Orthobiologics: Today and Tomorrow

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Zaamin B. Hussain, Jorge Chahla, Robert F. LaPrade, and Bert R. Mandelbaum

Introduction

Biologic-based therapies for cartilage pathology have gained popularity in the last decade and garnered significant expectation as the future of sports medicine, based on theoretical advantages including minimal invasiveness, greater healing potential, faster recovery, and a less expensive alternative to surgery.

These treatment options are likely to have the greatest therapeutic potential for focal chondral defects and early osteoarthritis (OA). Identifying and treating cases of early OA have recently become a major focus, because many patients with painful late-stage OA already have extensive structural disease, which may preclude treatment with non-operative modalities. In addition, isolated chondral lesions are also highly prevalent and could benefit from biological therapy before progression to further degenerative changes.

Z. B. Hussain
School of Clinical Medicine, University of Cambridge, Cambridge, UK

J. Chahla
Department of Sports Medicine, Santa Monica Orthopedic and Sports Medicine Group, Santa Monica, CA, USA

R. F. LaPrade
The Steadman Clinic, Vail, CO, USA

B. R. Mandelbaum (✉)
Cedars Sinai – Kerlan Jobe Institute, Santa Monica, CA, USA

Biological therapies for cartilage repair include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), cellular-based therapies, and tissue engineering. This chapter aims to review the existing literature for biologic-based treatment options for cartilage and identify potential avenues for development.

Platelet-Rich Plasma (PRP)

The use of PRP to treat cartilage injuries, and other musculoskeletal injuries, has rapidly expanded over the last decade. PRP (Fig. 11.1) aims to provide an abundance of local growth factors, which modify the inflammatory response and may affect cell proliferation and differentiation [1]. PRP was originally defined as a volume of plasma that has a platelet count "above baseline" [2]. However, this definition has more recently been amended to include quantitative criteria, requiring PRP to contain more than one million platelets per milliliter (ml) of serum or five times the amount of baseline platelets [3]. It is thought that a platelet count in PRP beyond this level is required to stimulate targeted injured cells to proliferate [4, 5].

Several studies have attempted to determine the optimal concentration of platelets for musculoskeletal healing [6–8]. It is possible that the most desirable platelet level for healing depends on the injured tissue being treated, and as such,

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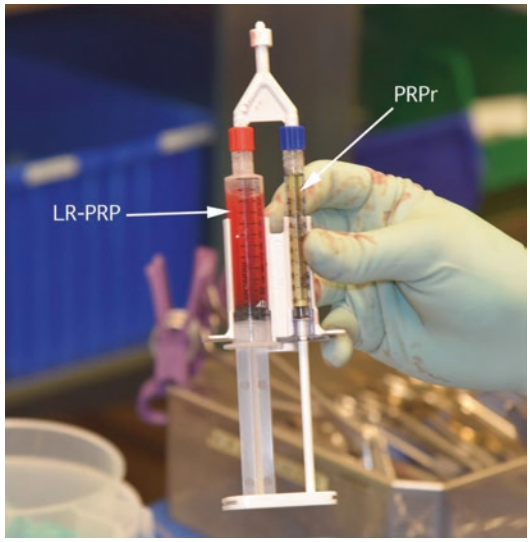

Fig. 11.1 Photograph of a double-syringe system for injection. The device provides a homologous mix of two solutions – LR-PRP (left) and PRP releasate (PRPr) (right)

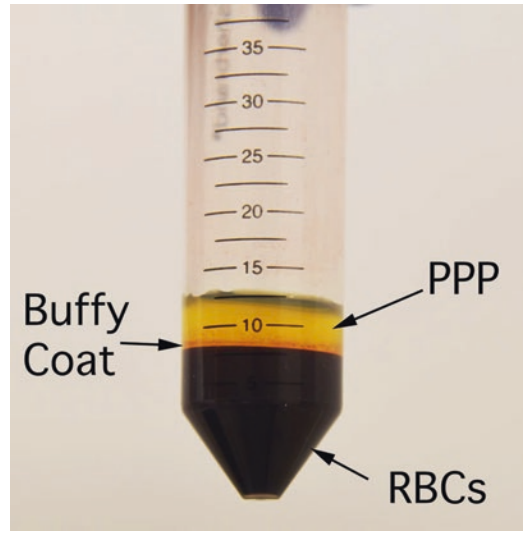

Fig. 11.2 Photograph illustrating three distinct layers of cellular material after the first centrifugation. At the top of the test tube is the platelet-poor plasma (PPP), beneath this layer is the buffy coat where most platelets lie, and at the bottom are the red blood cells (RBCs)

the optimal level for cartilage restoration is yet to be determined. In other tissues, Fleming et al. [6] recently evaluated the effect of PRP supplementation on graft healing following anterior cruciate ligament (ACL) reconstruction in minipigs using either 1× (n = 10), 3× (n = 10), or 5× (n = 10) PRP concentrations. Interestingly, only the 1× platelet concentration improved healing over traditional ACL reconstruction. Similarly, Yoshida et al. [8] found that, after suspending porcine ACL fibroblasts in various platelet concentrations of PRP, 1× PRP significantly outperformed 5× PRP in terms of type I and type III collagen gene expression, apoptosis prevention, and cell metabolism stimulation. However, Weibrich et al. [7] found that an intermediate concentration of platelets (2–6×) resulted in optimal peri-implant bone regeneration in rabbits. Thus, this may indicate that individual tissues may respond differently to different concentrations of platelets.

In addition to controlling the concentration of platelets, the white blood cell concentration may also be modified, with leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) both being used in the literature (Figs. 11.2, 11.3, and 11.4). No randomized or prospective

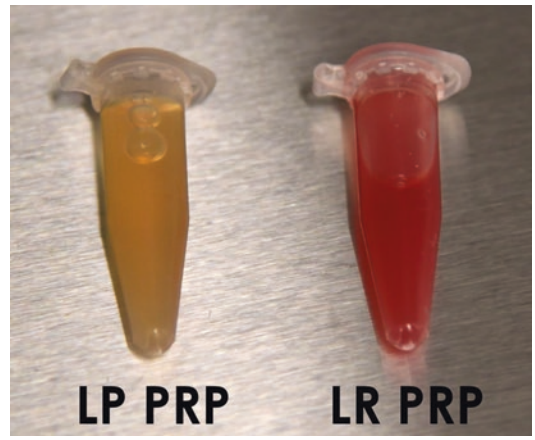

Fig. 11.3 Photograph illustrating the external appearance of leukocyte-poor (LP-PRP) (left) and leukocyte-rich (LR-PRP) (right) platelet-rich plasma. Both types have been used in the literature for attempted cartilage restoration; however, there is more consistent evidence for leukocyte-poor PRP for intra-articular usage

clinical studies have been performed to compare outcomes between leukocyte-rich versus leukocyte-poor PRP [9], though a recent meta-analysis found improved functional outcome scores with LP-PRP for the treatment of knee OA in comparison to hyaluronic acid (HA) and

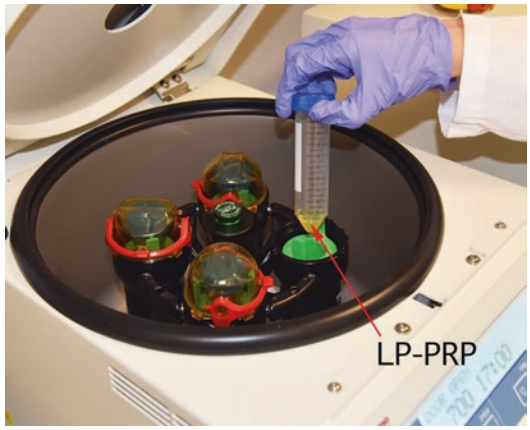

Fig. 11.4 Photograph illustrating the appearance of final leukocyte-poor platelet-rich plasma (LP-PRP) after removal from centrifuge

placebo [10]. A number of randomized controlled trials (RCTs) have demonstrated a positive effect of LP-PRP on OA in comparison with placebo [11] or HA [12, 13]. On the other hand, two RCTs have demonstrated no significant differences in outcomes between LR-PRP and HA for the treatment of OA [14, 15]. Based on these studies, there is more consistent evidence for LP-PRP for intra-articular usage. This could be explained due to the high inflammatory response elicited after the injection of a leukocyte-rich preparation, which is not beneficial within the intra-articular environment. Although several uncontrolled studies have reported pain reduction, functional improvement, and reduced prevalence of surgical revisions and arthrofibrosis [16], further basic science evidence is necessary to determine the effects of LP- or LR-PRP for intra-articular knee treatment and to evaluate whether a single formulation yields superior results.

PRP for Osteoarthritis

Early OA may provide a setting where cartilage restoration is obtainable before irreversible widespread damage has occurred. At the cellular layer, results from basic science studies have disputed the role of PRP in osteoarthritis. While some authors believe that the effects of PRP are mainly due to its anti-inflammatory effects, rather than altering the progression of OA [17], there is evidence that it promotes chondrogenic differentiation in vitro and leads to enhanced cartilage repair in animal models [18].

Duif et al. [19] performed a RCT of patients with Kellgren-Lawrence (K-L) grades II to IV knee OA undergoing knee arthroscopy and reported short-term improvement in patients receiving intra-articular injections of PRP during surgery compared with a control group. Patients in the intervention group demonstrated significantly better visual analog scale (VAS) pain scores ($p = 0.008$), Lysholm scores ($p = 0.033$), and SF-36 physical component summary scores ($p = 0.027$) at 6-month follow-up. However, no difference was found between intervention and control groups at 12-month follow-up in terms of pain and SF-36 scores.

In another RCT, Filardo et al. [14] compared outcomes of 3 weekly intra-articular injections of LR-PRP versus HA, in 192 patients with unilateral knee OA (K-L grades 0 to III). At 12-month follow-up, patients in both groups demonstrated significant improvement compared to pretreatment in terms of the subjective International Knee Documentation Committee (IKDC) and Tegner scores. However, no significant intergroup difference was demonstrated in IKDC, Tegner, Knee Injury and Osteoarthritis Outcome Scores (KOOS), or EuroQol visual analog scale (EQ-VAS) at 2-, 6-, or 12-month follow-up.

Fewer studies have investigated the effects of PRP on hip OA, though recently Dallari et al. [20] performed a RCT on 111 patients to compare the efficacy of autologous PRP, HA, and a combination of both for the treatment of hip OA. Patients and health-care providers were not blinded to the treatments used, although the data collectors and analysts were blinded. Patients received three intra-articular ultrasound (US)-guided injections 1 week apart during outpatient surgery, though the types of surgical procedures and the leukocyte concentration of the PRP formulations were not mentioned. Patients were assessed at 2, 6, and 12 months after treatment. The PRP group demonstrated lower VAS pain scores at all follow-up times and significantly better WOMAC scores at the 2- and 6-month follow-up periods.

Similarly, Battaglia et al. [21] performed a non-blinded, randomized trial comparing US-guided PRP versus HA injections for hip OA in 100 consecutive patients. Patients underwent three injections every 2 weeks of 5 mL autologous PRP or 2 mL HA. The PRP samples were obtained through a double-spin technique to create a sixfold platelet count. Using the Harris Hip Score (HHS) and VAS, patients in both groups demonstrated significant improvements between 1- and 3-month follow-up. Although patients showed progressive worsening of symptoms between 6- and 12-month follow-up, scores were still significantly improved compared to baseline ($p < 0.0005$). However, no significant differences were found between the PRP and HA groups.

PRP for Focal Chondral Defects

For focal chondral defects (FCDs), limited studies have been conducted. Lui et al. [22] demonstrated superior cartilage healing after intra-articular injections of PRP compared to HA controls for 5 mm focal defects in rabbits at 6 and 12 weeks after injection. Milano et al. [23] evaluated the effect of local injections of autologous conditioned plasma (ACP) on medial femoral condyle focal chondral defects in sheep, and the authors found superior histological appearance at 6 months posttreatment compared to untreated controls but found no difference between the two groups at 12 months. Goodrich et al. [24] assessed the role of an autologous platelet-enriched fibrin scaffold and found thicker repair tissue of full-thickness chondral defects in horses, compared to when bone-marrow-derived MSCs were added. There is currently limited evidence for the utility of PRP in humans, and this remains an area of further investigation.

PRP Reporting and Future Directions

The variability of outcomes that PRP has reported may be secondary to the lack of standardized preparation protocols for the various clinical applications. Chahla et al. [16] recently performed a systematic review of preparation protocols reported in the literature and found that only 11.5% of studies reported on all necessary variables of PRP processing required to repeat the protocol.

Intra-articular platelet-rich plasma injections have shown promising results in the treatment of knee and hip OA at short-term follow-up periods up to 12 months following injection. However, the long-term effects of these treatments are still unknown, and their results in comparison to injections of hyaluronic acid (viscosupplementation) are also undetermined. Furthermore, the effects of PRP injections on focal chondral defects in human subjects have not been demonstrated. There is a paucity of literature with consistently used methodology to process and activate these PRP formulations, making duplication of similar clinical results after PRP therapy or comparison of the effects of PRP on various musculoskeletal conditions between studies challenging.

Bone Marrow Aspirate Concentrate (BMAC)

The use of BMAC as a technique for cartilage restoration has recently grown in popularity because it is one of the few approaches to deliver progenitor cells that are currently acceptable under US Food and Drug Administration (FDA) guidelines and it can be implemented in a single-stage procedure [25].

Bone marrow is typically aspirated from the iliac crest (Fig. 11.5), and the quality can be improved by aspirating at multiple locations with a small syringe as progenitor cells have been reported to lie in the trabecular bone, which can be accessed by changing the orientation of the trochar [26]. Hernigou et al. [26] found that, when aspirating bone marrow from the iliac crest, progenitor cell concentrations were on average 300% higher using a 10 mL syringe compared with a 50 mL syringe ($p < 0.01$).

Centrifugation of the bone marrow allows concentration and isolation of the mononucleated cells (white blood cells (WBCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and platelets). MSCs are of particular interest because they are capable of self-renewal and differentiation into mature muscle, bone, and cartilage [27]. Despite centrifugation, the concentration of stem cells in BMAC

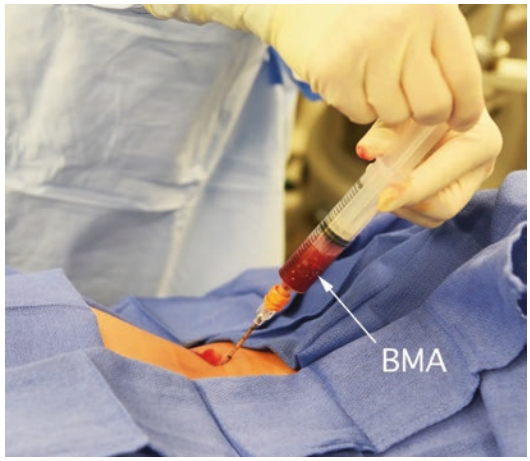

Fig. 11.5 Intraoperative photograph of bone marrow being aspirated (BMA) from the left iliac crest with a patient in prone decubitus

remains relatively low (0.001–0.01%), but the MSCs present may play a role in healing through homing capabilities that recruit more cells to the injury site [28, 29]. The regenerative potential of MSCs, in conjunction with the ability to signal the surrounding tissue to secrete growth factors that modulate the immune response and encourage regeneration at the injury site, suggests that MSC presence provides BMAC with potentially strong regenerative properties, even for avascular tissues like articular cartilage. BMAC has also been reported to contain increased levels of interleukin-1 receptor antagonist (IL-1RA) and interleukin-1-beta (IL-1β) and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and bone morphogenetic protein (BMP)-2 and BMP-7 [30] that have anti-inflammatory and anabolic properties and have critical roles in regeneration through immune response modulation in the joint space [27, 31]. Among these, IL-1 RA is particularly important as it inhibits IL-1 catabolism. Cassano et al. [32] reported that BMAC has a high concentration of monocytes and IL-1RA, which is thought to be responsible for the early beneficial effects of the biologic autologous conditioned serum [33]. Similar to PRP, BMAC is thought to offer the most benefit to early OA and focal chondral lesions before widespread joint disease has manifested.

BMAC for Osteoarthritis

Several studies have evaluated the efficacy of BMAC in the presence of OA. Kim et al. [34] evaluated outcomes of BMAC injection with adipose tissue, in a case series of 41 patients (75 knees) with knee OA (K-L grades I to IV). At 12-month follow-up, VAS pain, IKDC, SF-36, KOOS, and Lysholm scores increased among the group compared to preoperative scores, though statistical significance was not reported. A significant association was found between higher K-L grade and inferior outcomes at follow-up.

Hauser et al. [35] performed intra-articular injections (mean 4.1 injections per patient) with unfractionated whole bone marrow (WBM) in combination with hyperosmotic dextrose, in a small case series of seven patients with hip, knee, or ankle OA. At a minimum 6-week follow-up, five of seven patients noted complete relief or strong functional improvement. Based on a visual analog scale from 0 (complete relief) to 10 (maximum limitation), average pain intensity scores improved from 6.2 preoperatively to 0.07 at follow-up ($p = 0.002$). Likewise, joint stiffness improved from 7.0 to 0.7 ($p = 0.002$).

Of interest, encouraging results have also been reported for patients with moderate to severe osteoarthritis (OA), demonstrating that BMAC injections improved functional activity scores and pain scores [36]. However, in contrast to these findings, Shapiro et al. [37] performed a prospective, single-blind, placebo-controlled pilot study in patients with bilateral OA and found that BMAC injections provided the same amount of pain relief and increased activity level as saline injected into the patient's contralateral knee after 6 months. The findings from this group need to be corroborated by data from longer-term follow-up that includes MRI visualization of any changes in the cartilage structure, but these data suggest that we do not completely understand the effects that BMAC has on the knee or how best to use it.

BMAC for Focal Chondral Defects

More studies have been performed using BMAC for patients with focal chondral defects. Gobbi and Whyte [38] demonstrated that, after receiving BMAC in a hyaluronic acid scaffold (HA-BMAC), 100% of 50 patients with grade IV

chondral lesions showed significantly improved activity and pain outcome scores at 2-years follow-up, and each patient's function was characterized as normal or nearly normal at 5 years. On the other hand, patients who received microfracture instead of HA-BMAC experienced a steeper decline in function, with the percentage of patients with normal or nearly normal knee function at 68% at 2 years to only 28% at 5 years in patients with grade IV chondral lesions [38]. However, Enea et al. [39] found that when microfracture was supplemented with a collagen membrane and BMAC, collagen matrix organization began to occur by 1-year follow-up in patients with focal chondral lesions.

Results from Krych et al. [40] support these positive outcomes by demonstrating that, in patients with grades III and IV chondral lesions who were treated with an artificial cartilage scaffold, both patients receiving platelet-rich plasma (PRP) and those treated with BMAC showed more cartilage fill by MRI after 1 year than patients who were treated with the control cartilage scaffold alone. However, only the BMAC group showed T2 relaxation values comparable to superficial hyaline cartilage [41]. Similarly, 88% of 25 active patients with grade IV chondral lesions who received a cartilage scaffold supplemented with BMAC showed integration of the scaffold, while 80% showed complete filling of their lesion by MRI after 3 years.

Similar to Gobbi and Whyte [38], Skowronski et al. [42] found positive outcomes after treating large chondral lesions with BMAC, yet they also concluded that, for a similar population of patients with large chondral lesions, treatment with peripheral blood rather than BMAC yielded better patient outcomes [43].

The studies discussed above found favorable results when BMAC was used in conjunction with a scaffold, while both Skowronski et al. and Shapiro et al. found negative and inconclusive results after treating patients with BMAC alone. Thus, despite the data in support of its use for articular cartilage restoration, the mechanism of action of BMAC on tissue homeostasis and repair is still not fully understood. The field requires further basic science studies to explain this, as well as strong randomized controlled trials to establish the efficacy for the use of BMAC by minimizing observer bias and utilizing effective controls, and to use MRI and histological analysis to appropriately assess the regenerative effects of BMAC.

BMAC Reporting and Future Directions

A systematic review by Chahla et al. [30] including 11 studies using BMAC in the knee reported a lack of high-quality studies despite growing interest in the use of BMAC. They also reported that the use of BMAC was safe and achieved good results; however, there was a varying degree of beneficial results after BMAC application with and without an additional procedure for the treatment of chondral defects and early stages of osteoarthritis.

In summary, early basic science and clinical studies have elucidated the benefits of BMAC for the treatment of cartilage disease in both animal and human models. In patients with OA, improved outcomes following BMAC injections have also been reported; however, these studies utilized a variable number of treatments and had limited follow-up intervals [34–36]. Patients with focal chondral defects who received a single BMAC injection have been reported to have improved outcomes [9–11]. However, similar to PRP, identifying the ideal number of BMAC treatments, the volume of treatment, and the timing of injections for BMAC has not been well characterized, and further clinical studies are needed to identify standardized preparation and application protocols.

Cellular-Based Therapies

Progenitor cells that proliferate and differentiate, depending on their surrounding biochemical environment, act as a highly attractive tool for cartilage restoration. However, there is still limited evidence of its outcomes and safety profile, and outcome-reporting characteristics are heterogeneous. As such, it has been proposed that a standardized nomenclature is essential to clarify communication of processing and results of this therapy [30, 44–48].

Connective tissue progenitors (CTPs) are defined as proliferative cells capable of differentiating into various connective tissue phenotypes [49]. Thus, the term CTPs encompasses not only pluripotent stem cells but also progenitors derived from stem cells, which may be at various stages of cellular differentiation (a heterogeneous sample).

Stem cells are defined as undifferentiated cells that are capable of proliferation, regeneration, self-maintenance, and replication [50]. Human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) have all been used for the treatment of osteoarthritis [17]. Due to their accessibility, MSCs are the most popular stem cell option for articular cartilage repair [51]. Furthermore, it is more difficult to assure homogeneity in cell division with iPSCs or hESCs than with MSCs [52]. Additionally, MSCs are present in a range of tissue types, have anti-inflammatory effects, can be harvested in large quantities, and are shown to produce proteins conducive to cartilage regeneration [53]. In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy defined the minimal criteria for a human cell to be classified as an MSC: (1) the ability to adhere to plastic when maintained in standard culture conditions; (2) expression of CD105, CD73, and CD90; (3) the lack of expression of CD45, CD34, CD14, or CD11b, CD79alpha or CD19, and HLA-DR surface molecules; and (4) the ability to differentiate to osteoblasts, adipocytes, and chondroblasts in vitro [54]. If the above criteria fail to be met, the term MSC should not be used (Fig. 11.6).

Chang et al. [51] suggested that MSCs also have anti-inflammatory elements, as preclinical trials in small mammals observed an anti-inflammatory response. Due to their easy accessibility and minimal morbidity caused during harvest, adipose-derived stem cells (ASCs) result in a high yield of stem cells and have gained recent attraction for this reason [55]. Furthermore, the growth properties of ASCs are superior to bone marrow-derived MSCs (BMSCs) [55]. ASCs may be obtained either through liposuction aspirates or from the infrapatellar fat pad [1]. When cultured with appropriate growth factors (TGF-β, BMP-2, BMP-6, BMP-7), ASCs may differentiate into chondrocytes in vitro or in vivo [56].

BMSCs are popular due to ease of collection (the procedure is minimally invasive) and the extensive laboratory characterization of these cells [1, 57]. Stem cells from adipose, peripheral blood, and synovium can also be used. However, following bone marrow aspiration, the cell yield

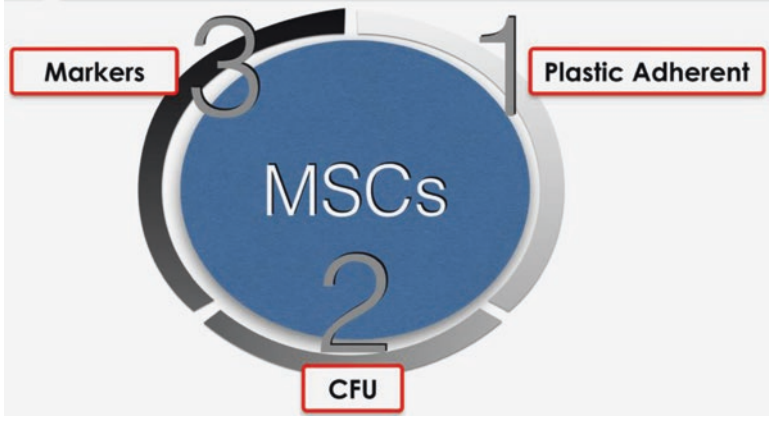

Fig. 11.6 Diagram demonstrating the minimal criteria for a human progenitor cell to be classified as a mesenchymal stem cell (MSC). (1) It must adhere to plastic when maintained in standard culture conditions. (2) It must be able to differentiate and proliferate in colonies (CFU, colony forming unit) of osteoblasts, adipocytes, and chondroblasts in vitro. (3) It must demonstrate a particular expression and lack of expression of cell markers

is low, and therefore these stem cells must be isolated and expanded in cell culture prior to clinical use. Common extraction sites are the iliac crest, the tibia, and the femur [51]. MSCs may differ between anatomic regions of the same tissue type in terms of yield and characteristics [58]. In the case of BMSCs, bone marrow is aspirated 3 weeks before the transplantation is set to occur. The aspirated cells are then cultured in a monolayer for expansion. Several factors can be used to induce these cells to differentiate into host mesenchymal tissue including the cartilage and bone. The cells can then be cultured in scaffolds in order to transplant into the affected joint. Synovial-derived MSCs have the most promising chondrogenic ability, but little literature exists exploring this topic [51].

There are two methods of incorporation of MSCs into articular cartilage: (1) surgical implantation by embedding the cells in a scaffold and (2) intra-articular injections [57]. Several animal models have been used to test the effects of matrix- or scaffold-assisted MSC transplantation [59, 60], as well as intra-articular injection of MSCs [61] for the treatment of focal chondral defects, with overall successful results in terms of macroscopic and histological observations. However, similar studies have not been conducted in human subjects with isolated cartilage defects.

Cell-Based Therapy and Clinical Outcomes

In a recent systematic review, Chahla et al. examined the literature of studies with level of evidence of III and higher, which discussed cell therapy delivered by intra-articular injection in the knee. Only six studies were included, and the studies varied widely with respect to cell sourcing, cell characterization, adjuvant therapies, and assessment of outcomes. All studies reported improved outcomes with intra-articular cell therapy or OA and FCDs and no major adverse events. However, the authors acknowledge that only modest improvement was found and the literature quality was poor. The authors suggested that a focus to improve study methodology is needed, including blinding, quantitative characterization of methods for cell harvest, processing and delivery, and standardized reporting of clinical and structural outcomes.

Tissue Engineering

Tissue engineering combines cells with a three-dimensional (3D) biomaterial scaffold to help regenerate damaged tissue. The scaffold is designed to create a 3D microenvironment that resembles specific tissues and stimulate native tissue regeneration by promoting cell-matrix and cell-cell interactions, which can lead to cell differentiation and tissue growth [62–64].

As discussed above, the use of cellular therapy has only yielded modest improvements in outcome. It is thought that the use of a suboptimal scaffold or isolated cell therapy may cause poor cell survival, cell death, and leakage of cells from the injury site [65]. Also, incorrect cell distribution, poor cell differentiation, and poor integration into the host tissues are common shortcomings with cell transplantation techniques. Improvement of the scaffold's structural, mechanical, and biochemical properties can enhance the cell survival and differentiation. Therefore, the ideal scaffold should initially favor cell migration and support the biomechanical environment in vivo. More specifically, it should encourage newly formed cartilage, be enzymatically resorbable or biodegradable, and not generate an inflammatory reaction. As such, several scaffolds have been proposed for cartilage tissue engineering [65].

Synthetic Biodegradable Scaffolds

Uemastu et al. [66] proposed a novel 3D poly-lactic-co-glycolic acid (PLGA) scaffold to provide architectural support for MSC differentiation and chondrogenesis for cartilage repair without using any growth factors. The PLGA scaffold showed promising results in repairing the whole-thickness cartilage defects with MSCs in vivo with good chondrocyte proliferation and extracellular matrix (ECM) formation in vitro. However, due to the hydrophobicity of PLGA, the adhesion and proliferation of osteoblasts, chondrocytes, and MSCs are limited, and it fails

to simulate the topographical features produced by collagen and ECM in native cartilage. As such, studies are ongoing to modify the PLGA scaffold surface which best mimics the ECM of the native cartilage, and composite scaffolds with a combination of natural and synthetic biodegradable material are being developed.

Composite (Natural-Synthetic) Scaffolds

Various attempts have been made to combine a synthetic scaffold with naturally occurring molecules to improve scaffold properties. A gelatin-PLGA composite scaffold was developed and showed excellent structural and biomechanical properties, degradation behavior, cell culture performance, tissue biocompatibility, and tissue integration, both in vitro and in vivo [67]. Also, genipin has been used to further improve the cross-linking between the collagen, gelatin, and chitosan, thereby increasing the mechanical strength of the scaffold. Additionally, collagen, chondroitin sulfate, and hyaluronate have been widely used to augment scaffolds – and the proportions of each of these constituents have been modified to optimize mechanical, biomechanical, and biodegradable properties of the scaffold and in turn the cell survival and proliferation [65].

Natural Biodegradable Scaffolds

Among these, biodegradable hydrogels have been suggested as a promising scaffold for articular cartilage, because they contain a unique composition and structural similarities to natural ECM. Hydrogels are cross-linked polymers that are insoluble, but swellable in aqueous environments. The high water content of hydrogels can be tuned, reaching values that are similar to native cartilage at ~80% water and even higher (i.e., >90% water), which helps facilitate the rapid exchange of nutrients to and waste from the embedded cells [68].

They offer several advantages such as their delivery as injectable systems; controlled polymerization in situ, which enables improved adhesion between the hydrogel and the surrounding native tissue; and controlled degradation times that can match the rate of new tissue synthesis. Incorporation with chondrocytes and MSCs within hydrogel systems has yielded promising results, and novel cell sources such as iPSCs may also be useful.

Lastly, the ability to use hydrogels for bioprinting offers the opportunity to print tissue-specific constructs that more closely resemble the native architecture and that could eventually allow biological resurfacing of a whole joint. Hydrogels will continue to evolve and offer a huge amount of promise for the future of cartilage restoration.

The body of literature concerning articular cartilage tissue engineering in animal models is rapidly expanding; however, it has been reported that 90% of the new approaches that are successful in animal studies subsequently fail clinical trials [69]. Therefore, effective translation of all tissue engineering methods will be crucial, and high-quality clinical studies are required to properly evaluate these treatment methods before market release.

Future Directions and Conclusions

As awareness increases in the orthopedic community about the importance of early diagnosis of cartilage disease processes, newer treatment modalities have been used in an attempt to prevent or delay progression to late-stage OA. Although successful surgical procedures exist, particularly for the treatment of isolated articular cartilage lesions, biological therapies carry the advantages of being less invasive and less expensive. The literature, especially that of a high level of evidence, regarding outcomes of these treatment options in the management of articular cartilage damage is deficient, though generally positive outcomes have been reported in studies included in this chapter.

Although many of the studies discussed have focused on the use of isolated treatment methods, some of these options can and have been used in conjunction with each other. PRP has been used to augment BMAC therapy, though it is still unknown if these treatments result in an additive or even a synergistic effect [30]. Additionally, future research should also evaluate the need for

scaffolds in BMAC treatment and, if one is necessary, what the optimal scaffold is. There has been increasing interest in the use of scaffolds for the treatment of focal chondral defects, and therefore designing optimal scaffolds with the best mechanical and biological properties to treat focal cartilage defects demands further investigation.

There are a number of variables within each of the biological treatment options discussed in this review. As a result of the variability that exists within each of these treatment options, further research is necessary (1) to establish benchmarks for preparation and formulation of each biological therapy and (2) to make comparisons between different biological options. For example, the viability and efficacy of BMAC or stem cell therapy are likely affected by harvest location, cell concentration, donor sex, [70, 71] donor age [71, 72] ,and donor health [73]. Likewise, the effectiveness of PRP likely depends on leukocyte concentration. [10].

More research is necessary for all biological options described here, in order to draw any definitive conclusions, especially to elucidate long-term effects. Most research involving these techniques has been performed in the knee, and the results may not be transferable to the hip, shoulder, and other joints.

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