Current Concepts Review

Current State of Platelet-Rich Plasma and Cell-Based Therapies for the Treatment of Osteoarthritis and Tendon and Ligament Injuries

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- Orthobiologics encompass numerous substances that are naturally found in the human body including platelet-rich plasma (PRP), isolated growth factors, and cell therapy approaches to theoretically optimize and improve the healing of cartilage, fractures, and injured muscles, tendons, and ligaments.
- PRP is an autologous derivative of whole blood generated by centrifugation and is perhaps the most widely used orthobiologic treatment modality. Despite a vast amount of literature on its use in osteoarthritis as well as in tendon and ligament pathology, clinical efficacy results remain mixed, partly as a result of insufficient reporting of experimental details or exact compositions of PRP formulations used.
- Mesenchymal stromal cells (MSCs) can be isolated from a variety of tissues, with the most common being bone marrow aspirate concentrate. Similar to PRP, clinical results in orthopaedics with MSCs have been highly variable, with the quality and concentration of MSCs being highly contingent on the site of procurement and the techniques of harvesting and preparation.
- Advances in novel orthobiologics, therapeutic targets, and customized orthobiologic therapy will undoubtedly continue to burgeon, with some early promising results from studies targeting fibrosis and senescence.

Over the past decade, there has been a surge in interest in and demand for biological techniques and approaches for the treatment of musculoskeletal conditions including cartilage injuries, osteoarthritis (OA), and tendon and ligament injuries. These "orthobiologic" agents encompass substances that are naturally found in the human body including platelet-rich plasma (PRP), isolated growth factors, and cell therapy approaches, and are used by providers to theoretically optimize and improve the healing of cartilage, fractures, and injured muscles, tendons, and ligaments. Promising results from preclinical laboratory studies[1,2], the modest nature of regulatory barriers for certain autologous preparations, celebrity endorsements, public appetite, and patient demand have all fueled a rush to find new applications in which biological treatments may yield clinical benefit.

Countless biological strategies are currently being utilized to treat an increasing array of clinical conditions in mainstream orthopaedic practice, despite a lack of robust clinical evidence supporting efficacy[3,4]. Presently, there are >400 complete or ongoing clinical trials evaluating the use of PRP and >1,000 evaluating the use of mesenchymal stromal cells (MSCs) in a range of clinical applications (see clinicaltrials.gov). Despite this

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race to identify and test promising therapeutics, the exact formulation of each biologic agent, the possible conditions for which they show promise, and the setting of their optimal application often remain poorly defined, leading to variability of results and uncertainty in their applicability[5].

The purposes of this review are to concisely summarize the current state of PRP and cell-based therapies in orthopaedic surgery as well as their application to and limitations regarding clinical practice and to highlight novel therapeutic strategies that may further our biologic armamentarium in the future.

Platelet-Rich Plasma

PRP is perhaps the most widely used orthobiologic treatment modality and has garnered a considerable level of attention among medical professionals over the last 2 decades[6]. PRP is an autologous derivative of whole blood generated by centrifugation and is defined as having a platelet concentration of at least 1,000,000 platelets/mL and contains a 3 to 8-fold increase in platelet concentration from baseline[7]. While the ideal concentration of platelets to treat specific pathologies remains undefined, current evidence suggests that concentrations of 2.5 to 6 times baseline may be ideal, with concentrations of >10 times yielding potentially slower healing[8,9]. PRP formulations may be further classified as leukocyte-rich PRP (LR-PRP), or leukocyte-poor PRP (LP-PRP), based on leukocyte concentrations above or below baseline, respectively[10]. The elevated leukocyte concentrations in LR-PRP are associated with proinflammatory effects and increased catabolic cytokines and metalloproteinases[11]. There have been few direct comparisons of LR-PRP and LP-PRP, and the exact clinical ramifications and cellular effects of these different PRP preparations remain to be fully elucidated; however, the available literature has supported the use of LR-PRP for lateral epicondylitis, LP-PRP for OA of the knee, and LR-PRP for patellar tendinopathy[10,12].

When the platelets in PRP are activated, they release various cytokines and growth factors that have positive effects on cell proliferation, angiogenesis, cell chemotaxis, and matrix synthesis[13-16]. The various growth factors include transforming growth factor-β1 (TGF-β1), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), epithelial growth factor, and connective tissue growth factors[14,17]. PDGF, in particular, has been shown to be a key growth factor that contributes to the mitogenic and proliferative effects that PRP imparts on human muscle-derived progenitor cells[18]. The goal of treatment with PRP is to provide damaged tissue with higher concentrations of these cytokines and growth factors to promote physiologic healing.

Clinical Evidence

Over the past several decades, countless studies have evaluated the use of PRP as a therapeutic product for musculoskeletal injuries, and an exhaustive comprehensive review is beyond the scope of this article. Many basic, preclinical, and even clinical case studies and trials have described the ability of PRP to improve musculoskeletal conditions, but paradoxically, just as many have concluded that it has no effect. We focus here on the use of PRP in joint, tendon, and ligament pathology (Table I).

The bulk of the literature on PRP for joint pathology has focused on knee OA. The growth factors released by platelets in PRP are thought to improve the joint milieu in OA by decreasing cartilage anabolism, promoting chondrocyte proliferation, and stimulating synoviocyte hyaluronic acid (HA) secretion[19]. Moreover, downregulation of the overall inflammatory state of the joint is theorized to result in pain reduction via the nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX-2) pathways[19]. However, while basic science and animal studies of PRP have been very promising, results from clinical studies have been more conservative. A recent review of PRP and OA, summarizing 5 meta-analyses and systematic reviews and 19 clinical trials (9 of which were Level-I randomized controlled trials [RCTs]), noted that the results overall seemed to favor the use of PRP over other intra-articular treatments to improve pain scale scores in the short and medium term (6 to 12 months), but the overall level of evidence was low[20].

PRP has also been used extensively to treat tendon and ligament injuries throughout the body. Basic-science in vitro studies have shown the ability of PRP to stimulate tendon proliferation, increased tenocyte growth factors, and total collagen synthesis[21-23]. However, despite this finding, clinical studies have been more inconclusive. A recent review by the Cochrane Collaboration evaluated the clinical efficacy of PRP in the treatment of soft-tissue injuries[24]. Of the 19 randomized and quasi-randomized trials that were identified, 16 were judged as having high or unclear risk of bias. In addition, elucidating the clinical efficacy of PRP for tendinopathy has proven quite challenging, with 6 systematic reviews accessing the same data yet noting different conclusions regarding the effectiveness of PRP in tendinopathy[8]. Most current clinical research has evaluated PRP for lateral epicondylitis and rotator cuff pathology. PRP treatment for lateral epicondylitis has been compared with dry needling, corticosteroid injections, and arthroscopic debridement. A systematic review and meta-analysis of 10 RCTs by Arirachakaran et al. found that PRP was superior to both autologous blood and corticosteroid injections in reducing pain and having lower complications[25]. Similarly, a meta-analysis by Chen et al. suggested that PRP may provide symptomatic relief both in the short term (<6.5 months) and long term (>1 year); however, not all trials in their study illustrated a positive benefit[26]. In contrast, a systematic review and meta-analysis of 36 RCTs performed by Franchini et al. demonstrated marginal or unclear evidence for the efficacy of PRP in the treatment of lateral epicondylitis compared with local anesthetic or saline solution, corticosteroid injections, autologous whole blood, or other treatments[27]. Because of the heterogeneity among the current RCTs, the data neither robustly support nor discourage the use of PRP for lateral epicondylitis despite substantial improvements with respect to pain and function.

Studies evaluating PRP for the treatment of rotator cuff tendinopathy and tears is similarly mixed[28]. When evaluating PRP for augmentation of rotator cuff repairs, a meta-analysis of

TABLE I Systematic Reviews and Meta-Analyses of PRP Treatment for Various Orthopaedic Conditions*

	Level of Evidence	No. of Studies; No. of Patients	Length of Follow-up	Summary of Outcomes
Knee OA				
Anitua et al.[75] (2014)	I	2 RCTs, 2 prospective studies, and 1 retrospective analysis; 530 patients	>4 wk	PRP intra-articular infiltration in patients with knee OA reduced pain and improved outcomes related to function and stiffness compared with controls.
Chang et al.[76] (2014)	I	8 single-arm studies, 3 quasi-experimental studies, and 5 RCTs; 1,543 patients	6-24 mo	PRP application improved function from basal evaluations in patients with knee OA and tended to be more effective than HA administration.
Laudy et al.[77] (2015)	I	10 RCTs and non-RCTs; mean 102 patients per trial	6-12 mo	PRP injections reduced pain more effectively than placebo or HA injections for OA of the knee (level of evidence limited to moderate because of a high risk of bias). Additionally, function improved significantly more when PRP injections were compared with controls (limited to moderate evidence).
Shen et al.[78] (2017)	I	14 RCTs; 1,423 patients	12 wk-12 mo	Compared with controls, PRP injections significantly reduced pain scores and improved physical function scores at 3, 6, and 12-mo follow-up. Four studies were considered at moderate risk of bias and 10 at high risk of bias
Meheux et al.[79] (2016)	I	6 RCTs; 739 patients	>6 mo	PRP injection resulted in significant clinical improvements up to 12 mo after injection. Clinical outcomes and WOMAC scores were significantly better after PRP versus HA at 3 to 12 mo after injection.
Lateral epicondylitis				
Arirachakaran et al.[25] (2016)	I	10 RCTs or quasi-RCTs; 20-72 patients per trial	1.5-12 mo	PRP injections showed significantly improved VAS and DASH scores compared with corticosteroid and autologous blood injections.
Chen et al.[26] (2018)	I	21 RCTs; 1,031 patients	<6.5-12 mo	Long-term follow-up demonstrated significantly less pain in the PRP group compared with the control group for patients with lateral epicondylitis or rotator cuff injuries. Significant heterogeneity in the studies was noted.
Franchini et al.[27] (2018)	I	36 RCTs; 20-225 patients per trial	3-6 mo	Marginal or unclear evidence for the efficacy of PRP in the treatment of lateral epicondylitis compared with local anesthetic, saline solution, corticosteroid injections, or autologous whole blood treatments.
Rotator cuff pathology				
Chen et al.[80] (2020)	I	18 RCTs; 1,781 patients	<6.5-12 mo	Significantly improved short and long-term Constant scores in patients receiving PRP. Significantly improved VAS scores. Reduced odds of retears in patients treated with PRP. Patients receiving LR-PRP had significantly better Constant scores compared with LP-PRP, with no difference in VAS scores.
A Hamid and Sazlina[30] (2021)	I	8 RCTs; 7-200 patients per trial	2-24 mo	No significant difference in VAS pain scores between patients treated with PRP and controls at 1 and 3-mo follow-up. However, a significant difference favoring PRP was observed at 12 mo after intervention.
General soft-tissue pathology				
Moraes et al.[24] (2014)	I	19 RCTs and non-RCTs; 23-150 patients per trial	12 wk-12 mo	There is currently insufficient evidence to support the use of PRP for treating musculoskeletal soft-tissue injuries. Furthermore, there was a high or unclear risk of bias in 16 of the studies.

*OA = osteoarthritis, RCT = randomized controlled trial, PRP = platelet-rich plasma, HA = hyaluronic acid, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, VAS = visual analog score for pain, DASH = Disabilities of the Arm, Shoulder and Hand, LR-PRP = leukocyte-rich PRP, and LP-PRP = leukocyte-poor PRP.

TABLE II Summary of Notable Studies of MSC Treatment for Various Orthopaedic Conditions*

	Level of Evidence	No. of Studies; No. of Patients	Length of Follow-up	Summary of Outcomes
Knee OA				
Xia et al.[42] (2015)	I	7 RCTs; 12-72 patients per trial	1-25 mo	MSC injection had no significant effect on pain and tended to improve self-reported physical function.
Maheshwer et al.[43] (2021)	II	25 studies; 12-50 patients per trial	1 wk-100 mo	No significant difference in pain improvement between MSC treatment and controls. MSC treatment was significantly favored for functional improvement. There was improvement in cartilage volume after MSC treatment.
ACL reconstruction				
Wang et al.[46] (2017)	II	Single RCT; 17 patients	24 mo	Compared with HA alone, injection of HA and mesenchymal precursor cells resulted in greater improvements in KOOS pain, symptoms, and activities of daily living, and SF-36 bodily pain scores
Achilles tendinopathy				
Usuelli et al.[47] (2018)	II	Single RCT; 44 patients	6 mo	Compared with PRP, treatment with stromal vascular fraction from adipose tissue resulted in improved VAS, AOFAS, and VISA-A scores at 15 and 30 days only.

*MSC = mesenchymal stromal cell, OA = osteoarthritis, ACL = anterior cruciate ligament, RCT = randomized controlled trial, HA = hyaluronic acid, KOOS = Knee Injury and Osteoarthritis Outcome Score, SF-36 = Short Form-36, PRP = platelet-rich plasma, VAS = visual analog scale for pain, AOFAS = American Orthopaedic Foot & Ankle Society, and VISA-A = Victorian Institute of Sport Assessment-Achilles.

18 Level-I studies found that long-term retear rates were significantly decreased in patients who received PRP[29]. Similarly, PRP-treated patients had significant improvements in multiple functional outcomes; however, none reached their respective minimal clinically important differences (MCIDs). In contrast, A Hamid and Sazlina, in a systematic review and meta-analysis of 8 RCTs comparing PRP and either normal saline solution injection or a rehabilitation program and dry needling for the treatment of patients with rotator cuff tendinopathy, found no differences in short-term (3-week) pain relief after PRP injection compared with control interventions[30]. However, PRP injections were significantly better for medium (6-month) and long-term (12-month) pain relief.

Limitations

A major limitation in interpreting the currently published studies on PRP is the insufficient reporting of experimental details or exact compositions of PRP formulations used. A 2017 systematic review concluded that only 16% of published clinical studies provided any quantitative metrics of the composition of PRP delivered[31]. These findings not only make interpretation of results difficult but also preclude comparisons between studies and replication of experiments and clinical trials to confirm results. As a result, the clinical efficacy of PRP therapy in orthopaedic surgery remains an open and ongoing debate. The need for PRP characterization and standardization for particular indications for which clinical efficacy has been demonstrated is well recognized. In addition, the application of potency assays has also been proposed to help confirm the quality of PRP-derived products and ensure their efficacy for the desired indication[32].

Mesenchymal Stromal Cells

MSCs can be isolated from a variety of tissues, including bone marrow aspirate, adipose tissue, umbilical cord blood tissue, and synovial tissue, and are frequently used because of their multipotent ability, defined as their ability to differentiate into multiple tissues of interest[33]. While initially termed "mesenchymal stem cells," it is now understood that MSCs isolated in vitro are not a homogeneous population of stem cells but are more accurately termed "mesenchymal stromal cells" or "medicinal signaling cells."[34] By acting as reservoirs of repair cells through their anti-inflammatory and immunomodulatory effects, MSCs can act to preserve healthy tissues[35].

The first source of MSCs identified, and the most commonly used, in orthopaedic settings was bone marrow aspirate concentrate (BMAC), because of the increased concentration found in bone marrow compared with the peripheral circulation[36]. BMAC preparations are often procured from the iliac crest and are then contrifuged to increase concentrations of MSCs, hematopoietic stem cells, platelets, and cytokines[37]. While bone marrow is the most common source of MSCs,

TABLE III Grades of Recommendation*

Orthopaedic Pathology†	Grade of Recommendation
Knee osteoarthritis	
PRP	C
Mesenchymal stromal cells	C
Lateral epicondylitis	
PRP	I
Rotator cuff pathology	
PRP	I
Ligament and tendon injuries	
PRP	I
MSCs	I
Fibrosis	
Angiotensin-II receptor blockers	I
HMG CoA reductase inhibitors	I
Senescence	
Navitoclax	I
Rapamycin	I

*According to Wright[81], grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention; grade B, fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention; grade C, poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention; and grade I, insufficient or conflicting evidence not allowing a recommendation for or against intervention. †PRP = platelet-rich plasma, MSCs = mesenchymal stromal cells, and HMG CoA = 3-hydroxy-3-methyglutaryl coenzyme A.

adipose tissue-derived MSCs (AMSCs) are an increasingly popular choice because of the ease of harvest, purported higher proliferative capacity, and anti-inflammatory properties[38]. Recent studies have shown that the paracrine function of MSCs is the primary mechanism by which they participate in tissue repair[39]. The MSCs from BMAC or adipose tissue are multipotent stem cells whose strong self-renewal capacity and potential to differentiate into musculoskeletal lineages of interest (osteoblasts, chondrocytes, and adipocytes) have been the source of much excitement in the orthopaedic field.

Clinical Evidence

Similar to PRP, most studies have focused on the use of MSCs for knee OA (Table II). Through their paracrine effect, MSCs are thought to promote chondrogenesis and synthesis of type-II collagen and extracellular matrix and exhibit anti-inflammatory properties after tissue damage[40,41]. Xia et al., in a review of 7 RCTs involving knee OA, found that patients undergoing MSC injections had improved physical function scores, with 2 studies showing a net positive effect of MSC injections on patients' pain scores[42]. Similarly, a systematic review by Maheshwer et al. found significant improvements in function and cartilage volume; however, no significant difference in pain scores was found[43]. It is worth noting, however, that the quality of evidence for both of these systematic reviews is low because of the considerable heterogeneity of the studies.

Following ligament or tendon injuries, a healing process is initiated that is typically divided into 3 chronological stages: inflammation, proliferation, and remodeling[44]. Type-III collagen, which is weaker than native type-I collagen, is initially formed. As remodeling occurs, type-I collagen replaces the type-III collagen, improving the strength of the injured region. MSCs have been considered since the early 1990s to potentially enhance ligament and tendon healing, decrease scar formation and inflammation, and increase type-I collagen. Despite this interest, few clinical studies have directly examined the impact of MSCs on ligament and tendon injuries. A recent review identified only 1 RCT, 2 non-RCTs, and 8 noncontrolled studies related to MSCs in the treatment of tendon injuries, with even fewer studies related to ligament injuries[45]. A double-blinded RCT of MSCs combined with HA versus HA alone in 17 patients who underwent anterior cruciate ligament (ACL) reconstruction demonstrated improvement, both clinically and on magnetic resonance imaging (MRI), with the addition of MSCs, although the particular and unique effect of MSCs was unclear[46]. Another Level-I RCT compared PRP and MSCs from the stromal vascular fraction of adipose tissue in the management of Achilles tendinopathy, and while it demonstrated some clinical improvements in favor of MSCs in the short term (15 to 30 days), these clinical differences disappeared at 6 months and were not accompanied by any structural changes on evaluation with MRI[47]. While several other studies with low-level evidence have also evaluated MSCs in the treatment of rotator cuff injuries, lateral and medial epicondylitis, and patellar tendinopathy, with some promising clinical results[45], additional higher-level studies are necessary to confirm the therapeutic benefit of MSCs in such soft-tissue injuries and define the exact mechanisms by which MSCs exert their effects.

Limitations

There are a number of limitations to using MSCs as a biologic agent. First, the quality and concentration of MSCs are highly contingent on the site of procurement, and notably the etiology of the stromal cell is highly linked to its therapeutic effects, e.g., MSCs acquired from adipose tissue demonstrate inferior chondrogenic capability compared with bone-marrow-derived MSCs[48]. Donor site morbidity, particularly with iliac crest harvesting, is also a concern and often necessitates general anesthesia as well as postoperative analgesia[49,50]. Additionally, the process of harvesting and preparing MSCs is complex, involving bone marrow aspiration, gradient centrifugation, and mononuclear cell separation[37]. Due to variation in MSC harvest techniques and complexity in preparation, there is a substantial degree of heterogeneity, which makes consistent conclusions about the therapeutic potential of MSCs difficult (Table III).

Regulation and Economics of PRP and MSCs

Title 21 of the U.S. Code of Federal Regulations, Part 1271 (21 CFR 1271) regulates transplantation of human cells, tissues, and cell and tissue-based products (HCT/Ps). HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." MSCs and BMAC are considered HCT/Ps under section 361 of the Public Health Service Act, and their regulations follow 21 CFR 1271[51]. However, PRP is not considered an HCT/P, despite being a biologic drug[52]. PRP was brought to the market by the 510(k) pathway, which "clears" products that are "substantially equivalent" to an already cleared predicate device[53]. In the case of PRP, the predicate device is a platelet and plasma separator that is intended to be used with bone graft materials to enrich its handling properties or for PRP gel to help maintain moisture in a wound[52]. This U.S. Food and Drug Administration clearance permits PRP to be used for a wide variety of orthopaedic conditions, although it is not specifically approved for any particular indication. Hence, most current PRP treatments for musculoskeletal conditions are considered "off-label" use and liability is transferred from the manufacturer to the provider[52].

PRP and MSC therapies are both typically not currently covered by insurance, resulting in a wide distribution in costs of production and treatment for the patient. Several agencies have estimated that the global market for PRP will increase to between US$380 million and $4.5 billion over the next 5 years[52]. Direct patient costs for PRP therapy can vary widely depending on the musculoskeletal pathology being treated and the exact treatment protocol used (e.g., 1 to 3 injections). Out-of-pocket costs for PRP therapy have been estimated to be approximately $500 to $2,500[52]. There are currently limited data on the economic costs of MSC treatment. However, in our experience, the cost of preparation for BMAC can be highly variable depending on the company and manufacturing product used for processing BMAC, ranging from approximately $250 to $1,995. Similarly, because BMAC is not covered by insurance, the out-of-pocket cost for patients is hard to determine exactly but can range from approximately $3,000 to $8,000.

Novel Orthobiologics and Therapeutic Targets

Fibrosis

Fibrosis, or deposition of fibrous tissue, is considered an irreversible change in the structure and function of injured muscles. Following muscle injuries, the healing process occurs in stages, with an early inflammatory stage marked by neutrophil, monocyte, and macrophage attraction to the injury site. Macrophages have 2 phenotypes: M1, which is proinflammatory, and M2, which is profibrotic. The balance between these 2 phenotypes is crucial as a shift toward an M2-predominant population tends toward increased fibroblast activation and pathologic deposition of collagen via TGF-β1 release from the M2 macrophages[54].

Inhibiting or reversing muscle fibrosis thus provides a promising target to improve outcomes following muscle injury and repair. The use of angiotensin-II receptor blockers (ARBs) has been shown to modulate TGF-β1 and reduce fibrosis in several tissues including skeletal muscle[55]. Clinically, losartan (Cozaar) is an ARB that is currently used to treat high blood pressure. Bedair et al., in an animal model of gastrocnemius lacerations, demonstrated that systemic treatment with losartan resulted in dose-dependent histologic improvement in muscle regeneration and a measurable reduction in fibrous tissue formation compared with controls at 3 and 5 weeks postinjury[56]. Statins, or 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors, have also been shown to markedly reduce fibrosis in an animal model of supraspinatus tears, likely through downregulation of type-I collagen expression[57]. The implications of utilizing these commercially available, generally well-tolerated, safe, and widely used medications in treating fibrosis are clinically appealing and potentially far-reaching, although further clinical trials are necessary.

Senescence

Aging is a major risk factor for numerous pathologies including cancer, cardiovascular disease, diabetes, osteoporosis, OA, and neurodegenerative disorders[58]. Hayflick first described the limited replicative potential of cultured human fibroblasts in the 1960s and termed this phenotype "cellular senescence."[59] Since that time, cellular senescence has come to be described as a complex stress response of cells that induces a stable growth arrest accompanied by distinct phenotypic alterations, including chromatin remodeling, metabolic reprogramming, increased autophagy, and the implementation of a proinflammatory senescence-associated secretory phenotype (SASP)[58,60]. While senescent cells normally make up a small proportion of healthy tissues, they have been causally implicated in aging and in an ever-expanding list of diseases. Interestingly, transplantation of senescent cells has been shown to induce an OA-like condition in mice, with articular cartilage erosion, increased pain, and impaired function[61].

Targeting senescence, and hence the aging process, is thus a tantalizing prospect to delay and treat multiple age-related diseases. A senolytic pharmacological agent, navitoclax (also named ABT263), has been used to treat various cancers and works by promoting apoptosis of senescent cells[62,63]. Recent work in vitro and in an animal model demonstrated the ability of ABT263 to reduce the expression of inflammatory cytokines and promote cartilage matrix aggregation in OA chondrocyte pellet culture and decrease pathological changes in cartilage and subchondral bone in posttraumatic OA[64]. Other therapeutics targeting the SASP have also been proposed, including rapamycin, BRD4 (bromodomain-containing protein 4), NF-κB, or p38 inhibitors[58]. The mammalian target of rapamycin (mTOR) signaling pathways have been shown to play a role in the progression of aging, and inhibition of mTOR in yeast, worms, and flies extends their life spans[65,66]. In several progeroid (accelerated aging) murine models, mTOR has been found to be elevated in various progenitor cell populations, and treatment with rapamycin, an mTOR inhibitor, has been demonstrated to improve muscle-derived stem cell (MDSC)

function through induction of autophagy, restored differentiation and proliferation potential, and reduced senescence[67,68]. Intra-articular injection of rapamycin in mice was also shown to significantly reduce the severity of articular cartilage degradation at 8 and 12 weeks after destabilization of the medial meniscus[69]. A growing array of drugs and compounds with senolytic properties including dasatinib (a tyrosine kinase inhibitor), quercetin (a flavonoid), and fisetin (a phytonutrient) are being discovered and tested and could yield potentially transformative clinical interventions.

Customizing Orthobiologics

Customizing orthobiologics to improve tissue repair is a major area of investigation and holds tremendous potential for research and development. Strategies to combine orthobiologics to improve biological efficacy through complementary or synergistic mechanisms have also only recently been explored. As our understanding of the molecular and cellular framework underlying human physiology increases, often so does the complexity of biologic processes. For example, it has been shown that TGF-β1, the major cytokine implicated in fibrosis, is unfortunately also present in PRP[70]. Work in animal models has shown that blocking fibrosis, by neutralizing TGF-β1, can improve the regenerative potential of adult stem cells and PRP in skeletal muscle healing[71,72]. Similarly, combining losartan with PRP improves skeletal muscle healing after contusion by enhancing angiogenesis and follistatin expression and reducing the development of fibrosis[73]. When losartan was given in conjunction with a bone marrow stimulation (BMS) procedure for an osteochondral defect, the repair cartilage tissue was found to be superior to that formed by BMS alone and consisted primarily of hyaline rather than fibrocartilage[70].

It has recently been discovered that senescent cells and their SASPs exist within PRP and BMAC and increase with age[74]. How this population of cells and their phenotype influence the effectiveness of orthobiologic treatment, and whether their presence and effect can be influenced, remains unknown and is the subject of several ongoing clinical trials at our institution examining how the combination of PRP with losartan and senolytics impacts patient outcomes following surgery. Together, these findings provide a glimpse of the many novel therapeutic avenues that remain to be explored in the use of biologics to supplement orthopaedic surgical interventions.

Conclusions

Orthobiologics represent a rapidly progressing field that shows promise for delivering therapeutic patient benefit, but their full mechanisms, potential, and applications remain to be fully elucidated. It is clear that additional high-quality, well-documented, sufficiently powered clinical studies are necessary to better define the properties and efficacy of established and novel biologic treatments. Ultimately, strategies to perfect the composition and delivery of orthobiologics should improve their therapeutic effects in supplementing orthopaedic surgical interventions for individual patients. ■

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