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## Platelet-rich plasma vs bone marrow aspirate concentrate: An overview of mechanisms of action and orthobiologic synergistic effects

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### Abstract

The use of orthobiologics as a novel therapy for the treatment of numerous musculoskeletal disorders has increased considerably over the past decade. Currently, there are multiple alternatives available as suitable treatments; however, the use of autologous blood-derived products such as platelet-rich plasma (PRP), bone marrow aspirate (BMA) and BMA concentrate (BMAC), specifically, is expanding. Although many investigations attempted to demonstrate the effectiveness of these therapies, even with positive results, the literature lacks standardized protocols and overall accuracy in study designs, which leads to variance and difficulty in reproducibility of protocols. The efficacy of PRP for the treatment of cartilage, bone and muscle tissues is well known.

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Although BMAC has generated optimistic results for the same purposes, its applicability in clinical trials is still relatively recent when compared to PRP. Both products demonstrate the potential to set forth reparative processes, each in their own distinct mechanism. The combination of these biological products has been previously proposed, yet little is known about their synergism. Evidence indicates that growth factor, cytokine, and chemokine profiles seen in both PRP and BMAC vary but are likely to work synergistically to enhance musculoskeletal healing. BMAC products seem to work well without PRP; however, the addition of PRP to BMAC has been shown to act as a rich and natural source of culture medium for stem cells located either peripherally or in the bone marrow itself. Nevertheless, additional variables associated with the use of BMAC and PRP in orthopedics must be further evaluated in order to consolidate the efficacy of this therapeutic strategy.

**Key Words:** Orthobiologics; Platelet-rich plasma; Bone-marrow aspirate; Regenerative medicine; Musculoskeletal diseases; Stem cells

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**Core Tip:** Degenerative musculoskeletal disorders are one of the top causes of pain and disability in the adult population. The use of certain analgesics delivers short term results but do not address the etiological source of pain and disability. The demand for musculoskeletal tissue regeneration has led to an alternative approach referred to as orthobiologics, which is based on cellular and molecular components capable of promoting tissue repair. Platelet-rich plasma and bone marrow aspirate concentrate are popular orthobiologic products that may work synergistically in order to enhance the treatment of musculoskeletal conditions.

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## INTRODUCTION

Musculoskeletal diseases have a high prevalence in adults. One out of every two adults may find themselves suffering from any sort of musculoskeletal disorders, and incidentally, knee pathologies are presented as one of the most common diseases in the United States. Additionally, in 2017, this pathology was the highest contributor to global disability<sup>[1]</sup>, leading to the greatest proportion of lost productivity in the workplace and higher costs of treatment, reaching up to US\$ 874 billion<sup>[2]</sup>. A major gap for the treatment of these musculoskeletal conditions exists between conservative therapy and surgery. Orthobiologics are substances that are naturally found in the human body and are used by orthopedic surgeons to improve the healing of cartilage, injured muscles, tendons, ligaments, and fractures. They provide a less invasive alternative and potential disease-modifying properties that might be beneficial for injured patients<sup>[3]</sup>.

In regenerative medicine, the use of orthobiologics as a novel therapy for the treatment of several orthopedic conditions has increased over the past decade. Current therapies include platelet-rich plasma (PRP), bone marrow aspirate (BMA), BMA concentrate (BMAC), stromal vascular fraction of adipose tissue, and cell-derived therapies<sup>[3]</sup>. Several studies attempted to demonstrate the effectiveness of those therapies. However, even with positive results there is still a need for standardization protocols and greater accuracy in the study design<sup>[4-6]</sup>. A growing number of preclinical and clinical trials have demonstrated the efficacy of PRP to treat cartilage, bone, and muscle lesions<sup>[7]</sup>. The use of BMAC in clinical trials is relatively new when compared to PRP. However, good to excellent results have been demonstrated, especially in the

treatment of chondral lesions<sup>[8,9]</sup>.

Either PRP or BMAC has the potential to support tissue repair but with different intensity and in distinct pathways. The use of these biological products together has been described, yet little is known about their synergism. This study aims to explore the literature in regard to the combined use of PRP and BMAC in musculoskeletal injuries and review their applicability in the clinical setting.

## PRP

PRP is a bioproduct that has a higher number of platelets, usually three to five times above baseline in a small fraction of plasma or greater than  $1.0 \times 10^6$  platelets/ $\mu\text{L}$ , and it is obtained through centrifugation<sup>[10,11]</sup>. Concentrations over 1.5 million platelets/ $\mu\text{L}$  might cause inhibition on stem cell proliferation in an *in vitro* setting. The biological mechanism driving the clinical use of PRP involves the action of growth factors (GFs) which are released from alpha granules of activated platelets. Examples include vascular endothelial GF (VEGF), epidermal GF (EGF), platelet-derived GF (PDGF), transforming GF-beta1 (TGF- $\beta$ 1), basic fibroblast GF (b-FGF), hepatocyte GF, and other bioactive compounds released from dense granules in a lesser amount<sup>[12,13]</sup>. Upon activation, platelets will seek out the receptors on the cell membrane surface of a stem cell. These cells have receptors that bind GFs and, in turn, elicit local downstream effects. In general, most GFs play important roles associated with migration, differentiation, and proliferation of cells as well as extracellular matrix biosynthesis, driving tissue repair and regeneration<sup>[14]</sup>. PRP also contains a number of different cell types including neutrophils (which represent 40%-75% of the circulating leukocytes), monocyte/macrophages (representing 2%-10% of the circulating leukocytes), fibroblasts (which produce collagen, reticular fibers, glycosaminoglycans and glycoproteins), endothelial cells, and possibly a very small amount of primitive mesenchymal type stem cells<sup>[15]</sup>.

Recently, the participation of other blood components in the tissue healing process (in addition to the involvement of GFs) has been discussed. White blood cells, for example, upon combination with platelets can stimulate the generation of anti-inflammatory cytokines even though they are naturally involved in important roles in microbicidal activity with the production of inflammatory cytokines<sup>[16,17]</sup>. Another component that should be taken into account is the fibrin biopolymer, which is a final product of platelet cascade activation and acts as a temporary three-dimensional extracellular matrix, providing a suitable vehicle for the delivery of bioactive molecules, such as GFs<sup>[18]</sup>. As the fibrin bio-scaffold is degraded, the platelet masses are gradually decomposed, and the steady release of GFs is maintained for 7 to 10 d in the local microenvironment<sup>[19]</sup>. Basically, when platelets are activated, there is an initial burst of GFs that is later stabilized and kept under a sustained release.

Indeed, much has been debated about the presence or absence of leukocytes<sup>[20]</sup>, type of activation, and the use of the fibrin polymer, which generates several blood-derived sub-products: plasma rich in GFs, pure or leukocyte-poor PRP (Lp-PRP), leukocyte-rich PRP (Lr-PRP), pure platelet-rich fibrin, leukocyte- and platelet-rich fibrin<sup>[21,22]</sup>. Lr-PRP and leukocyte-poor PRP may have similar safety profiles in regard to adverse reaction<sup>[23]</sup>, and Lr-PRP does not modify systemic and local levels of proinflammatory cytokines in osteoarthritic knees, for example<sup>[24]</sup>. The rationale for the use of Lr-PRP seems to be the crosstalk between platelets and neutrophils. After initial release of inflammatory molecules (arachidonic acid, leukotrienes, and prostaglandins), lipoxin A4 is released from activated platelets and serves as a stop signal from primed neutrophils to prevent neutrophil activation<sup>[17]</sup>. In regard to the influence of type of PRP on mesenchymal stem cell (MSC) cultures, Lr-PRP is able to induce significantly higher proliferation of bone marrow (BM)-MSCs when compared with pure PRP or platelet-poor plasma samples, with faster release and better biological activity of GFs<sup>[25]</sup>.

Over the past decade, several studies evaluating the use of PRP as a therapeutic product for musculoskeletal injuries have been published, as [Table 1](#) indicates. Numerous authors evaluated the effect of PRP after muscle injuries in athletes and found a reduction in pain, an improvement in the physical recovery and faster regeneration when compared with conventional conservative treatments<sup>[26]</sup>. Some randomized controlled trials reported positive outcomes in the reduction of pain scores on total knee arthroplasty<sup>[27]</sup>, plantar fasciitis<sup>[28]</sup>, and arthroscopic rotator cuff repair<sup>[29]</sup>, for example. However, some systematic reviews exhibit no functional improvements following anterior cruciate ligament (ACL) reconstruction<sup>[30]</sup> and knee

**Table 1** Relevant article conclusions (preclinical and clinical) in the pertinent literature on the use of bone marrow aspirate concentrate-platelet-rich plasma products and the comparison between both products

Ref.	Conclusions
Moatshe <i>et al</i> <sup>[3]</sup> (2017)	Strong data supporting the optimal preparation methods and composition for widely used biologic agents, such as PRP and BMAC, largely remain absent from the literature
Yamaguchi <i>et al</i> <sup>[8]</sup> (2019)	Different formulations of biomaterials have been used as carriers for PRP and BMAC in order to increase regenerative processes. The most common biomaterials utilized in conjunction with PRP and BMAC clinical trials are organic scaffolds and natural or synthetic polymers
Burnham <i>et al</i> <sup>[55]</sup> (2019)	Evidence for use of percutaneous, fluoroscopy-guided, intradiscal PRP or BMAC for the treatment of suspected discogenic low back pain appears safe, potentially positive but is limited due to low-quality studies, natural history of discogenic pain, and variable reporting characteristics
Rubio-Azpeitia <i>et al</i> <sup>[58]</sup> (2014)	Overall PRP stimulates MSC proliferation, preserves MSCs multipotency and does not interfere with any lineage differentiation. PRP (as platelet lysate or releasate) preserves the immune-privileged potential of MSCs and may delay the appearance of the senescent phenotype
Mishra <i>et al</i> <sup>[60]</sup> (2009)	Results confirm that PRP enhances MSC proliferation and suggest that PRP causes chondrogenic differentiation of MSC <i>in vitro</i>
Krüger <i>et al</i> <sup>[61]</sup> (2013)	Results suggest that human PRP may enhance the migration and stimulate the chondrogenic differentiation of human subchondral progenitor cells known from microfracture
Zhong <i>et al</i> <sup>[62]</sup> (2012)	Both human BMACs and PRP may provide therapeutic benefits in bone tissue engineering applications. These fractions possess a similar ability to enhance early-phase bone regeneration
Wojtowicz <i>et al</i> <sup>[63]</sup> (2007)	Newly formed bone augmented under the influence of PRP shows the closest similarity to the control contralateral bone in comparison to BM-MSCs
Lee <i>et al</i> <sup>[65]</sup> (2014)	Autologous BMAC combined with PRP injection at the osteotomy site helped improve bone healing in distraction osteogenesis of the tibia, although the effect size was small
Centeno <i>et al</i> <sup>[66]</sup> (2018)	ACL treatment with percutaneous injection of BMC and platelet products shows promise as a nonsurgical alternative. However, a larger randomized controlled trial is warranted to confirm these findings
Hede <i>et al</i> <sup>[67]</sup> (2019)	Treatment of cartilage injuries using combined BMAC and PRP improved subjective clinical outcome scores and pain scores at 1 and 2 yr postoperatively. MRI and histology indicated repair tissue inferior to the native hyaline cartilage
Campbell <i>et al</i> <sup>[68]</sup> (2013)	A series of orthobiologic treatments with PRP and BMAC improved the patient's pain and strength as well as the morphologic appearance of the hip capsule and gluteus minimus tendon on MRI
Martin <i>et al</i> <sup>[70]</sup> (2013)	The use of a minimally invasive femoral head decompression augmented with concentrated bone marrow and PRP resulted in significant pain relief and halted the progression of disease in a majority of patients
Centeno <i>et al</i> <sup>[71]</sup> (2020)	Findings suggest that ultrasound-guided BMC and platelet product injections are a safe and useful alternative to conservative exercise therapy of torn, nonretracted supraspinatus tendons
Kim <i>et al</i> <sup>[72]</sup> (2018)	BMAC-PRP improved pain and shoulder function in patients with partial tear of the rotator cuff tendon
Cassano <i>et al</i> <sup>[73]</sup> (2018)	Colony-forming units were increased in both BMAC compared to BMA ( $P < 0.0001$ ). Platelet counts were not significantly different between BMAC and PRP. TGF- $\beta$ 1 and PDGF were not different between BMAC and PRP. IL-1ra concentrations were greater ( $P = 0.0018$ ) in BMAC samples than in PRP. The IL-1ra/IL-1 $\beta$ ratio in all BMAC samples was above the value reported to inhibit IL-1 $\beta$
Sugaya <i>et al</i> <sup>[74]</sup>	The concentration of b-FGF was higher in BMAC than in PRP ( $P < 0.001$ ), whereas no significant differences in the levels of PDGF-BB, VEGF, TGF- $\beta$ 1, and BMP-2 were observed between the two types of samples. BMAC

(2018)	had an average of 1.90% CD34+ and 0.03% CD31-45-90+105+ cells (no cells in PRP) and higher levels of b-FGF than those of PRP
Ziegler <i>et al.</i> <sup>[75]</sup> (2019)	BMAC is a clinically relevant source of anti-inflammatory biologic therapy that may be more effective in treating osteoarthritis and for use as an intra-articular biologic source for augmented healing in the postsurgical inflammatory and healing phases, owing to its significantly higher concentration of IL-1Ra as compared with Lr-PRP and Lp-PRP. Additionally, Lr-PRP had a significantly higher concentration of IL-1Ra than Lp-PRP. In cases where increased vascularity and healing are desired for pathological or injured tissues, including muscle and tendon, Lr-PRP may be optimal given its higher overall concentrations of PDGF, TGF- $\beta$ , EGF, VEGF, and soluble CD40 ligand

BMAC: Bone marrow aspirate concentrate; PRP: Platelet-rich plasma; MSC: Mesenchymal stem cell; BM-MSCs: Bone marrow mesenchymal stem cells; ACL: Anterior cruciate ligament; BMC: Bone marrow concentrate; MRI: Magnetic resonance imaging; BMA: Bone marrow aspirate; TGF- $\beta$ : Transforming growth factor  $\beta$ ; PDGF: Platelet-derived growth factor; IL: Interleukin; b-FGF: Basic fibroblast growth factor; VEGF: Vascular endothelial growth factor; BMP-2: Bone morphogenetic protein-2; Lr-PRP: Leukocyte-platelet-rich plasma; Lp-PRP: Leukocyte-poor platelet-rich plasma; EGF: Epidermal growth factor.

function<sup>[31,32]</sup>. This contradictory functionality of PRP may occur due to the lack of standardization of protocols for PRP preparation and the variety of methods for evaluating effectiveness as well as the high availability of scores that may vary among them<sup>[33]</sup>. In fact, a recent analysis reporting PRP processing for musculoskeletal conditions (105 studies) showed that only 11.5% of studies reported on all necessary variables of PRP processing required to reproduce the protocol<sup>[34]</sup>.

Despite promising results, most of the literature has reported PRP to be beneficial only for a short period. Besides, the association of PRP and additional therapeutic components such as hyaluronic acid or cell therapy may potentially provide better functional outcomes in the clinical setting<sup>[35,36]</sup>. Research on these combinatory treatments possibly provides insights into the involved processes in physiological healing and pathological failure.

## BMAC

MSCs present in BMAC products are multipotent stem cells and have been used in the orthopedic field due to their strong self-renewal capacity along with the potential to differentiate into all musculoskeletal lineages. MSCs are a secretory organ of cytokines, chemokines, GFs, and anti-inflammatory molecules that promote the recovery of the injured tissue<sup>[8]</sup>. According to The International Society for Cellular Therapy Position Statement, there are four minimum criteria for MSC identification: (1) MSCs must be plastic-adherent when cultured under standard conditions; (2) MSCs must demonstrate the capacity for osteogenic, adipogenic, and chondrogenic differentiation; (3) MSCs must express CD73, CD90, and CD105; and (4) MSCs must lack expression of hematopoietic lineage markers (*e.g.*, CD34, CD45, CD14, HLA-DR)<sup>[37]</sup>. The number of progenitor cells in BMAC correlates with positive outcomes; however, obtaining a high number of cells depends on several factors like age of the patient, the method used to prepare BMAC as well as association with other biological products, such as PRP<sup>[14]</sup>. Also, BM aspiration seems to be technique-driven depending on the skills of the physician.



Recently, the capacity of MSCs towards differentiation has been debated, and several studies highlight their potential role in the regenerative microenvironment. In *in vivo* scenarios, they act as a sort of medicinal drugstore for immunomodulation and anabolic stimulation of the host microenvironment<sup>[38]</sup>. MSCs make up a small fraction of BMA, in a proportion of approximately 1 cell for every 10000 cells on average depending on the individual's age. On the other hand, they are easy to isolate because MSCs can be obtained from BM, adipose tissue, dental pulp, umbilical cord blood, fetal liver, and amniotic fluid<sup>[39,40]</sup>. They also possess a strategic role in the regenerative process mainly *via* the capacity of self-renewal, proliferation, differentiation, and homing effects in order to recruit more cells to the injury site<sup>[41]</sup>. MSCs can be found in every vascularized tissue in the body because these cells are perivascular in nature, which is why they are often referred to as pericytes by many authors<sup>[42]</sup>. In fact, some pericytes are attracted to the injury site and become activated MSCs. These MSCs present in BMAC have immunomodulatory, anti-inflammatory, and antiapoptotic mechanisms that will vary according to the environment and as a response will secrete large quantities of different bioactive molecules<sup>[43,44]</sup>.

After birth, BM becomes the only responsible tissue for the production of hematopoietic and stromal cells. Briefly, hematopoietic stem cells (HSCs) are responsible for giving rise to other blood cell lines, such as red blood cells, leukocytes, platelets, and granulocytes<sup>[45]</sup>. On the other hand, MSCs can differentiate into fibroblasts, osteoblasts, osteocytes, adipocytes, and chondrocytes<sup>[46,47]</sup>. It has been suggested that HSCs are the drivers of tissue regeneration by upregulating cytokine release and stimulating additional stem cells from intact bone to travel to the site of injury. Also, HSCs have been shown to directly form bone by differentiating into MSCs and then osteoblasts<sup>[48]</sup>. In other words, the presence of HSCs augments the limited number of available stromal cells, orchestrating cellular cooperation to achieve tissue regeneration. Another advantage for the use of BMAC is that the technique is considered minimal cellular manipulation and thus having FDA approval for the delivery of stem cells<sup>[48]</sup>. BMAC contains a mixed cell population, which is believed to enhance its performance as MSCs are in contact with their physiological cell niche<sup>[49]</sup>. It is considered a low complication procedure concerning hemorrhage, joint pain, and swelling<sup>[50]</sup>.

Much like PRP, BMAC has some discrepancies in its obtainment and processing protocol. Therefore, in a recent review it was recommended for BM aspiration procedures to be made from the posterior iliac crest due to the highest concentration of MSCs because it is the safest area due to the remoteness to neurovascular structures<sup>[51,52]</sup>. Syringe sizes (preferably 10 ccs syringe) and aspiration volumes (3-4 ccs per syringe) should be considered because higher sizes and volumes per puncture might induce diluted samples and fewer MSCs and other regenerative cells<sup>[53]</sup>. Another concern is the use of commercial kits. Most of these automatic systems are based on gradient separation by centrifugation that allows achievement of 2-8 × more total nucleated cells in comparison to unprocessed BM. Gaul *et al*<sup>[54]</sup> reported an extensive comparison of technical features classified into two groups: (1) Fully automated and closed-loop systems; and (2) Manual extraction of the buffy coat. Despite the quality criteria between those products (based on hematocrit, the platelet count, and the concentration of MSC), the study concluded that they could not recommend a single system because the reported data could not be compared between devices.

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## PRP AND BMAC SYNERGISM

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There are appreciable studies in the body of literature that investigate the synergistic effects between PRP and BMAC (Table 1). A recent study evaluating stem cell culture in PRP medium revealed a 5-fold or greater increase in the number of HSCs produced when compared to culturing them in whole blood or platelet poor plasma<sup>[55]</sup>, which can be translated into clinical practice. PRP injections have also been shown to stimulate MSC proliferation and ACL cellular growth enhancement *in vivo*<sup>[56]</sup>. Interestingly, it has been previously demonstrated in a rabbit model that PRP in combination with BMAC does improve ACL integrity whereas PRP alone yielded mixed results<sup>[57]</sup>.

An extensive review of the *in vitro* perspective on PRP and MSC partnership revealed that PRP stimulates MSC proliferation in a nontumorigenic manner, preserves MSC multipotency, and does not interfere with multilineage differentiation<sup>[58]</sup>. PRP may also delay the appearance of senescent features. In all 57 articles included in the review, PRP increased the number of cells and velocity of

population doublings<sup>[58]</sup>. PRP also protected MSCs from chromosomal instability. Additionally, MSCs cultured with PRP were able to preserve their immune-privileged potential by altering cytokine secretion of immune cells (T lymphocytes, B cells, and natural killer cells) to an anti-inflammatory profile and inhibited amplification of adaptive immune response<sup>[58]</sup>.

These findings encourage the clinical application of MSCs along with PRP in a delicate balance between multiple pro- and antiproliferative molecules because increasing PRP concentrations in culture does not necessarily increase proliferation of MSCs<sup>[59]</sup>. MSCs are also difficult to obtain in large quantities as their concentration in peripheral blood and BM is low (0.001%-0.010% of mononuclear cells in BMA). In spite of this disadvantage, MSCs have consistently shown the potential to increase their proliferation when cultured with PRP<sup>[60]</sup>. For cartilage healing, subchondral progenitor MSCs were stimulated to migrate in the presence of PRP and underwent chondrogenic differentiation with an increase in type II collagen matrix deposition<sup>[61]</sup>.

Based on *in vivo* studies, it seems logical that PRP increases vascular ingrowth and mitogenic effects on bone-forming cells<sup>[62]</sup>. At the same time, BMAC provides progenitor cells as a natural source of autologous bone tissue embedded in cytokines, GFs and also platelets. Nevertheless, well-controlled comparative studies regarding the bone regenerative capability of these two concentrates isolated from peripheral blood and BM remain scarce, and results are controversial. A clinical study showed that PRP had better potential for alveolar bone augmentation when compared with BM-MSCs<sup>[63]</sup>. Conversely, an experimental study claimed that BM-MSCs displayed superior effects on bone regeneration in comparison to PRP<sup>[64]</sup>. The differences revealed by the literature so far prompt a better understanding of both orthobiologic products and their complementary use.

A recent level I study with the use of autologous BMAC combined with PRP injection at the site of osteotomy in the same procedure assisted in the improvement of bone regeneration with a better cortical consolidation in distraction osteogenesis of the tibia in comparison to the control group<sup>[65]</sup>. In another prospective study, BMAC and PRP were applied percutaneously in 23 patients with grade 1, 2, or 3 ACL tears with less than 1 cm retraction under fluoroscopic guidance. The majority (77%) of patients showed significant improvements ( $P < 0.01$ ) in objective measurements of ACL integrity at an average of 8.8 mo. Mean scores were found to be significantly different ( $P < 0.05$ ) for the Numerical Pain Scale at 6, 18, and 24 mo, and Lower Extremity Functional Scale and International Knee Documentation Committee at all-time points (*i.e.*, 1, 3, 6, 12, 18, 24, and 36 mo) relative to baseline<sup>[66]</sup>.

In a clinical study, ten patients were treated with the combined use of BMAC and PRP for full-thickness cartilage lesions in the knees. All patients improved in clinical and pain scores at 1 and 2 years postoperatively. Magnetic resonance imaging MOCART scores also improved significantly from baseline<sup>[67]</sup>. The authors emphasized that the combination of BMAC with PRP is an attractive one-step procedure for cartilage repair although no quantification of BMAC and PRP cells were made in the study. The combination also demonstrated a benefit for the treatment of gluteus minimus tendon tear and hip capsular defect in high-performance athletes<sup>[68]</sup>. This may be attributed to the accelerated cell replication and collagen production that PRP promotes as demonstrated on MSCs contained in BMAC<sup>[69]</sup>.

Treatment of osteonecrosis of the femoral head (Ficat stage I or II) with BMAC plus PRP has also been shown to be a good augmentation strategy during minimally invasive decompression of the femoral head in 77 hips with significant pain relief in 86% of patients and only progression to further stages of osteonecrosis in 21%<sup>[70]</sup>. In respect to discogenic low back pain, a recent comprehensive review found that percutaneous, fluoroscopy-guided, intradiscal PRP and BMAC application appears to be safe and potentially positive but is limited due to low-quality studies, natural history of discogenic pain, and variable reporting characteristics<sup>[55]</sup>.

In the first randomized controlled trial of BMAC and PRP injections for partial and full-thickness nonretracted supraspinatus tears in a nonsurgical setting, the combined biological therapy showed better outcomes in comparison to exercise therapy<sup>[71]</sup>. Patients reported a mean 89% improvement at 24 mo with sustained functional gains and pain reduction. Magnetic resonance imaging blinded reviews showed a size decrease of most tears post-treatment. Similar results were shared by another study for partial tear of the rotator cuff with the BMAC-PRP treatment<sup>[72]</sup>. It was previously demonstrated that BMAC-PRP enhanced the proliferation and migration of tendon derived stem cells and prevents the aberrant chondrogenic and osteogenic differentiation of tendon derived stem cells in rotator cuff tendon tears<sup>[72]</sup>.

From a cellular composition and cytokine concentrations analysis, BMAC and PRP present overlapping results. In a well-analyzed study, BMAC showed more PDGF,

TGF- $\beta$ , and VEGF in comparison to PRP preparation with no statistically significant difference. Interleukin (IL)-1 $\alpha$ , a potent anti-inflammatory cytokine, was significantly increased in BMAC compared to PRP<sup>[73]</sup>. In another similar study, it was verified that BMAC and PRP had no significant differences in the level of three GFs (PDGF, TGF- $\beta$ , and VEGF), but PRP still appeared to be more favorable overall. BMAC presented significantly higher basic fibroblast GF levels than PRP<sup>[74]</sup>. This GF is known to induce cell proliferation and chondrogenic differentiation in human BM-MSCs. A recent study aimed to analyze BMA harvested from the posterior iliac crest, BMAC, Lr-PRP, and leukocyte-poor PRP for GF and cytokine concentrations. BMAC seemed to be a clinically relevant source of anti-inflammatory biologic therapeutic due to its significantly higher concentration of IL-1 $\alpha$ . Lr-PRP may be optimal in cases where increased vascularity and healing are desired given its greater overall concentrations of PDGF, TGF- $\beta$ , epidermal GF, VEGF, and soluble CD-40 ligand<sup>[75]</sup>.

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To address the concerns of possible inferior regeneration capacity of orthobiologics as a single treatment, studies have recently been practicing the combined treatment of PRP and BMAC for specific types of musculoskeletal injuries. This is encouraged by a premise of having the benefits of progenitor cells, including hematopoietic cells, and a great amount of GFs (Figure 1). Stromal-derived factor-1 $\alpha$  is a major homing chemokine stored in the alpha-granules<sup>[76]</sup> for stem cells (*via* CXCR-4) to act in the site of injury. Additionally, the macrophage, as part of the mononuclear cells found in the BM, has a great plasticity potential and can switch phenotypes from the M1 to the M2 subtype in order to attenuate chronic inflammation (Figure 1).

The combination of PRP with BMAC appears to mimic the natural cascade that occurs in fractured bone healing. Initially, there is a major influx of neutrophils into the fracture hematoma; these cells are then replaced by macrophages *via* the secretion of several macrophage chemo-attractants, such as monocyte chemoattractant protein-1<sup>[77]</sup>. Subsequently, there is a shift to the anti-inflammatory M2 macrophage and selectively recruited lymphocytes. M2 macrophages secrete high levels of anti-inflammatory cytokines and fibrogenic and angiogenic factors that serve to resolve inflammation and stimulate tissue regeneration. Posteriorly, granulation tissue is formed along with fibrinolysis of the fracture hematoma. Fibrin degradation attracts and facilitates MSC invasion and further proliferation and differentiation within the injured area.

For PRP preparation, two centrifugations ( $320 \times g$  for 5 min and then  $700 \times g$  for 17 min) with collection of the buffy coat (Lr-PRP) followed by cold preconditioning at 4 °C and light (LED) bath for 20 min is recommended as described in the literature<sup>[78-80]</sup>. For BMAC preparation, double centrifugation is also set ( $40 \times g$  for 20 min and then  $800 \times g$  for 10 min) along with the same storage and activation parameters described in PRP preparation.

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## CONCLUSION

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Although essential developments have been made in the field of orthobiologics, this combined therapy deserves further substantial improvements. From the basic science to clinical application, evidence shows that GF, cytokine, and chemokine profiles seen in PRP and BMAC are different and likely work synergistically to enhance musculoskeletal healing. Nevertheless, there are still numerous potential variables associated with the use of BMAC and PRP in orthopedics that must be further evaluated. These variables include the optimal number of cells required for superior healing, steady rate of GF release, ideal time interval for the introduction of cells and GFs, dose-response curves, and the method of processing (*i.e.*, centrifugation and activation). It is then important to define a minimal standard for each of these treatments and set a clear nomenclature system for appropriate communication. Although BMAC seems to work well without PRP, evidence supporting PRP as an orthobiologic is massive. The addition of PRP to BMAC provides a natural source of culture medium for MSCs located either peripherally or in the BM. Future randomized clinical trials with well-designed protocols and well-defined controls and parameters are needed in order to consolidate the efficacy of this combined therapy.



**Figure 1 Cell and platelet interactions in platelet-rich plasma-bone marrow aspirate concentrate milieu.** Monocytes contained in bone marrow aspirate concentrate are further stimulated in the presence of platelet-rich plasma. Macrophage (M $\Phi$ ) 1 is characterized by inflammatory cytokine secretion (interferon- $\gamma$ ) and nitric oxide production, resulting in an effective pathogen killing mechanism. The M $\Phi$ 1 phenotype also produces vascular endothelial growth factor and fibroblast growth factor. The M $\Phi$ 2 phenotype consists of anti-inflammatory cells with a high phagocytosis capacity. M $\Phi$ 2 produces extracellular matrix components, angiogenic and chemotactic factors, and interleukin-10. In addition to pathogen defense, M $\Phi$ 2 can alleviate the inflammatory response and promote tissue repair. Orange: Monocyte; Dark purple: Neutrophil; Light blue: Macrophage; Dark blue: Mesenchymal stem cells; Light purple: Activated platelets; Green: Growth factors; Dark yellow: Fibrin fibers.

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