Platelet Rich Plasma for the management of knee osteoarthritis: a review of biological role and potential mechanism of action

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ABSTRACT

Knee osteoarthritis (KOA) is a progressive degenerative disease characterised by joint cartilage damage, interindividual variation in clinical manifestations and severe end-stage clinical symptoms. It is one of the most common arthritis types, with increasing prevalence as life expectancy and obesity rise. It is quite a significant public health issue as it reduces physical function, causes chronic pain, and severely impacts the quality of life. The early and middle KOA stages are usually managed conservatively, and the end-stage KOA with knee arthroplasty. Emerging evidence suggests that platelet-rich plasma (PRP) has a potentially regenerative effect on various tissues. Intraarticular PRP has been shown to provide symptomatic relief in early KOA, at least as effective as hyaluronic acid and steroid injections. The combined effects of PRP positively impact inflammation, angiogenesis, cell migration and metabolism of many degenerative joints. However, the PRP's biological activity and mechanism of action are not yet fully understood. This article aims to resume the critical evidence highlighting all reported biological, biochemical and cellular PRP actions in KOA to help physicians better understand this molecular treatment type.

KEYWORDS: platelet-rich plasma, osteoarthritis, knee, PRP

Introduction

Knee osteoarthritis (KOA) is a degenerative disease with gradual joint cartilage damage. KOA is mechanical arthritis with a multifactorial origin[1]. Click or tap here to enter text. It is one of the most common arthritis types, with increasing prevalence as life expectancy and obesity rise[1]. Knee pain, stiffness, and swelling are the typical clinical symptoms[2]. End-stage KOA eventually leads to disability. Conservative treatment is used for the early and middle stages, and knee arthroplasty is for end-stage KOA. Conservative management includes pharmacologi-

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cal and non-pharmacological therapies. Non-pharmacological interventions involve orthotics, weight loss, activity modification and physiotherapy. Pharmacological treatment includes analgesics, anti-inflammatories, opioids to manage painful crises, and orally or intraarticularly administered disease-modifying osteoarthritis drugs to deal with the KOA progression[2].

However, new metabolic and biochemical pathways have been recognised in KOA aetiopathogenesis. Emerging evidence suggests that platelet-rich plasma (PRP) has a potentially regenerative effect on various tissues. Intraarticular PRP has been shown to provide symptomatic relief in early KOA, at least as effective as hyaluronic acid and steroid injections[3]. However, the PRP's biological activity and mechanism of action are not yet fully understood[3]. This article reviews PRP biology and all reported biological, biochemical and cellular PRP actions to help physicians better understand this molecular treatment type.

Anatomy and structure of the knee cartilage

KOA affects mainly the joint cartilage, subchondral bone, and capsule[1]. Cartilage comprises chondrocytes and the collagenous extracellular matrix (ECM) rich in proteoglycan and elastin fibres. Chondrocytes are specialised metabolically active cells synthesising variable components, providing a stable anabolic and catabolic ECM equilibrium[4]. ECM contains organic ingredients, mainly water, aggrecan, proteoglycans, collagens, glycosaminoglycans and glycoproteins. Proteoglycans are protein complexes formed by negatively charged glycosaminoglycans. They are bound to aggrecan, which is linked with hyaluronic acid at the inner matrix part. The outer part is made of a cross-linked collagen type II network. Pericellular matrix encircles chondrocytes and is formed by other proteins such as collagen VI, fibromodulin and matrilin[4].

Histologically, the articular cartilage consists of four layers, the tangential, transitional, radial, and mineralised zone. Chondrocytes and collagen fibers' number, scheme, and orientation differ between zones. The superficial tangential area consists of disk-shaped chondrocytes and collagen fibrils. The middle transitional zone has round-shaped chondrocytes, and the deeper radial zone has chondrocytes' stocks and aligned collagen fibrils[4]. Tidemark is a small, mineralised zone in calcified cartilage, separating the non-mineralised cartilage layers from the subchondral bone[5].

KOA Pathogenesis and Pathophysiology

KOA is mainly caused by articular cartilage integrity loss; however, bone, synovial and other joint changes are described. In the early KOA stages, the atypical action of aggrecanases imbalance the ECM. Aggrecanases are degrading enzymes that cleave the aggrecan core proteins from superficial layer proteoglycans. Subsequently, chondrocytes increase their synthetic activity to restore the aggrecan loss[6]. ECM degradation is also caused by the matrix metalloproteinases (MMPs), mainly MMP3, that disrupt the collagen type II network[7]. On the other hand, chondrocytes form clusters increasing their synthetic activity and trying to repair the ECM structure and cartilage stability—however, the released synovial inflammatory factors and mechanical loading further damage the cartilage[7]. The subchondral bone alterations may further promote KOA development[8]. During KOA progression, subchondral bone osteoblasts and osteoclasts adapt their metabolic activity, secreting pro-inflammatory factors and degradative enzymes, leading to abnormal cysts, osteophyte formation and subchondral bone sclerosis.

Typically, the synovial membrane produces the synovial fluid providing essential nutrients and products for cartilage metabolism. In KOA, the synovial membrane is inflamed by inflammatory macrophages, growth factors and highly active synoviocytes[9]. Synovitis induces the T, B lymphocytes and mast cell infiltration[15]. Inflammatory mediators stimulate MMPS and proteinases production, causing the regulatory cells (chondrocytes, synovial cells and lymphocytes) to extensively produce interleukins (ILs 6,8,15,17) and prostaglandin E2 (PGE2), further damaging the extracellular matrix[10].

Cytokines are signalling molecules playing a vital role in OA pathogenesis[11]. The cytokines' secretion regulates the inflammatory response that causes

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symptoms and controls genes' expression in KOA. Various studies support that IL-1β, IL-6, IL-8, IL-17 and Tumor Necrosis Factor-a (TNF-α) are the principal inflammatory cytokines, and IL-1Ra, IL-4, IL-10, and IL-13 are the main anti-inflammatory factors[11]. Especially for KOA, IL-1β, type IX collagen and TNF-a, stimulates the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), extracellular signal-regulated kinases (ERKs), Jun N-terminal kinases (JNKs) and p38 mitogen-activated protein kinases that enable the chondrocytes' catabolic pathway[12]. Activating NF-κB promotes osteoarthritis inflammation, producing many inflammatory factors, including hypoxia-inducible factor 2α (HIF2α), cyclooxygenase-2 (COX2), IL-1 and nitric oxide synthase (NOS2). The activated NF-kB pathway induces degrading enzymes and enzymes that enhance chondrocyte apoptosis[13]. IL-8 promotes the NF-kB path attracting neutrophils in the knee, and IL-6 promotes the Janus kinases signal transducer and activator of transcription proteins (JAK/STAT) pathway leading to MMP production and joint inflammation[14,15]. Growth factors such as the VEGF and Transforming growth factor β (TGF-β) are also involved in KOA pathology. VEGF produced by affected chondrocytes suppresses the ECM's aggrecan and type II collagen synthesis. In healthy individuals, TGF-β has an anabolic effect; however, during abnormal catabolic function, TGF-β activates stem cells that inhibit cartilage and bone degradation[16].

PRP: Definition, production, and main components

PRP is an autologous biological product, a part of the blood plasma fraction with a high platelet concentration above the standard, various cells and growth factors[17]. Platelets are 2-3 μm in diameter discoid anucleate elements produced by the bone marrow megakaryocytes and released into the bloodstream. Biomolecules present in platelets interact with plasma components to maintain homeostasis. Several platelets' glycoprotein receptors enable numerous functions every time the extracellular matrix is exposed. The platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is critical to platelet aggregation, thrombus formation and tissue repair. Upon activation, platelets secrete hundreds of active molecules from their intracellular granules, involved in hemostasis or tissue healing. Platelets secrete seven essential protein growth factors [platelet-derived (PDGF), TGF-β, VEGF, epidermal (EGF), fibroblast (FGF), connective tissue (CTGF) and insulin-like (IGF)] in the wound healing process and three secretory proteins acting as cell adhesion molecules (fibrin, fibronectin and vitronectin)[17]. Platelets contain three different granule types:

a. **Lambda granules** (lysosomes)[18] contain enzymes necessary for carbohydrate, lipid, and protein degradation that remove debris from damaged tissues and eradicate infectious agents. They also include various proteins such as cathepsin D and E, lysozyme, elastase, and hydrolases; their role has not been fully clarified yet.

b. **Delta granules** (dense bodies)[19] contain several factors (serotonin, dopamine, calcium ions, histamine, adenosine polyphosphates, and epinephrine) involved in coagulation, platelet activation and immunomodulation. Histamine and serotonin increase the capillaries' permeability, allowing the inflammatory cells' migration and stimulating Mesenchymal Stromal Cells (MSCs), fibroblasts and autologous chondrocytes.

c. **Alpha-granules** contain growth factors (PDGF, IGF1, VEGF, FGF, CTGF, TGF). PDGF, IGF1, TGFβ and bone morphogenetic proteins (BMPs) are anabolic GFs, inhibiting pain and inflammation and enhancing the bone matrix and cartilage[20-21]. GFs recruit and activate immune cells, induce endothelial cell inflammation, and inhibit the local inflammatory response and pain caused by TNF-α, IL-1, IL-1b and IL-6[22]. GFs are responsible for cartilage matrix synthesis, chondrocyte stimulation, cellular proliferation and microenvironment regulation. Alpha-granules also contain chemokines and cytokines (pro-platelet basic protein, platelet factor 4, P-selectin) that can stimulate cellular chemotaxis involved in maturation, clotting, migration, cell proliferation growth, angiogenesis, and inflammatory regulation[17-18,23]. Literature supports that a-granules secrete more than 300 soluble proteins, bioactive molecules with heterogeneous functions (inflam-

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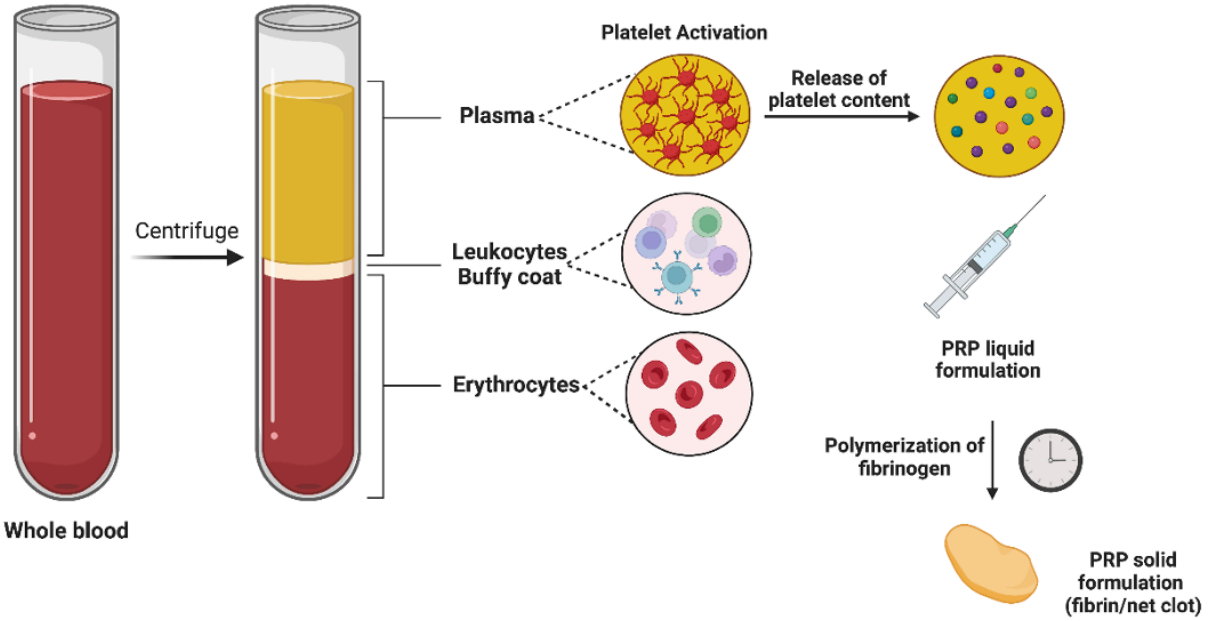

Figure 1: *PRP is obtained by the patient's whole blood sample. After blood collection, a centrifugation process is performed separating the PRP from other blood components.*

mation, clotting, cell adhesion, cell growth, host defence)[24].

The preparation method critically affects the PRP composition and therapeutic potential. PRP is prepared by the patient's whole blood sample. After blood collection, the blood sample is placed in tubes with anticoagulant (sodium citrate)[25]. Centrifugation separates the PRP from other blood components by applying centrifugal force between 350-2000g for 3-15 minutes. Centrifugation must be performed in a sterile microbial environment and can be single or double, depending on the protocol used. Following spinning, the blood separates into layers; the bottom layer, almost half of the blood amount, including mainly red blood cells; a thin intermediate layer lying above RBCs and consists of leukocytes (buffy coat) and the superficial layer containing the plasma fraction and platelets (Fig. 1)[25]. The PRP products may include the leukocyte layer or not. The PRP that has a leukocyte concentration above baseline is named Leukocyte Rich-PRP (LR-PRP), and this with leukocyte concentration below average Leukocyte Poor-PRP (LP-PRP). LR-PRP can release high levels of pro-inflammatory cytokines inhibiting cell proliferation, chondrogenic differentiation and articular cartilage regeneration, and it is not recommended as a KOA treatment. However, further studies are needed.

After centrifugation, PRP activation initiates; this is a crucial step in efficient PRP protocols leading to the platelet degranulation process, involving the fusion of activated platelets granules to the cell membrane and the GFs release promoting cell mitosis, chondrogenesis, angiogenesis and chemotaxis. Platelets secrete almost 70% of GFs stored within the first ten minutes of activation and more than 95% of the pre-synthesized GFs within one hour. However, they continue to produce additional GFs for approximately eight days. The activation begins with the blood clot formation but lasts ten minutes after the clot is complete. Therefore, PRP should be generated in an anticoagulant environment and used within ten minutes of the onset of thrombus formation.

On the other hand, several limitations of PRP preparation exist. The platelet aggregate must be extracted from the whole blood precipitate without

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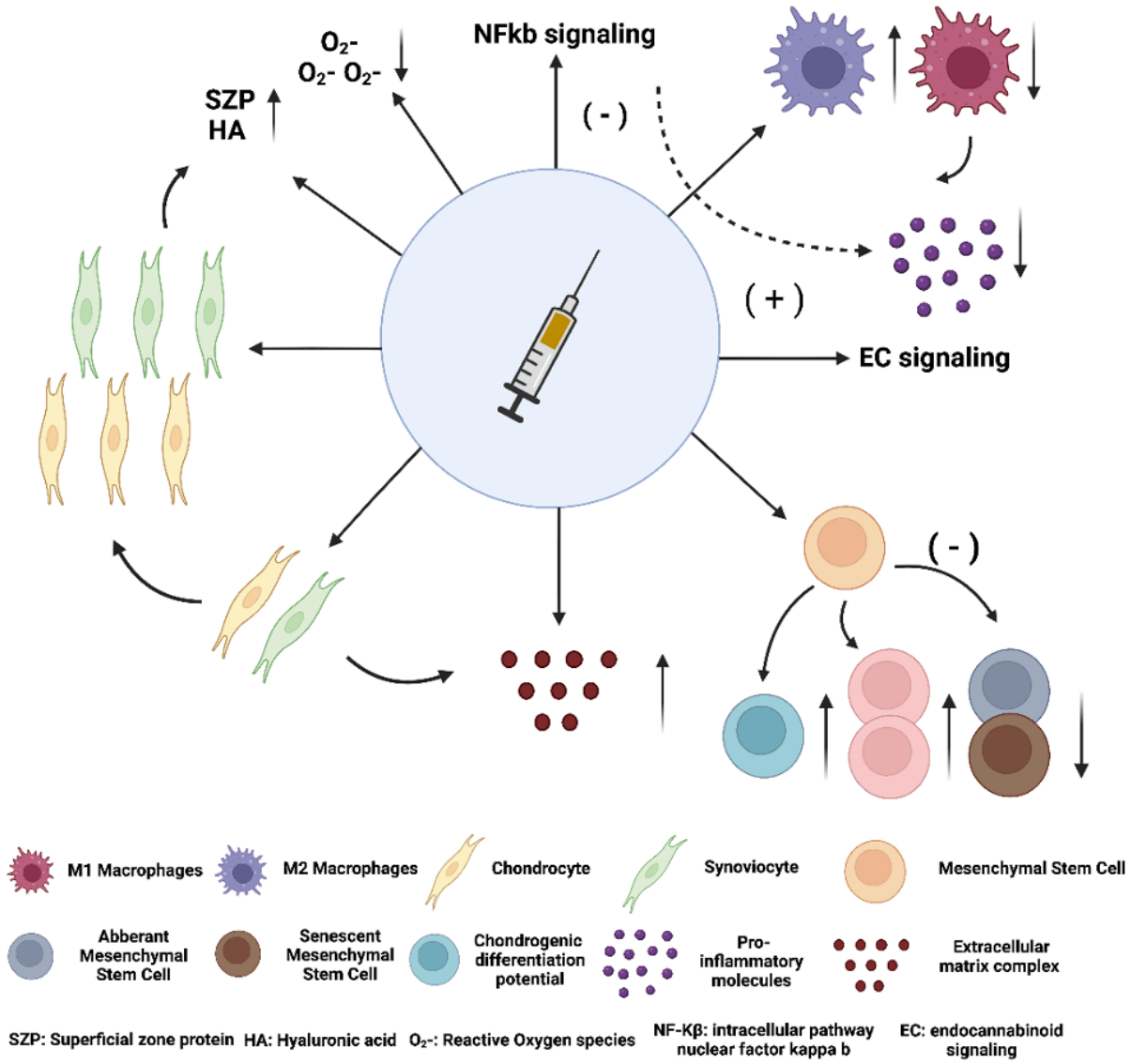

***Figure 2**: Intra-articular PRP injections are involved in numerus molecular and biochemical mechanisms affecting the cartilage.*

mixing or damage; if this happens, it can no longer actively secrete GFs. The apparatus of PRP production must be certified by internationally recognised organisations. Improper production may reduce the platelet concentrate content and the number of released active agents. The lack of standardization is another limitation of PRP production. Different PRP compositions may result in various biological and clinical outcomes. Thus, PRP protocol standardization for KOA treatment is necessary.

The PRP role in KOA

PRP contains numerous GFs with a variety of biological functions:

1. **CTGF**: stimulates angiogenesis and enhances cartilage regeneration[26].
2. **EGF**: promotes angiogenesis, endothelial cells chemotaxis, MSCs mitosis, and epithelisation and significantly shortens the healing process. EGF also increases MSCs and epithelial cells' cytokine secretion[27].

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3. **FGF**: stimulates osteoblasts and chondrocyte differentiation and growth. It positively affects cartilage repair and, together with VEGF, promotes angiogenesis[28].

4. **Hepatocyte growth factor (HGF)**[29] involves cartilage regeneration and chondroinductive actions. HGF reduces IL-6 production, increases the anti-inflammatory cytokine IL-10 release and contributes to the NF-κB pathway inhibition.

5. **IGF**: enhances the other cartilage GFs effects, the MSCs differentiation and mitogenesis and stimulates cell growth and bone formation through osteoblasts' differentiation and proliferation[30,31]. Together with PDGF, it enhances collagen synthesis and prevents the NF-κB pathway activation.

6. **PDGF**: stimulates collagen and extracellular matrix synthesis, enhances macrophages, fibroblasts and neutrophils chemotaxis and promotes TGF secretion from macrophages. PDGF also prevents the NF-κB pathway activation[30,31].

7. **TGF-β:** stimulates collagen production, inhibits collagen breakdown and enhances angiogenesis. TGF-β may also enhance osteoblast proliferation, prevent osteoclast formation and enable connective tissue regeneration and immune cells chemotaxis[32].

8. **VEGF:** regulates angiogenesis and tissue regeneration, crucial in nutrient transport and higher blood flow to the injury site[33]. VEGF stimulates neutrophils and macrophages through chemotaxis.

Some GFs can interact with each other, thus activating a variety of intracellular signalling pathways and enhancing tissue repair[32].

Numerous molecular and biochemical mechanisms are involved in cartilage healing following PRP intraarticular injections (Fig. 2):

a. Anti-inflammatory effect

1. NF-κB pathway inhibition

PRP therapy aims at anti-inflammatory action, restoring articular cartilage homeostasis and promoting tissue repair. Many PRP GFs (IGF-1, HGF) have anti-inflammatory activity by inhibiting the NF-κB pathway and chondrocyte, fibroblast, and macrophage activation. The NF-kB plays a crucial role in KOA's pathogenesis. NF-kb comprises five homo- or heterodimers; the p65/p50 heterodimer is the prototype. In normal conditions, the NF-kB dimers are unstimulated and bound with the inhibitor proteins IkB into the cytoplasm. Following a pro-inflammatory signal stimulation, NF-kB complexes can bind into NF-kB response elements, enabling immunomodulatory proteins and pro-inflammatory factors[34]. The NF-kB pathway expresses matrix-degrading enzymes and abnormal catabolic pathways that affect the cartilage, causing hypertrophy and inflammation[35]. Numerous studies have demonstrated that PRP inhibits the NF-kB pathway. In vitro and in vivo studies supports that PRP secretes HGF, IGF-1, and PDGF that inhibit the NF-kB signalling pathway by either acting directly on the NF-kB transcription factor or suppressing the NF-kB-produced inflammation factors such as macrophages and fibroblasts[36,37]. Thus, the NF-kB signalling pathways understanding and their role in KOA may provide insight into possible pharmaceutical targets.

2. Macrophage phenotype alterations and suppression of reactive oxygen species

Many studies demonstrated the phenotype shifting of inflammatory M1 macrophages into reparative M2 macrophages resulting in tissue repair[38-39]. The increase in anti-inflammatory macrophage action mainly affects the synovial membrane. Another PRP anti-inflammatory action involves suppressing reactive oxygen species (ROS), achieved by activating the antioxidant pathway NrF2-ARE in osteoblasts**.**

b. Analgesic action and cartilage healing

OA patients experience high pain levels, limiting activities and affecting their quality of life. The analgesic PRP mechanism of action is complicated. The macrophage phenotype change mentioned above suppresses the PGE2 production, mainly produced by pro-inflammatory macrophage M1[40]. The NF-Kβ pathway inhibition also reduces joint synovitis[40]. The PRP's GFs reproduce the tissue healing complex process, improving angiogenesis, inflammation and immune response[27]. GFs reduce the local inflammatory response, enhance cartilage healing and promote chondrocyte antiapoptotic

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properties, mediating beneficial anabolic effects in KOA[41,42]. Intra-articular PRP injections may decrease the pain mediators' expression (PGE2, dopamine, 5-hydroxytryptamine and substance P) and contribute to tissue and cartilage healing, regulating catabolic enzymes and critical pro-inflammatory mediators and maintaining joint homeostasis[43-44]. Studies have shown that intra-articular PRP injections enable the healing process by inhibiting chondrocyte apoptosis, remodelling bones and vessels, modulating inflammation and stimulating collagen synthesis[29]. PRP stimulates the healing process through cell differentiation and proliferation[41] and reduces the expression of inflammatory enzymes[18].

c. Cellular regulation

Preclinical studies have shown that PRP improves KOA symptoms by stimulating the MSCs' migration, proliferation and differentiation into articular chondrocytes[29]. PRP contains the essential cytokines (EGF, TGF-β, PDGF, IGF-1) to support and stimulate the MSCs' growth and differentiation. Literature supports that the MSCs' recruitment to the injury site is due to PRP cell adhesion molecules and chemotactic properties[29]. Other studies demonstrated that PRP could promote cell migration, maintaining the adipogenic, chondrogenic and osteogenic differentiation capacity of MSCs, enhancing the cell clones' formation and maintaining an immunosuppressive state. Zhang et al. discovered that PRP promoted a variable cell osteogenic ability but restrained cell adipogenic ability, in line with other studies[29]. The PRP chemotactic properties are also mediated through the chemokine stromal factor 1 (SDF-1a), which is stored in a-granules and acts through CXCR-4 to promote cell migration and homing[45].

Discussion

A thorough understanding of KOA pathogenesis is needed to produce disease-modifying drugs. PRP may be the future new KOA treatment. Platelets' granules secrete several essential protein GFs and secretory proteins that may be beneficial in KOA. The PRP preparation method critically affects its composition and therapeutic potential. PRP is produced from the patient's blood, thus avoiding an immune response, disease transmission or other allografts side effects. The main PRP limitation is the lack of standardization of protocols of therapeutic efficacy, such as platelet concentration, dose number and cost-effectiveness. Anti-inflammatory, analgesic, tissue healing, and cellular regulation are PRP's primary modes of action in KOA. The main reported PRP biological actions include the NF-κB pathway inhibition, macrophage phenotype alterations, suppression of reactive oxygen species and the other regulatory and tissue healing processes mediated through GFs.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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