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Review Article

Biological Effects and Molecular Mechanisms of Platelet-Rich Plasma on Periodontal Bone Regeneration

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Abstract: Objective: The study investigated the biological effects and molecular mechanisms of platelet-rich plasma (PRP) on periodontal bone regeneration. **Methods:** Electronic and manual searches were searched up to 1 October 2022 in the following databases: Pubmed, Scopus, Cochrane Library and Embase. [Platelet rich plasma or platelet or growth factors] and [periodontal] or [bone regeneration or bone defect or bone reconstruction] were used for searching. This study reviewed and analyzed published papers associated with PRP and periodontal bone defect restoration or bone regeneration or bone reconstruction. **Results:** Different growth factors exhibited varied biological characteristics and function. In-vitro studies, animal experiments and clinical studies confirmed that PRP displayed assorted role in periodontal bone defects repair. The growth factors secreted from PRP can promote new bone formation, soft tissue regeneration and wound healing. The fiber three-dimensional structure in PRP is conducive to the growth and migration of cells and provides strong support for the regeneration of periodontal soft and hard tissues. The anti-inflammatory characteristics of PRP are also closely related to the repair of periodontal bone defects. **Conclusion:** PRP played an important biological effect on periodontal bone regeneration. The mechanism is closely related to PRP promoting the growth, proliferation, differentiation and migration of periodontal ligament cells and osteoblasts, and the fiber stereo configuration of PRP and the anti-inflammatory effect of leukocytes.

Keywords: Platelet-Rich Plasma; Biological Effects; Molecular Mechanism; Periodontal Bone Regeneration; Signal Transduction; Anti-Inflammatory; Growth Factors

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1. Introduction

Periodontal bone defect is the most common clinical symptom and the most difficult problem to solve. Although there are many methods to treat bone defects, none of them proved to be completely satisfactory [1]. Therefore, it is of great significance to study a new, better and more widely used periodontal bone defect repair technology and method.

Platelet rich plasma (PRP) derived from centrifugation of autologous whole blood, with thrombin and calcium chloride. PRP includes a high concentration of platelets and a native concentration of fibrinogen [2]. PRP released various growth factors and cytokines when activated. These growth factors included platelet derived growth factor (PDGF), basic fibroblast growth factor (FGF2), insulin growth factor-1 (IGF-1), and transforming growth factor β (TGF-β), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF). They can promote wound healing and bone regeneration when tissues are damaged [3].

Marx proved that PRP can promote bone regeneration and wound healing [4]. In clinical and experimental studies, Grageda et al. proved the role of PRP in the repair of periodontal and maxillofacial bone defects [5, 6]. However, Khairy demonstrated that PRP enrichment did not significantly improve bone density or morphometric value at 3 months post graft [7, 8]. Faratzis showed that autogenous PRP had not significant effects on HA/ β- TCP promoting rabbits bone defects repair at 6 weeks post graft [9, 10]. Currently, there is no consensus on the biological characteristics of PRP and the mechanism of promoting new bone formation [11].

Although studies on PRP promoting periodontal bone defect repair and bone regeneration have been reported [12, 13]. However, the mechanism of PRP configuration and its secretion of multiple growth factors to promote bone regeneration are complex and controversial. Therefore, this paper reviews the literature to study the biological characteristics of PRP and growth factors and their biological role and molecular mechanism in periodontal bone regeneration, so as to provide a basis for the clinical application of PRP in periodontal bone defect repair [14].

2. Biological characteristics of growth factors secreted by PRP

The characteristics of growth factor in periodontal bone defect repair include osteoconductive, osteoinduction, osteogenic potential and vascularization. Growth factors can stimulate periosteal bone formation and endosteal bone resorption to achieve durable healing by regulating the growth, differentiation, and metabolism of cell [15], and regulate osteoblast proliferation and synthesis of bone matrix. PDGF can promote the synthesis of phospholipids, cholesterol esters, glycogen and prostaglandins to regulate extracellular matrix proteins [16]. The effector cells of PDGF include fibroblasts, osteoblasts, vascular smooth muscle cells and chondrocytes. FGF2 can promote bone regeneration and increase the repair of periodontal bone defects [17]. The proliferation and differentiation of bone marrow stromal cells were induced by high affinity transmembrane protein tyrosine kinase. IGF-I enhances periodontal bone regeneration by locally controlling the delivery of IGF-I in dextran co-gelatin microspheres. IGF-I can stimulate the mRNA expression of alkaline phosphate, osteopontin and osteocalcin in bone marrow stromal cells, and regulate cell proliferation and differentiation [18].

The synergistic induction of bone formation by the osteogenic proteins of the TGF-β supergene family and played a key role in the formation and development of new bone [19]. VEGF regulates angiogenesis during development. Hypoxia induces VEGF secretion, promotes angiogenesis and osteogenesis. VEGF scaffold provides a new method for tissue engineering in low vascular environment and angiogenesis and bone regeneration in bone defects [20]. EGF increased in wound fluid with burn injury. EGFR deficiency may lead to delayed primary ossification. Inhibition of EGFR tyrosine kinase activity can reduce the generation of osteoclasts in bone marrow cells [21].

3. Biological effects of PRP on periodontal bone regeneration (Table 1 [22-37], Figure 1)

Animal experiments [38, 39] and clinical studies [40, 41] showed that PRP could promote bone regeneration, mandibular reconstruction and wound healing of periodontal root bifurcation and bone defects. In vitro studies have shown that PRP can stimulate the proliferation and differentiation of fibroblasts, osteoblasts, mesenchymal stem cells (MSCs) and periodontal ligament cells, and induce bone defect repair and periodontal tissue regeneration [42, 43]. It also stimulates the proliferation of fibroblasts and induces collagen synthesis, showing beneficial effects on wound healing [44].

Table 1. Clinical Study of PRP on Periodontal Bone Regeneration

Study authors	Design groups	Study design	Patients	Follow up (month)	Main results
Jalaluddin M,et al.2018[22]	PRP vs bone graft	RCT	20	6	Both groups enhanced periodontal regeneration, no significant difference between two groups.
Hanna et al. 2004 [23]	PRP/BDX vs. BDX	Split-mouth RCT	13	6	PRP/BDX showed significant PD reduction and CAL gain than that of BDX.
Sammartino , et al.2005 [24]	PRP	Parallel RCT	18	3	PRP showed PD reduction, CAL gain and bone formation increased.
Okuda et al. 2005 [25]	PRP/HA vs. Saline/ HA	Parallel RCT	70	12	PRP/HA showed significant intrabony defects filling, PD reduction and CAL gain.
Camargo PM, et al. 2005[26]	PRP/BPBM /GTR vs OFD	Split-mouth RCT	28	6	PRP/BPBM/GTR can improve PD reduction, CAL gain and intrabony defects filling.
Do ri F, et al. 2007[27]	PRP/BM/GTR vs BM/GTR	Parallel RCT	30	12	Both PRP/BM/GTR and BM/GTR resulted in significant PD reductions and CAL gains.
Christgau M,et al. 2006[28]	PRP/GTR/ b-TCP vs. GTR/b-TCP	Split-mouth RCT	25	12	PRP accelerated bone density gain and reduced the occurrence of membrane exposures.
Dori et al. 2007 [29]	PRP/BM /GTR vs. BM/GTR	Parallel RCT	24	12	Both groups for intrabony defects can improve clinical parameter significantly.
Ilgenli T, et al. 2007[30]	PRP/DFDB vs PRP	Parallel RCT	22	18	The DFDB/PRP exhibited more favorable gains than PRP alone.
Demir B, et al. 2007 [31]	PRP /BG vs. BG.	Parallel RCT	29	9	Both PRP/BG and BG are effective in intra-bony defects filling.
Dori F, et al. 2008 [32]	PRP/β-TCP/ e-PTFE vs. β-TCP/ e-PTFE	Parallel RCT	28	12	Both groups showed a significant PD reduction and CAL gain.
Piemontese et al. 2008 [33]	PRP/DFDB vs. saline / DFDB	Parallel RCT	60	12	PRP/DFDB exhibited a significantly greater clinical improvement than that of DFDB/saline.
Dori et al. 2008 [34]	PRP /BM / EMD vs. BM / EMD	Parallel RCT	26	12	Both groups resulted in a significant clinical improvement.
Harnack et al. 2009[35]	PRP / β-TCP vs β-TCP,	Split-mouth RCT	22	6	PRP/β-TCP showed no significant improvement on intrabony defects filling than that of β-TCP.
Pradeep AR,et al. 2009[36]	PRP vs OFD.	Split-mouth RCT	40	6	PRP displayed a significant improvement to clinical parameters than that of OFD.
Yilmaz S,et al. 2010[37]	Smoker :PRP/ BDX vs Non-smoker: PRP/ BDX	parallel RCT	24	12	Clinical efficacy of PRP in smoking group was significantly lower than that in non-smoking group

Abbreviations: BPBM, bovine porous bone mineral; BDX, bovine-derived xenograft; BM, bone mineral; GTR, Guide tissue regeneration; OFD, open-flap debridement; HA, Hydroxyapatite; BG,bioactive glass; e-PTFE, expanded polytetrafluoroethylene membrane; β-TCP, β-tricalcium

phosphate; PAM, polylactic acid membrane; DFDB, demineralized freeze-dried bone allograft; EMD, enamel matrix protein derivative; RCT, randomised controlled trial.

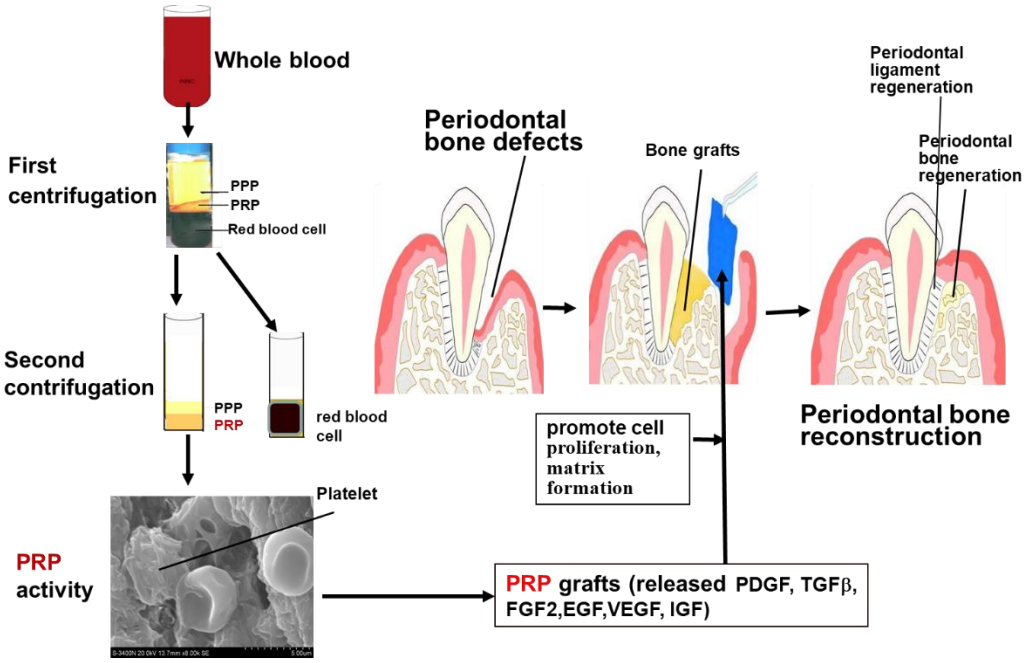

Figure 1. Preparation of PRP and its application in periodontal bone defect to promote periodontal bone reconstruction.

PRP enhanced bone formation in the first two weeks of healing, while others reported that PRP improved bone formation in 4 weeks or more [45]. Although the detailed efficacy and mechanism of PRP are still unclear, it is possible to find evidence to support the role of PRP in periodontal bone defect repair and wound healing [46].

As a controlled delivery system, PRP can release different growth factors, and then directly stimulate the growth, proliferation and differentiation of fibroblasts and osteoblasts by binding with high affinity of growth factor receptors on the cell surface. However, the half-life of growth factors is short, and it is limited to achieve long-term efficacy [47]. The study found that PRP combined with decalcified bone or BPBM/GTR or β-TCP/ePTEM treatment of bone defects showed significant bone regeneration and wound healing, indicating that the combination of PRP and biomaterials has a good effect on bone regeneration of periodontal bone defects [48, 49]. The combination of PRP and HA in the treatment of periodontal bone defects can significantly improve the periodontal clinical parameters or repair of bone defects. Chen TL [50, 51] showed that the filling and guidance of xenograft materials Bio-oss and Bio-gide membrane could be used for the repair and regeneration of periodontal bone defects or bone defects with bifurcation lesions. At present, common graft materials used in combination with PRP include BPBM, GTR, hydroxyapatite (HA), β- TCP and ePTEM.

PRP can induce osteoblasts or MSCs to proliferate and differentiate, reconstruct bone defects and repair wound healing. Osteoblasts were cultured with PDGF treated matrix, and cell proliferation was significantly enhanced [52]. The combination of PRP with MSCs and autologous bone showed a significant increase in new bone formation and bone reconstruction at the early stage [53]. The advantages of PRP delivery system for periodontal bone defects include minimally invasive, better biocompatibility, excellent plasticity, easy access, better bone formation, non-immune response, non-degradation in the first few weeks after transplantation, and secretion of growth factor in three-dimensional scaffolds [54]. Lucarelli E found that 10% PRP can induce the proliferation of

human stromal stem cells and mineralization of extracellular matrix, showing a better effect [55.

Various growth factors secreted by PRP can be used to repair periodontal bone defects through bone tissue engineering (Figure 2). Yamada Y found that the combination of PRP and MSCs has good osteogenesis and angiogenesis [56]. PRP rich in growth factors can promote MSCs expansion and differentiation into osteoblast like cells. The combination of PRP and osteoblasts can shorten the treatment cycle [57]. MSCs cells co cultured with platelet lysates can maintain osteogenic, chondrogenic and adipogenic differentiation characteristics [58]. The combination of PRP and stem cells can promote the formation of new bone in periodontal bone defects and shorten the treatment cycle [59].

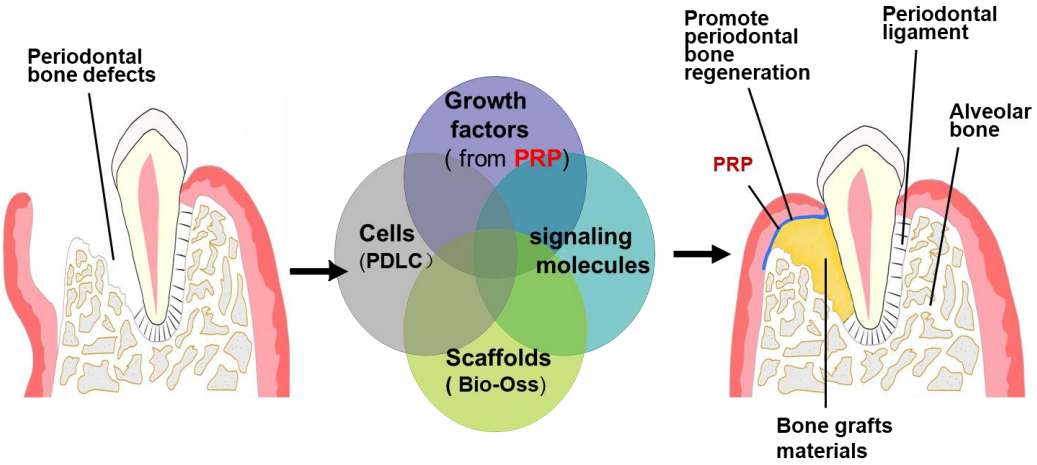

Figure 2. Simulation diagram of PRP used in bone tissue engineering to promote periodontal tissue regeneration.

Research shows that the growth factors released after PRP activation can promote the proliferation and differentiation of adipose derived stem cells into adipocytes, promote the vascularization of fat transplantation, prevent the apoptosis of transplanted adipocytes, and improve the success rate of fat grafts [60].

Meta-analysis showed that pure platelet rich plasma (P-PRP) had a significant impact on new bone formation, improved bone density, and increased alveolar bone regeneration potential [61]. Mijiritsky showed that autologous platelet concentrates (APCs) contained high levels of growth factors beneficial for periodontal regeneration and facial rejuvenation. The APCs mainly includes PRP, platelet rich fibrin (PRF) and concentrated growth factor (CGF). PRP can deliver a large number of growth factors to the target position faster to promote the formation of mature bone by mixing with autologous bone, which can be used for soft and hard tissue repair. PRF has the potential to stimulate dermal enhancement and used for soft tissue repair, such as gingival recession coverage and bifurcation defects. CGF is used for oral surgery, mainly for hard tissue regeneration [62].

4. Possible molecular mechanisms of PRP on periodontal bone regeneration (Table 2 [63-74], Figure 3)

Growth factors play a vital role in cell proliferation, migration, differentiation and angiogenesis [62]. When PRP activated and released growth factors induced bone formation, mineralized bone matrix was formed under the regulation of chemotaxis, cell migration, proliferation and differentiation [75]. This process is regulated by a complex signal network of multiple growth factors, cytokines and chemokines, involving the

synergistic effect of fibroblasts, endothelial cells, MSCs, osteoblasts, macrophages and platelets, promoting cell migration, proliferation and differentiation, and further inducing new bone formation and wound healing [76].

Growth factors activate intracellular signal transduction pathways, induce cell chemotaxis, proliferation and angiogenesis, control the synthesis of collagen and extracellular matrix proteins, and promote bone regeneration and wound healing through their receptor regulated signals and signals that bind to the extracellular domain of growth factor receptors. Each stage of bone defect repair is controlled by a variety of growth factors, which use autocrine, paracrine and endocrine mechanisms to regulate the function of cells. Cell proliferation plays a role by activating protein kinase C (PKC), mitogen activated protein kinase (MAPK) and MAPK kinase (MEK) [77].

Table 2. Molecular mechanism of growth factor released by PRP on periodontal bone regeneration

Key Growth factors	Cell membrane receptor	Molecular mechanism
PDGF[63-64]	PGEFR	Activating PI3K induced downstream gene transductions, regulating cell movement and inhibiting apoptosis. Improved cell mitogenic, proliferation, migration, including MSCs, osteoblasts, fibroblasts, periodontal ligament cell.
VEGF[65-66]	VEGFR	Promoted angiogenesis and osteogenesis in osteoblasts. Improved mitogen of vascular endothelial cells, and differentiation of adipocytes.
FGF2[67-68]	FGF2R	Activating downstream signal transduction. Improved angiogenesis and mitogenic. Increased proliferation and differentiation of BMSC, and osteoblasts.
IGF-1 [69-70]	IGF-1R	Activating downstream signal transduction cascades. PI3K-Akt triggers to activate transcription factor NF-κB. Increased alkaline phosphatase, osteopontin and osteocalcin. Induced proliferation and differentiation on osteoblasts.
EGF [71-72]	EGFR, PDGFR	Control proinflammatory signaling to modulate proliferation in BMSC. Regulated cell growth, proliferation and differentiation.
TGF-β [73-74]	TGF-β1, TGF-β2	Regulate osteoblastic and adipogenic differentiation. Improved proliferation of pre-osteoblasts and fibroblasts. Stimulate growth of fibroblasts and osteoblasts.

Abbreviations: PDGFR, Platelet-derived growth factor receptor; VEGFR, Vascular endothelial growth factor receptor; FGF2R, Fibroblast growth factor receptor;IGF-1R, Insulin-like growth factor-1 receptor; EGFR, Epidermal growth factor receptor; TGF-βR, Transforming growth factor β receptor; MSCs, Mesenchymal stem cells; BMSC, bone marrow stromal cells.

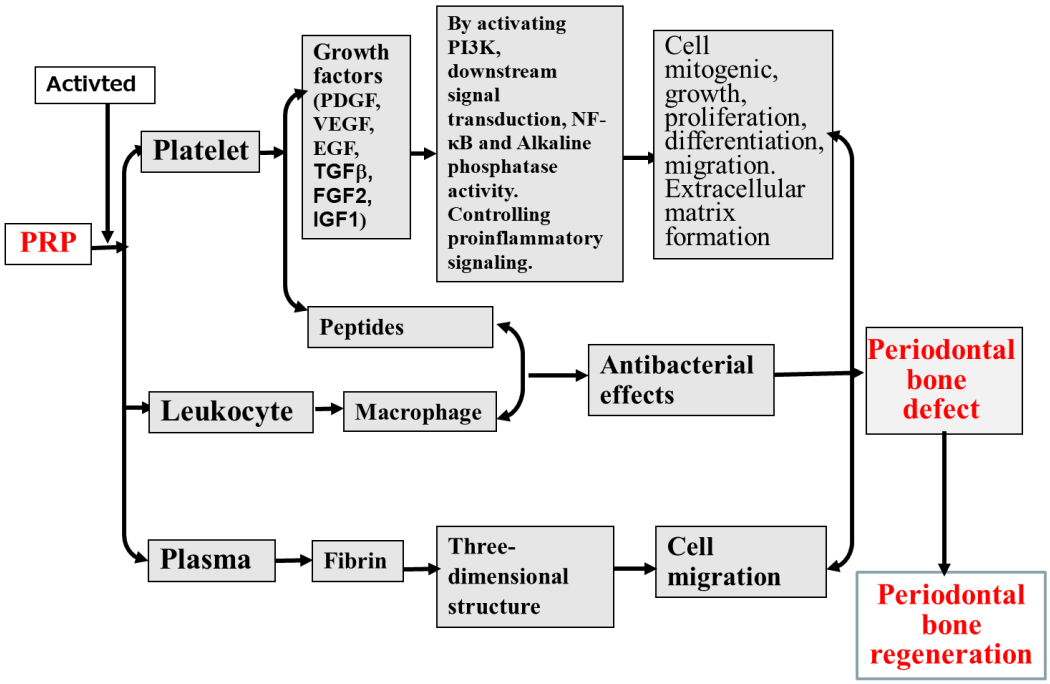

Figure 3. Possible mechanism diagram of PRP used in periodontal bone defect to promote periodontal bone regeneration.

The interaction between the cell membrane receptor and its ligand causes the conformational change of the receptor, leading to the phosphorylation of the receptor domain and messenger molecules in the cell, thereby triggering cascade events. The signal is transmitted from the cytoplasm to the nucleus, where DNA binding proteins bind to regulate DNA sequences, leading to DNA replication or transcription. Thereafter, the DNA mediated reaction returns to the cytoplasm through messenger RNA, which is converted into functional proteins, and then regulates cell function. Initially, tyrosine kinase is activated, leading to phosphorylation of receptor at tyrosine residues, leading to receptor binding with other proteins, including phosphatidylinositol 3-kinase (PI3K) and phospholipase C-γ （PLCγ）、 GTPase activating protein, and various media are activated downstream, such as PI3K and PLCγ、 MAPK [78]. Under certain conditions, the serine/threonine kinase is activated, thereby phosphorylating the serine/threonine residues of the target protein. Receptor phosphorylation activates the kinase domain, which in turn activates a transcription factor named as small mother against decapentaplegic (Smad). The Smad interacts with several DNA binding proteins, leading to biological reaction of diverse gene transcripts [79].

Studies have shown that autologous platelet-poor plasma (PPP) can promote bone formation. When PPP is used for bone defects, PPP is activated, and fibrin in serum is first induced to form a network structure, which helps cell growth and promotes angiogenesis and osteogenesis at the early stage of injury [80]. In the early stage of wound healing, PPP forms fibrin scaffold to promote cell migration to the tissue defect area. This three-dimensional fiber scaffold configuration of PRP is conducive to the growth of cells, blood vessels and the formation of new bone. In the later stage, platelets support the recruitment, differentiation and crosstalk of cells by releasing a variety of bioactive factors. The fibrin network structure in serum is essential to promote angiogenesis and osteogenesis, especially in the early stage of wound repair. In conclusion, platelets and fibrin in PRP play a synergistic role in periodontal bone defect repair and tissue healing [81].

Chen LH studied the antibacterial effect of autologous platelet rich gel from diabetic skin ulcer patients in vitro, and proved the antibacterial effect of PRP on ulcer [82]. The

antibacterial mechanism of PRP is mainly related to the antibacterial peptides secreted by platelets, which are the products of the host's multifunctional antibacterial defense. PRP can regulate the molecular mediators of inflammation and myogenic pathways to control the regulatory pathway of heat shock proteins and promote tissue regeneration. PRP can enhance the proliferation of PDLC and stem cells through signal transduction to form mineralized bone matrix and new bone [83]. Sundman EA [84] showed that PRP could resist infection through vitamin D binding protein, a1 macroglobulin and a2 microglobulin. Activated macrophages induce the expression of tumor necrosis factor-α, vascular endothelial growth factor, interleukin-1b, interleukin-6, etc. through toll like receptor-4, showing antibacterial effect. PRP can also increase the mRNA level of cytokines IL-1b and TGF-β1, induce the expression of myogenic regulatory factors mRNA and protein of MyoD1, Myf5, Pax7 and IGF-1, and improve the cell survival regulated by caspase-3 and NF-kB-65 apoptosis factors. In addition, it can promote tissue regeneration by regulating inflammation and myogenesis [85].

5. Conclusion

PRP activation can release a large number of growth factors, promote the migration, proliferation and differentiation of osteoblasts and fibroblasts, and thus promote periodontal bone regeneration. The three-dimensional structure and anti-inflammatory effect of fibrin in PRP are conducive to cell growth and migration, and promote periodontal tissue regeneration. According to the author's limited reading and practice, the growth factors, cytokines and chemokines secreted by PRP participate in complex signal integration, regulate the metabolic process of osteoblasts and fibroblasts through autocrine, paracrine and endocrine mechanisms, and promote wound healing and periodontal tissue regeneration. A more accurate conclusion and meta-analysis of the current theme needs further study.

Conflict of interest

None.

Acknowledgments

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Ethical approval

Not required.

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