells [9]. The biological activity of IGFs is through binding with its receptors or proteins on specific target cell surfaces [19]. It exhibits its actions through the activation of PI3K/AKT Pathway, RAS/MAPK Pathway [20].

Biological Functions of IGF1 [18,9]

1. **Mitogenesis and Differentiation**: GF1 is significantly mitogenic; it encourages cell division and differentiation in many cell types, especially in the mesenchymal cells. This action

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

is paramount to the growth and repair of tissues because it encourages the proliferation of fibroblasts and osteoblasts which plays a major role in wound healing and fracture repair.

2. **Survival Signals**: IGF1 offers survival signals that keep the cells from undergoing apoptosis. It supports cell viability by activating certain intracellular signalling pathways. In this way, it plays a more positive role in scenarios where cells usually undergo massive death, like during inflammation or in the case of any injury.

3. **Metabolic Effects**: IGF1 also has effects on metabolism. It increases glucose uptake in many tissues, thereby maintaining insulin sensitivity and optimizing metabolic homeostasis overall. As such, IGF1's contribution to the maintenance of energy homeostasis and to the general support of tissue functions during growth and repair is of considerable significance.

4. **Contribution to Odontogenesis**: Importance to Oral Health IGF1 contributes towards the process of odontogenesis or the development of the teeth in the oral cavity. IGF1 is instrumental in controlling the proliferation and differentiation of General Dentist , Eastern Riyadh Dental center , Riyadh Second Health Cluster,Riyadhodontoblasts, which are responsible for the dentin formation. In essence, it thus also contributes towards the formation and maintenance of teeth.

5. **Periodontal Homeostasis**: IGF1 plays a significant role in maintaining health of the periodontium. This hormone is important in regulating the turnover of periodontal ligament cells, structural integrity within the periodontal tissue, and maintaining healthy alveolar bone that supports the teeth through stimulation of activity in osteoblasts, thus facilitating bone formation.

6. **Chemotaxis and Osteoblast Activation**: IGF1 promotes chemotaxis wherein the osteoblasts are guided to the injury or remodelling locations of the bone. Such action is necessary for effective bone repair since it brings the cells necessary for new bone formation and repairing the damaged tissues.

Fibroblast Growth Factor (FGF):

FGFs are a family of signalling proteins secreted by many cell types. They are known to be involved in cellular proliferation, survival, metabolism, morphogenesis, differentiation, embryonic development, angiogenesis, repair, and regeneration processes. FGFs initiate the process of signalling through their interaction with a family of tyrosine kinase receptors, collectively called FGF receptors (FGFRs) [21]. Such signally pathways controlled by FGFs include RAS/mitogen-activated protein kinase (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)–protein kinase B (AKT), phospholipase C gamma (PLCγ), and signal transducer and activator of transcription (STAT) [22].

Biological Functions of FGFs [21]:

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

1. **Cellular Proliferation and Survival:** FGFs play an important role in promoting cellular proliferation, especially in fibroblasts, endothelial cells, and other mesenchymal cells. Upon binding to their corresponding receptors FGFRs, FGFs initiate crucial signalling events that promote cell cycle and survival. Such plays a critical role during tissue repair when cells need to proliferate rapidly to replace damaged or lost tissues.

3. **Angiogenesis:** Angiogenesis is a prominent feature of FGF function; this term is used to refer to the process whereby new blood vessels originate from pre-existing ones. FGFs, especially FGF-2, also called basic FGF, promote the proliferation and migration of endothelial cells-the lining cells of blood vessels-to facilitate the delivery of oxygen and nutrients to healing tissues and thus support healing and recovery.

4. **Tissue Repair and Regeneration:** FGFs play a crucial role in tissue repair at the wound site. It not only modulates inflammation but also recruits several types of immune cells and fibroblasts to the injury site for effective repair. It is thereby involved in three consecutive phases of tissue repair: formation of granulation tissue, remodelling of the newly formed ECM, and its structural support to the newly formed tissue.

4. **Differentiation and Metabolism:** The FGFs further play a role in differentiating some cell types for the formation of cartilage and bone. FGFs also have additional roles in metabolism by affecting energy metabolism as well as regulation of function in adipose tissue. FGFs modulate metabolic homeostasis by regulating insulin signalling and enhancing glucose uptake by peripheral tissues.

4.2 Mechanisms of Growth Factor Release

One pivotal element for the regenerative potential of PRF could be its ability to release various growth factors. In addition to the activated platelets and leukocytes, the fibrin network acts as a stock for growth factors, enabling an uninterrupted release profile [23]. Vascular endothelial growth factor (VEGF), platelet-derived growth factor-BB (PDGF), and transforming growth factor-β1 (TGFβ-1) are considered proponents of wound healing and can be discovered in the fibrin network [24].

Once the GFs attach to specific cell membrane receptors of target cells, intracellular signalling pathways are initiated, which generally results in the activation of genes that may ultimately change cellular activity and phenotype. The outgrowth of each GF is regulated through a complex system of feedbacks, which include other GFs, enzymes, and binding proteins.

PDGF is locally released by blood platelets during clotting following soft or hard tissue injury Once it is released from the platelets, PDGF binds to specific cell surface receptors promoting prompt cell migration (chemotaxis), and proliferation (mitogenesis), at the site of the injury [25].

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Matrix Degradation-Dependent Release: In PRF, enveloped growth factors are contained within its three-dimensional fibrin matrix. The progressive degradation of this matrix, first by MMPs and other proteolytic enzymes, releases the growth factors slowly. This slow-release guarantees growth factors to be available for a considerable period, making tissue repair and regeneration more robust [26].

Controlled Kinetics: Several studies have shown that PRF exhibits a kinetic profile of releasing growth factors in a controlled manner over days to weeks. This kinetic profile is useful in regenerative therapies whereby growth factor administration achieves high, local, sustained concentration at injury sites, thereby enhancing the processes of tissue repair and healing [27].

PRF possesses a fibrin matrix that favours cell adhesion and proliferation. The cells, due to the interaction with the matrix, will produce additional growth factors and cytokines in a snowball effect that will enhance the healing process. This may be considered as one of the main interactions between the cells and the PRF matrix in the effective processes of tissue regeneration [28].

Mechanism of Action of GFs in periodontal regeneration involves the following steps:

A. Cell Proliferation and Differentiation

The growth factors are vital in the proliferation and differentiation of periodontal cells, and they are prominent players in wound healing and regeneration process.

Platelet-Derived Growth Factor (PDGF):

PDGF is involved in periodontal regeneration as it is associated with stimulation of proliferation and migration of periodontal ligament fibroblasts. PDGF binds to the receptor on fibroblasts surface, PDGF receptor (PDGFR), which activates the receptor, leading to activation of other receptor signalling pathways: PI3K/Akt and MAPK [29]. These signalling pathways, in turn, promote expressions tied to cell division, migration, and ECM production. Current studies support PDGF as a stimulant for periodontal ligament cell proliferation and also being capable of promoting matrix production and healing [9].

Transforming Growth Factor beta (TGF-β):

TGF-β has many actions that positively affect the regenerative process in periodontium. TGF-β stimulates odontoblastic differentiation of mesenchymal stem cells and also affects fibroblasts, osteoblasts, and cementoblasts differentiation and function. TGF-β has cell-surface receptors (TGF-β receptors) and is involved in the activation of smad proteins that affect transcription of numerous genes related to cellular differentiation and ECM synthesis. More recently, TGF-β has received attention for its role in promoting the regenerative capacity of periodontal tissues by regulating cellular responses and ECM production [30].

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

B. Matrix Production

One of key aspects in generating tissue is making ECM to create scaffolds to promote growth of new cells and repair of tissue.

Bone Morphogenetic Proteins (BMPs):

BMPs, with emphasis to BMP-2, BMP-4, and BMP-7 have been found to be important in bone and periodontal tissue repair. BMPs interact with their targeted receptors on the cell surface of target cells and activate both Smad dependent and Smad independent signalling pathways which in turn cause the differentiation of osteoblasts and cementoblasts and increased synthesis of ECM [31,32]. Research has shown that BMPs also induce the synthesis of additional extracellular matrix components, such as collagen and osteocalcin, which are important for tissue repair and bone formation [32].

TGF-β: TGF- β is another important cytokine that plays a role in the deposition of ECM components. TGF-β promotes the deposition of collagen and glycosaminoglycans on which the organization of Periodontal tissues is dependent [33]. TGF-β influences the deposition of the ECM by inducing genes that regulate the synthesis of collagen and the matrix remodelling process as a part of periodontal tissue repair and regeneration process [32].

C. Angiogenesis

Angiogenesis is the process of creation of new blood vessels, it is necessary for providing nourishment for growing tissues.

Vascular Endothelial Growth Factor (VEGF):

VEGF plays a critical role in the process of angiogenesis. When the VEGF receptor sites on endothelial cells are stimulated, it produces proliferation and migration, leading to the formation of blood vessels. New blood vessels are thus formed that are said to be essential in improving the blood flow in the recovering tissues of periodontal tissues. Recent studies report that VEGF had a positive impact on the formation of capillary networks and promoted tissue regeneration in periodontal therapy [34].

D. Regulation of Inflammation

Periodontal inflammation in particular must be controlled because high levels of inflammation are known to hinder regeneration of tissues.

TGF-β:

TGF-β is pro-inflammatory and anti-inflammatory depending on the circumstance as it affects the immune response. This interferes with inflammation cell activation and decreases the synthesis of the cytokines which are pro-inflammatory and, therefore, reduces inflammation too much, while at the same time encouraging tissue repair. Latest studies have supported TGF-

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

β's role in both modulating inflammation and regulating tissue repair in the periodontal region [35].

E. Reversal of Tissue Damage

Several aspects of growth factors have influence on cells including cell growth, promotion, cell survival, enhancement, and inhibition of apoptosis.

Fibroblast Growth Factor (FGF):

FGF accelerates epithelialization, enhances the proliferation of fibroblasts that are crucial for the healing process [36]. Hence, FGF acts through engaging FGF-receptors to stimulate signalling processes that promote fibroblast motility, proliferation, and ECM deposition [37]. Some studies also show evidence of FGF, which positively influences periodontal tissue regeneration by promoting fibroblast activities and tissue remodelling [38].

5. Scaffold Properties of PRF

In periodontics, a scaffold refers to a three-dimensional (3D) structure used to support and guide the growth of cells, tissues, and bone in the treatment of periodontal defects. The excellence and quality of fibrin scaffold are controlled by an array of elements like, rotation speed, centrifugal unit duration, temperature, and blood haematocrit values [39].

These scaffolds provide a framework for [40]:

1. Cell attachment and proliferation

2. Tissue regeneration

3. Bone growth

For the ease of understanding the scaffold properties of PRF, it can be divided as Mechanical and Biological Properties.

5.1 Mechanical Properties:

It is a network of fibrin mesh in which the platelets and leukocytes are also enmeshed. These three-dimensional structures describe a good environment by attachment of cells, their proliferation and migration [41,21].

Mechanical Stability

Fibrin Matrix Properties: The fibrin matrix of PRF provides structural integrity and stability. This network remains intact under physiological conditions, an important requirement for scaffolding during tissue regeneration.

Load-Bearing Capacity: The mechanical strength of PRF makes it suitable to bear physiological loads, especially important in bone regeneration applications where the scaffold must bear stress until new bone tissue replaces it.

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Controlled Degradation [42].

Mechanisms of Degradation: PRF degrades through natural enzymatic processes, in the main action of plasmin that breaks down fibrin. Controlled degradation is necessary to allow cellular infiltration and tissue remodelling.

Healing Implications: Gradual degradation allows for a smooth scaffold-to-nature transition, ensuring cells have ample time to proliferate and differentiate with support during the healing process [42].

Lower modulus of elasticity and hardness:

PRF membranes have a lower modulus of elasticity and hardness than collagen membranes because they are autologous membranes with no external additives. Hence more flexible and easily adaptable [43].

Porosity:

High porosity and adequate pore size to allow cell seeding and diffusion [5].

Barrier membrane [44]:

Blocks the early invasion of undesired cells, thereby acts as a viable barrier between desired and undesired cells.

5.2 Biological Properties:

Biocompatibility [45]:

Autologous Nature: Since it is derived from the individual's own blood, PRF shows high biocompatibility with less potential for immune rejection and adverse reactions.

Clinical Evidence: It has been shown to heal several clinical applications with fewer signs of inflammatory response.

Three-Dimensional Structure [8]:

Formation Process: Whole blood centrifugation creates a porous 3D fibrin matrix that is rich in platelets and leukocytes facilitating cell migration and proliferation.

Significance: This matrix provides enhanced spatial cell architecture which allows complex inter-cellular interactions that are required to be effective for tissue repair

Release of Growth Factors [10, 11]:

Constituent Growth Factors: PRF consists of a set of growth factors (such as PDGF, TGF-β, VEGF) which are essential for cell proliferation, differentiation, and angiogenesis

Relax and Release Profile: These growth factors are released gradually, which simulates the natural healing processes and, therefore, providing the bio-active environment through time

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Cell Adhesion and Proliferation [46]:

Cellular Interaction Mechanism: The fibrin matrix provides specific binding to enhance the adhesion of several cell types. These include mesenchymal stem cells and endothelial cells.

Enhanced Proliferation Rate: There are incidences of increased rate of cell proliferation on PRF scaffolds that is attributed to the synergic action of growth factors combined with a conducive physical environment.

Anti-inflammatory Effects [47]

Cytokine Profile: PRF contains a number of different cytokines, modulated to regulate inflammatory responses, leading to a balanced response and minimizing chronic inflammation.

Clinical Implications: Because PRF increases the inflammatory response on the positive side, it can thus create an environment that will favour healing and minimize complications associated with excessive inflammation, such as delayed healing and fibrosis.

Cell seeding:

Cell seeding is the process of distributing cells into a culture vessel or scaffold for cell culture or tissue engineering. Researchers have demonstrated that cells seeded with PRF have shown better proliferation as compared to other scaffolds [41,48]**.**

Cell viability:

Cell viability is the measure of the proportion of living, healthy cells in the population.

DPSC and OB-DPSC were remarkably improved for viability in scaffolds supplemented with PRF. Thus, it enhances the biological properties of PRF as a scaffold.

6. Specific Clinical Aspects in Periodontal and Peri-Implant Healing:

PRF has been clinically applied, mainly in periodontal regeneration and also in the peri-implant therapy. A rational for such uses can be extrapolated from clinical information.

The following scientific studies demonstrate the exemplary evidence of PRF in aiding periodontal healing:

a. The slow polymerization during centrifugation and fibrin-based structure makes PRF a better healing biomaterial than PRP and other fibrin adhesives [21].

b. PRF, a new generation of platelet concentrate, is a novel step in regenerative periodontal treatment with simplified processing and without biochemical modification [50].

c. I-PRF is helpful and crucial in periodontics for bone regeneration and wound healing. Additionally, it affects osteoblastic behaviour, which aids in the significant release of growth factors when combined with a variety of biomaterials. Therefore, the presence of platelets and growth factors can convert an osteoconductive graft into an osteopromotive one [51].

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

d. The use of A-PRF+ as a human autologous product can give a beneficial influence on periodontal healing [52].

e. The non-surgical application of PRF as an adjunct to scaling and root planing significantly improved the clinical periodontal parameters through raising periostin level in GCF [53].

The following scientific studies demonstrate the exemplary evidence of PRF in aiding peri-implant healing:

PRF could aid in the development of soft tissues of the mucosa in the surgical area of the oral cavity at all stages. PRF could soothe the pain during the surgery, have a superior medium-term recovery effect, reduce the reinfection of peri-implantitis and rejection, as well as promote the growth of regenerated bone and increase the regenerated bone density, so as to lower the wear and tear on the patient's defect site [54].

a. There is comparable efficacy of PRF to FDBA for marginal bone and alveolar ridge preservation following implant loading; however, PRF outperformed FDBA in minimizing gingival recession; therefore, considering its optimal efficacy, easy preparation, and low cost, it could be a promising substitute material for ridge preservation [55]

b. PRF can increase implant stability after implant surgery. PRF may also have a role in hastening bone healing and tends to encourage new bone formation at the implant site [56].

c. The PRF membrane enhances peri-implant tissue wound healing, with gains in soft tissue width and thickness around non-submerged implants [57].

d. Implants coated with platelet-rich fibrin exhibited better osseointegration than implants without platelet-rich fibrin [58].

7.Conclusion, Future Directions and Research:

Despite the wide range of the possible uses, there are probably many more applications of the PRF remains undetermined and further research is required to improve preparations and methods of applying PRF and new fields of its application. The further improvement of the action mechanism of the PRF molecular structure and the development of new composites based on this material can even increase the positive effects of PRF on regenerative medicine. For the formation of protocol of PRF and to discover, more areas of application of regenerative medicine along with other technologies it is necessary to go for more research.

References:

1. Michaud, D. S., Fu, Z., Shi, J., & Chung, M. (2017). Periodontal Disease, Tooth Loss, and Cancer Risk. Epidemiologic reviews, 39(1), 49–58. https://doi.org/10.1093/epirev/mxx006

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

Gasner NS, Schure RS. Periodontal Disease. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan
2. Salvi GE, Roccuzzo A, Imber J-C, Stähli A, Klinge B, Lang NP. Clinical periodontal diagnosis. Periodontol 2000. 2023; 00: 1-19. doi:10.1111/prd.12487
3. Smeets, R., Henningsen, A., Jung, O. et al. Definition, etiology, prevention and treatment of peri-implantitis – a review. Head Face Med 10, 34 (2014). https://doi.org/10.1186/1746-160X-10-34
4. Chandran P, Sivadas A. Platelet-rich fibrin: Its role in periodontal regeneration. Saudi J Dent Res. 2014;5:117–22.
5. Choukroun, J., Adda, F., Schoeffler, C., & Vervelle, A. P. R. F. (2001). Une opportunité en paro-implantologie: le PRF. Implantodontie, 42(55), e62.
6. Shirbhate U, Bajaj P. Third-Generation Platelet Concentrates in Periodontal Regeneration: Gaining Ground in the Field of Regeneration. Cureus. 2022 Aug 16;14(8):e28072. doi: 10.7759/cureus.28072. PMID: 36127983; PMCID: PMC9477433.
7. Miron RJ, Chai J, Zhang P, Li Y, Wang Y, Mourão CFAB, Sculean A, Fujioka Kobayashi M, Zhang Y. A novel method for harvesting concentrated platelet-rich fibrin (C-PRF) with a 10-fold increase in platelet and leukocyte yields. Clin Oral Investig. 2020 Aug;24(8):2819-2828. doi: 10.1007/s00784-019-03147-w. Epub 2019 Dec 2. PMID: 31788748.
8. Chhabra P, Chhabra P, Sharma K. Platelet rich fibrin – its structural design and composition. Int J Oral Health Dent 2019;5(2):81-4.
9. Pavlovic V, Ciric M, Jovanovic V, Trandafilovic M, Stojanovic P. Platelet-rich fibrin: Basics of biological actions and protocol modifications. Open Med (Wars). 2021 Mar 22;16(1):446-454. doi: 10.1515/med-2021-0259. PMID: 33778163; PMCID: PMC7985567.
10. Ming Liu, Yu Liu, Feng Luo, The role and mechanism of platelet-rich fibrin in alveolar bone regeneration, Biomedicine & Pharmacotherapy, Volume 168, 2023, 115795, ISSN 0753-3322.
11. Chang, J., Blanchard, S. B., Windsor, L. J., Gregory, R. L., & Hamada, Y. (2020). Levels of growth factors from platelet-rich fibrin from chronic periodontitis versus periodontally healthy subjects: a pilot study. Clinical Oral Investigations, 24(2), 823–832. https://doi.org/10.1007/s00784-019-02944-7
12. Kardas, G. et al. Role of platelet-derived growth factor (PDGF) in asthma as an immunoregulatory factor mediating airway remodeling and possible pharmacological target. Front. Pharmacol. 11, 47 (2020).
13. Rolny, C. et al. Platelet-derived growth factor receptor-β promotes early endothelial cell differentiation. Blood 108, 1877–1886 (2006).

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

14. Hyun SY, Lee JH, Kang KJ, Jang YJ. Effect of FGF-2, TGF-β-1, and BMPs on Teno/Ligamentogenesis and Osteo/Cementogenesis of human periodontal ligament stem cells. Mol Cells. 2017;40:550–557. doi: 10.14348/molcells.2017.0019.
15. Niklander, S.; Bordagaray, M.J.; Fernández, A.; Hernández, M. Vascular Endothelial Growth Factor: A Translational View in Oral Non-Communicable Diseases. Biomolecules 2021, 11, 85. https://doi.org/10.3390/biom11010085
16. Papamanoli S, Fragkioudakis I, Kalamaki MS, Makris G, Doufexi AE (2021) The Role of Epidermal Growth Factor in Early Tissue Healing After Surgical Periodontal Therapy. J Oral Hyg Health 9: 278. DOI: 10.4172/2332-0702.1000278
17. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):e45–50. 10.1016/j.tripleo.2005.07.009.
18. Jan Reckenbeil, Dominik Kraus, Helmut Stark, Birgit Rath-Deschner, Andreas Jäger, Matthias Wenghoefer, Jochen Winter, Werner Götz, Insulin-like growth factor 1 (IGF1) affects proliferation and differentiation and wound healing processes in an inflammatory environment with p38 controlling early osteoblast differentiation in periodontal ligament cells, Archives of Oral Biology, Volume 73, 2017, Pages 142-150, ISSN 0003-9969,
19. Ayatollahi M, Soleimani M, Tabei SZ and Kabir Salmani M. Hepatogenic differentiation of mesenchymal stem cells induced by insulin like growth factor-I. World J Stem Cells 2011; 3: 113-121.
20. Werner H. The IGF1 Signaling Pathway: From Basic Concepts to Therapeutic Opportunities. Int J Mol Sci. 2023 Oct 4;24(19):14882. doi: 10.3390/ijms241914882. PMID: 37834331; PMCID: PMC10573540.
21. Gadaleta R.M., Moschetta A. Metabolic Messengers: Fibroblast growth factor 15/19. Nat. Metab. 2019;1:588–594. doi: 10.1038/s42255-019-0074-3.
22. Farooq M, Khan AW, Kim MS, Choi S. The Role of Fibroblast Growth Factor (FGF) Signaling in Tissue Repair and Regeneration. Cells. 2021 Nov 19;10(11):3242. doi: 10.3390/cells10113242. PMID: 34831463; PMCID: PMC8622657.
23. Al-Maawi, S.; Herrera-Vizcaíno, C.; Orlowska, A.; Willershausen, I.; Sader, R.; Miron, R.J.; Choukroun, J.; Ghanaati, S. Biologization of Collagen-Based Biomaterials Using Liquid-Platelet-Rich Fibrin: New Insights into Clinically Applicable Tissue Engineering. *Materials* **2019**, *12*, 3993. [**Google Scholar**] [**CrossRef**]
24. Lei, L.; Yu, Y.; Han, J.; Shi, D.; Sun, W.; Zhang, D.; Chen, L. Quantification of growth factors in advanced platelet-rich fibrin and concentrated growth factors and their clinical efficacy as adjunctive to the GTR procedure in periodontal intrabony defects. *J. Periodontol.* **2020**, *91*, 462–472.
25. Kaigler D, Avila G, Wisner-Lynch L, Nevins ML, Nevins M, Rasperini G, Lynch SE, Giannobile WV. Platelet-derived growth factor applications in periodontal and peri-

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

implant bone regeneration. Expert Opin Biol Ther. 2011 Mar;11(3):375-85. doi: 10.1517/14712598.2011.554814. Epub 2011 Feb 3. PMID: 21288185; PMCID: PMC3056074.
26. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb Perspect Biol. 2011 Dec 1;3(12):a005058. doi: 10.1101/cshperspect.a005058. PMID: 21917992; PMCID: PMC3225943.
27. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb Perspect Biol. 2011 Dec 1;3(12):a005058. doi: 10.1101/cshperspect.a005058. PMID: 21917992; PMCID: PMC3225943.
28. Wang X, Fok MR, Pelekos G, Jin L, Tonetti MS. In Vitro and Ex Vivo Kinetic Release Profile of Growth Factors and Cytokines from Leucocyte- and Platelet-Rich Fibrin (L-PRF) Preparations. Cells. 2022 Jun 30;11(13):2089. doi: 10.3390/cells11132089. PMID: 35805173; PMCID: PMC9266245.
29. Wang X, Fok MR, Pelekos G, Jin L, Tonetti MS. In Vitro and Ex Vivo Kinetic Release Profile of Growth Factors and Cytokines from Leucocyte- and Platelet-Rich Fibrin (L-PRF) Preparations. Cells. 2022 Jun 30;11(13):2089. doi: 10.3390/cells11132089. PMID: 35805173; PMCID: PMC9266245.
30. Paolini C, Agarbati S, Benfaremo D, Mozzicafreddo M, Svegliati S, Moroncini G. PDGF/PDGFR: A Possible Molecular Target in Scleroderma Fibrosis. Int J Mol Sci. 2022 Mar 31;23(7):3904. doi: 10.3390/ijms23073904. PMID: 35409263; PMCID: PMC8999630.
31. Zheng L, Shi Q, Na J, Liu N, Guo Y, Fan Y. Platelet-Derived Growth Factor Receptor-α and β are Involved in Fluid Shear Stress Regulated Cell Migration in Human Periodontal Ligament Cells. Cell Mol Bioeng. 2018 Aug 2;12(1):85-97. doi: 10.1007/s12195-018-0546-7. PMID: 31719900; PMCID: PMC6816651.
32. Smith, P. C., Martínez, C., Cáceres, M., & Martínez, J. (2014). Research on growth factors in periodontology. Periodontology 2000, 67(1), 234–250. doi:10.1111/prd.12068.
33. Smith, P. C., Martínez, C., Cáceres, M., & Martínez, J. (2014). Research on growth factors in periodontology. Periodontology 2000, 67(1), 234–250. doi:10.1111/prd.12068.
34. Bordukalo-Nikšić T, Kufner V, Vukičević S. The Role Of BMPs in the Regulation of Osteoclasts Resorption and Bone Remodeling: From Experimental Models to Clinical Applications. Front Immunol. 2022 Apr 26;13:869422. doi: 10.3389/fimmu.2022.869422. PMID: 35558080; PMCID: PMC9086899.
35. Lin X, Patil S, Gao YG, Qian A. The Bone Extracellular Matrix in Bone Formation and Regeneration. Front Pharmacol. 2020 May 26;11:757. doi: 10.3389/fphar.2020.00757. PMID: 32528290; PMCID: PMC7264100.
36. Ito JT, Lourenço JD, Righetti RF, Tibério IFLC, Prado CM, Lopes FDTQS. Extracellular Matrix Component Remodeling in Respiratory Diseases: What Has Been Found in Clinical

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

and Experimental Studies? Cells. 2019 Apr 11;8(4):342. doi: 10.3390/cells8040342. PMID: 30979017; PMCID: PMC6523091.

37. Baru O, Nutu A, Braicu C, Cismaru CA, Berindan-Neagoe I, Buduru S, Badea M. Angiogenesis in Regenerative Dentistry: Are We Far Enough for Therapy? Int J Mol Sci. 2021 Jan 19;22(2):929. doi: 10.3390/ijms22020929. PMID: 33477745; PMCID: PMC7832295.
38. Kany, S., Vollrath, J. T., & Relja, B. (2019). Cytokines in Inflammatory Disease. International Journal of Molecular Sciences, 20(23), 6008.
39. Rombouts, C., & Giraud T. (2020). Angiogenesis in regenerative dentistry. Journal of Oral Diseases, 26(2), 50-60.
40. Kany, S., Vollrath, J. T., & Relja, B. (2019). Cytokines in Inflammatory Disease. International Journal of Molecular Sciences, 20(23), 6008.
41. Koike Y, Yozaki M, Utani A, Murota H. Fibroblast growth factor 2 accelerates the epithelial-mesenchymal transition in keratinocytes during wound healing process. Sci Rep. 2020 Oct 29;10(1):18545. doi: 10.1038/s41598-020-75584-7. PMID: 33122782; PMCID: PMC7596476.
42. Miron, R. J., & Zhang, Y. (2018). Autologous liquid platelet-rich fibrin: A novel drug delivery system. Acta Biomaterialia, 75, 35-51.
43. Nagayasu-Tanaka T, Anzai J, Takedachi M, Kitamura M, Harada T, Murakami S. Effects of combined application of fibroblast growth factor (FGF)-2 and carbonate apatite for tissue regeneration in a beagle dog model of one-wall periodontal defect. Regen Ther. 2023 Apr 22;23:84-93. doi: 10.1016/j.reth.2023.04.002. PMID: 37122358; PMCID: PMC10141504.
44. Ghassemi T, Shahroodi A, Ebrahimzadeh MH, Mousavian A, Movaffagh J, Moradi A. Current Concepts in Scaffolding for Bone Tissue Engineering. Arch Bone Jt Surg. 2018 Mar;6(2):90-99. PMID: 29600260; PMCID: PMC5867363.
45. Egle K, Salma I, Dubnika A. From Blood to Regenerative Tissue: How Autologous Platelet-Rich Fibrin Can Be Combined with Other Materials to Ensure Controlled Drug and Growth Factor Release. Int J Mol Sci. 2021 Oct 26;22(21):11553. doi: 10.3390/ijms222111553. PMID: 34768984; PMCID: PMC8583771.
46. Ahmed, T. A. E., & Dare, E. V. (2014). Fibrin: A Versatile Scaffold for Tissue Engineering Applications. Tissue Engineering Part B: Reviews, 20(5), 477–491.
47. Nasirzade J, Kargarpour Z, Hasannia S, Strauss FJ, Gruber R. Platelet-rich fibrin elicits an anti-inflammatory response in macrophages in vitro. J Periodontol. 2020; 91: 244–252. https://doi.org/10.1002/JPER.19-0216
48. Sam G, Vadakkekuttical RJ, Amol NV. In vitro evaluation of mechanical properties of platelet-rich fibrin membrane and scanning electron microscopic examination of its surface characteristics. J Indian Soc Periodontol. 2015 Jan-Feb;19(1):32-6. doi: 10.4103/0972-124X.145821. PMID: 25810590; PMCID: PMC4365153.

Power System Technology
ISSN:1000-3673
Received: 16-10-2023 Revised: 05-11-2023 Accepted: 22-12-2023

49. Patel H, Bonde M, Srinivasan G. Biodegradable polymer scaffold for tissue engineering. Trends Biomater Artif Organs. 2011;25:20–9.
50. Mohan SP, Jaishangar N, Devy S, Narayanan A, Cherian D, Madhavan SS. Platelet-Rich Plasma and Platelet-Rich Fibrin in Periodontal Regeneration: A Review. J Pharm Bioallied Sci. 2019 May;11(Suppl 2):S126-S130. doi: 10.4103/JPBS.JPBS_41_19. PMID: 31198323; PMCID: PMC6555384.
51. Gollapudi M, Bajaj P, Oza RR. Injectable Platelet-Rich Fibrin - A Revolution in Periodontal Regeneration. Cureus. 2022 Aug 31;14(8):e28647. doi: 10.7759/cureus.28647. PMID: 36196318; PMCID: PMC9525133.
52. Csifó-Nagy, B.K., Sólyom, E., Bognár, V.L. et al. Efficacy of a new-generation platelet-rich fibrin in the treatment of periodontal intrabony defects: a randomized clinical trial. BMC Oral Health 21, 580 (2021). https://doi.org/10.1186/s12903-021-01925-1
53. Al-Rihaymee S, Sh. Mahmood M. The efficacy of non-surgical platelet-rich fibrin application on clinical periodontal parameters and periostin level in periodontitis: Clinical trial. J Cell Mol Med. 2023; 27: 529-537. doi:10.1111/jcmm.17675
54. Sun G, Cao L, Li H. Effects of platelet-rich fibrin combined with guided bone regeneration in the reconstruction of peri-implantitis bone defect. Am J Transl Res. 2021 Jul 15;13(7):8397-8402. PMID: 34377334; PMCID: PMC8340191.
55. Clark, D., Rajendran, Y., Paydar, S., & Ghassemi, A. (2018). Advanced platelet-rich fibrin and freeze-dried bone allograft for ridge preservation: A randomized controlled clinical trial. Journal of Periodontology, 89(4), 379–387. https://doi.org/10.1002/JPER.17-0466
56. Shuai Guan, Tiepeng Xiao, Jiuping Bai, Chunliu Ning, Xingkui Zhang, Lei Yang, Xiangjun Li, Clinical application of platelet-rich fibrin to enhance dental implant stability: A systematic review and meta-analysis, Heliyon, Volume 9, Issue 2, 2023, e13196, ISSN 2405-8440, https://doi.org/10.1016/j.heliyon.2023.e13196.
57. Cheruvu RNS, Katuri KK, Dhulipalla R, et al. Evaluation of soft tissue and crestal bone changes around non-submerged implants with and without a platelet-rich fibrin membrane: A randomized controlled clinical trial. Dent Med Probl. 2023;60(3):437–443. doi:10.17219/dmp/150408
58. Öncü, E., & Alaaddinoğlu, E. E. (2015). The effect of platelet-rich fibrin on implant stability. The International Journal of Oral & Maxillofacial Implants, 30(3), 578–582. https://doi.org/10.11607/jomi.3897