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REVIEW ARTICLE

Biological Therapies in Regenerative Sports Medicine

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Abstract Regenerative medicine seeks to harness the potential of cell biology for tissue replacement therapies, which will restore lost tissue functionality. Controlling and enhancing tissue healing is not just a matter of cells, but also of molecules and mechanical forces. We first describe the main biological technologies to boost musculoskeletal healing, including bone marrow and subcutaneous fat-derived regenerative products, as well as platelet-rich plasma and conditioned media. We provide some information describing possible mechanisms of action. We performed a literature search up to January 2016 searching for clinical outcomes following the use of cell therapies for sports conditions, tendons, and joints. The safety and efficacy of cell therapies for tendon conditions was examined in nine studies involving undifferentiated and differentiated (skin fibroblasts, tenocytes) cells. A total of 54 studies investigated the effects of mesenchymal stem-cell (MSC) products for joint conditions including anterior cruciate ligament, meniscus, and chondral lesions as well as osteoarthritis. In 22 studies, cellular products were injected intra-articularly, whereas in 32 studies MSC products were implanted during surgical/arthroscopic procedures. The heterogeneity of clinical conditions, cellular products, and approaches for delivery/implantation make comparability difficult. MSC products appear safe in the short- and mid-term, but studies with a long follow-up are scarce. Although the current number of randomized clinical studies is low, stem-cell products may have therapeutic potential. However, these regenerative technologies still need to be optimized.

Key Points

Biologics, including adult cells, platelet-rich plasma, and conditioned media, are under investigation for regenerative purposes in sports medicine.

Cell therapies under clinical assessment include dermal fibroblasts, tenocytes, chondrocytes, and various products containing stem cells, mainly bone marrow concentrate, stromal vascular fraction, bone marrow-derived mesenchymal stem cells, and adipose stem cells.

The use of adult cell therapies is safe. Most articles report improvement in clinical outcomes, but overall the quality of evidence is low, with the absence of adequately powered controlled clinical trials.

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1 Introduction

Impairment of biological and mechanical homeostasis is common in orthopedic sports medicine where musculoskeletal tissues are often subjected to excessive stresses

and multiple injuries. Major injuries in athletes result in a high incidence of chronic problems such as osteoarthritis (OA), for which effective treatments are not yet available [1]. Both acute and chronic sports lesions have promoted a surge of novel biological therapies aiming to improve the quality of life of athletes and active individuals.

Currently, most expectations in regenerative sports medicine are focused on the potential of cell therapies, typically adult mesenchymal stromal/stem cells (MSCs). Regenerative medicine seeks to harness the potential of cell biology for re-establishment of lost tissue functionality. However, controlling and enhancing musculoskeletal tissue regeneration is not just a matter of cells. Molecules, cells, and mechanical forces are hardwired and cooperate in healing mechanisms. For example, platelet-rich plasma (PRP), an autologous regenerative technology, is based on the delivery of a pool of growth factors and cytokines with tissue healing potential, and has been widely used in sports medicine settings aiming to enhance tissue healing [2]. Both PRP and adult MSCs are physiological means to combat injury. In this context, regenerative medicine seeks to enhance these endogenous resources to help tissue homeostasis prevail over hostile microenvironments.

Regenerative technologies, both allogeneic and autologous, have emerged as an industry, and the potential market is expected to reach US$8 billion by 2020 [3, 4]. Orthopedics and sports medicine are among the areas that will have the greatest applications. Athletes (professional and recreational) seek novel regenerative medicine interventions to heal injuries, and to rapidly resume their desired sports activities. Cell therapies are offered in several stem-cell centers around the world, not only for sports injuries [5], but also to treat devastating illnesses including cerebral palsy, Alzheimer disease, or multiple sclerosis, among others. Medical tourism is an internet-driven business, mediating a rapid expansion of stem-cell clinics, mostly in countries with permissive regulatory conditions [6].

However, stem-cell therapies are still in their first stages of implementation, and much research is still necessary before they can meet the hope that has been put on them. To refrain from pursuing unproven expensive cell therapies, the International Society for Stem Cell Research (ISSCR) offers clear information about disproved efficacy and associated risks (ISSCR, 2013) [7]. Also, a set of performance guidelines is available for responsible administration of stem-cell therapies (ISSCR, 2008) [8].

Aiming to provide an update for healthcare professionals interested in regenerative therapies, we address what is known about the composition of cell-based products (i.e., adult mesenchymal stromal/stem-cell products) and other differentiated cell therapies, their combination with PRP, and the assumptions or paradigms on which to base their mechanisms of action. We also review the current literature about clinical outcomes following the use of cell therapies in sports medicine for tendon and joint conditions.

2 Regenerative Medicine Technologies

2.1 Regenerative Medicine Products

The three main regenerative medicine injectable products undergoing investigation for tissue healing are (1) most importantly, cells, which drive healing mechanisms; (2) PRP; and (3) conditioned media (CM) from cells (Fig. 1). In general, cells or other regenerative products for musculoskeletal injuries are delivered locally. This is in contrast to the systemic route of administration in some other pathologies, such as systemic lupus erythematosus [9].

2.1.1 Cellular Products

Cell therapies include a broad range of subtypes, from injectable mixtures of cell populations, as is the case with bone marrow concentrate (BMC), and stromal vascular fraction (SVF), to refined MSC preparations with trilineage differentiation capacity and characteristic surface proteins. Despite these specific features, there are not unequivocal markers of cell quality and functional efficacy in vivo. Furthermore, comparability between intertrial clinical outcomes can be hindered because of variability in the quality of MSCs associated with fabrication reagents and procedures. Central to progress in the field is a description of manufacturing procedures and the development of products based on standardized parameters. Therefore, for laboratory-expanded cells, authors are encouraged to provide specific in-process data, such as initial yield ($\times 10^6$)/days at passage zero (P0), passage 2 (P2) cumulative population doublings, and P2 epitopes (+/−) [10].

As an alternative, tissue-specific biopsies can be harvested and differentiated cells, such as chondrocytes for cartilage, and tenocytes or skin fibroblasts for tendon conditions, are implanted after 3–4 weeks of growth in vitro. Presently, the main interest is focused on injecting cells and PRPs; both are mostly used on an autologous basis to avoid any host immune responses.

Hereinafter, we address the main characteristics of bone marrow and fat-derived regenerative products as well as PRP and CM.

2.1.1.1 Stromal Vascular Fraction and Adipose Stromal/Stem Cells Adipose tissue can be considered the richest source of stem cells in our body. A simple adipose graft has been injected in joint conditions as an adjuvant to BMC.

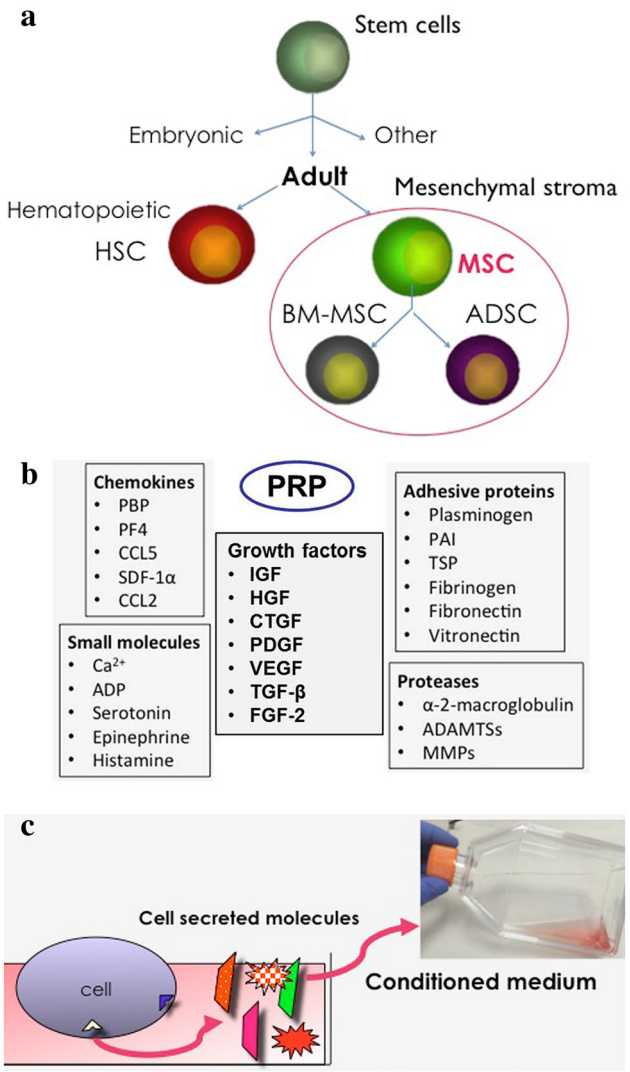

Fig. 1 Current regenerative technologies for musculoskeletal injuries. **a** Adult mesenchymal stromal cells, also known as mesenchymal stem cells (MSCs), which are cells with high proliferative and self-renewal capabilities, adhesive to plastic surfaces, showing specific cell surface proteins, and with potential to differentiate in at least three lineages including bone, cartilage, and adipose tissue. **b** Platelet-rich plasma (PRP) that consists of a pool of signaling proteins including growth factors, cytokines, and other adhesive proteins involved in healing mechanisms (the list is not exhaustive). **c** Conditioned culture media (CM), which contain biologically active molecules secreted by cells in vitro; these molecules affect cell functions. *ADAMTS* A disintegrin-like and metalloprotease with thrombospondin, *ADP* adenosine diphosphate, *ADSC* adipose stem cells, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *CCL* chemokine (C-C motif) ligand, *CTGF* connective tissue growth factor, *FGF* fibroblastic growth factor, *HGF* hepatocyte growth factor, *HSC* hematopoietic stem cells, *IGF* insulin growth factor, *MMP* matrix metalloproteinase, *MSCs* mesenchymal stem cells, *PAI* plasminogen activator inhibitor, *PBP* platelet basic protein, *PDGF* platelet-derived growth factor, *PF* platelet factor, *PRP* platelet-rich plasma, *SDF* stromal cell-derived factor, *TGF* transformed growth factor, *TSP* thrombospondin, *VEGF* vascular endothelial growth factor

Alternatively, adipose tissue can be fractionated into mature adipocytes, blood, and the SVF (Fig. 2). In 1964, Rodbell [11] isolated SVF for the first time using proteolytic enzymes and centrifugation. SVF can be obtained in a few hours using kits and following commercial protocols, without altering the relevant biological characteristics of the cells. SVF is a fresh product prepared at the point of care but qualifies as an advanced therapy medicinal product (ATMP) because it involves the use of proteolytic enzymes to obtain a cell suspension. This cell suspension is then centrifuged and the cell pellet is termed SVF. Thus, the use of SVF for orthopedic conditions requires Food and Drug Administration (FDA) and institutional review board (IRB) approval.

The injection of these preparations provides the host tissue with a heterogeneous cell population including hematopoietic stem cells, endothelial cells, and adipose-derived stromal/stem cells representing 2–10 % of SVF. $CD34^+$ cells (angiogenic cells) are present in large numbers and could compose up to 63 % of SVF [12, 13]. Overall, $CD34^+$ cells constitute the main part of the stem-cell niche, and may also favorably influence modulation of neovascularization. Vascularization is crucial in early healing mechanisms to provide oxygen and nutrients for the metabolic needs of activated cells but it is downregulated in the later stages of healing.

Alternatively, to improve purity and obtain a larger number of MSCs, SVF can be culture expanded (Fig. 2a). Zuk et al. [14], pioneered the characterization of multipotent stem cells from human fat-derived SVF, currently named ASCs (adipose stromal/stem cells).

The International Society for Cellular Therapy (ISCT) has proposed four criteria for adult mesenchymal stem-cell characterization: (1) plastic adherence, (2) at least tri-lineage differentiation capabilities, (3) expression of CD73, CD90, and CD105, and (4) lack of expression of CD14, CD11b, CD34, CD45, CD19, CD79, and human leukocyte antigen–antigen D related [14].

Interestingly, the potential of ASCs is independent of the anatomical fat source [15]. However, ASCs from aged people are less proliferative, and can be of lower quality, because of telomere shortening and DNA damage, compromising their clinical success [16].

2.1.1.2 Bone Marrow Concentrates, and Bone-Marrow-Derived Mesenchymal Stromal/Stem Cells Bone marrow aspirates, from the iliac crest or other sites, can be processed (most often by centrifugation) at the point of care to concentrate the nucleated cells of the marrow, which contain various populations of progenitors (Fig. 2b). This 'fresh' product obtained through minimal manipulation is named BMC or BMAC, bone marrow concentrate or bone

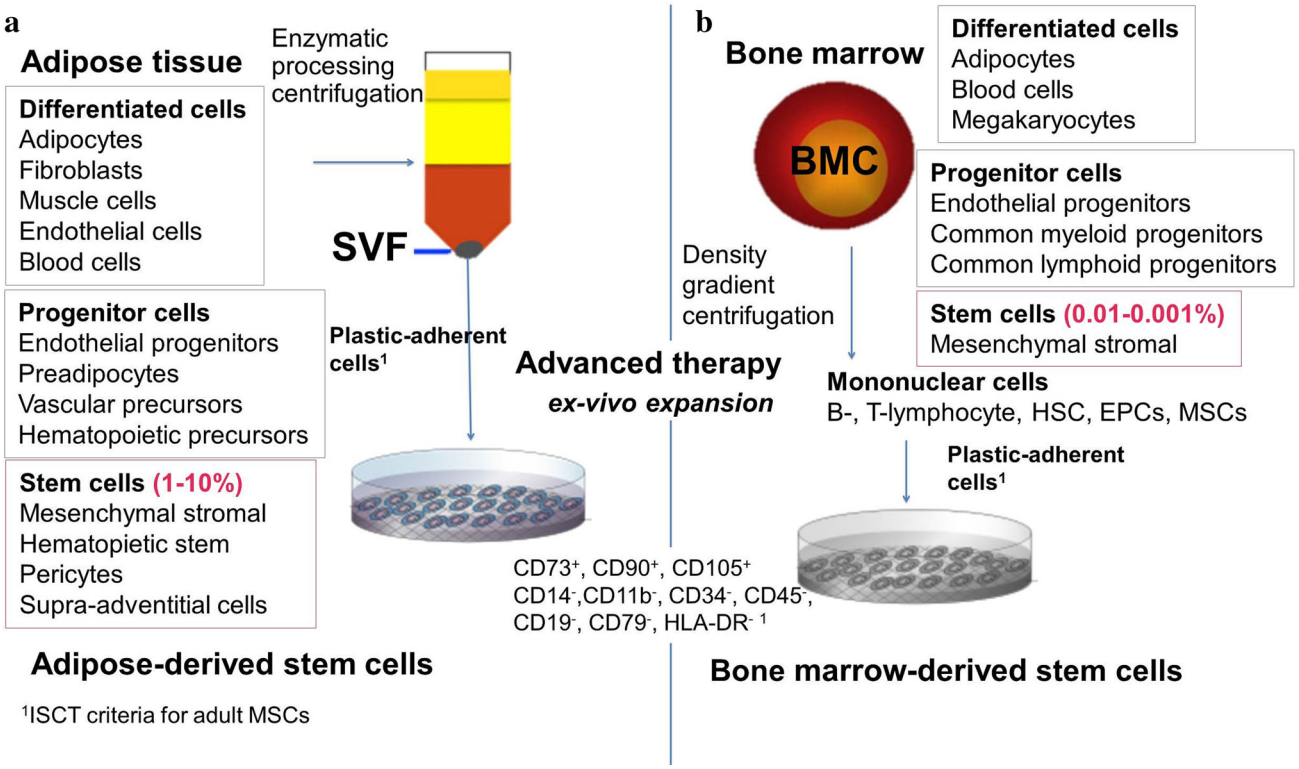

Fig. 2 Regenerative products obtained from adipose tissue and bone marrow. **a** Adipose tissue. Common steps to process cells from lipoaspirates/adipose tissue include washing, enzymatic digestion/mechanical disruption, and centrifugal separation for isolation of SVF as a pellet at the bottom of the tube. Purity can be improved and a higher number of MSCs can be prepared in sizeable doses after a few weeks of ex-vivo expansion. The latter involves substantial manipulation (more than 'minimal manipulation'), thus is considered as an advanced therapy from a regulatory point of view. This fact involves additional complexity and a considerable increase in costs. **b** Bone marrow. Common steps to process cells from bone marrow include centrifugation and cell-culture expansion of plastic-adherent cells. ISCT criteria to define adult MSCs: MSCs express CD73, CD90, and CD105. MSCs lack expression of hematopoietic lineage markers c-kit, CD14, CD11b, CD34, CD45, CD19, CD79, and human leukocyte antigen (HLA)-DR. ASCs meet the majority of ISCT's criteria for MSCs but it has been found that ASCs can exist as $CD34^+$, $CD31^-$, $CD104b^-$, smooth muscle actin cells. *ASCs* adipose stem cells, *BMC* bone marrow concentrate, *EPC* endothelial progenitor cells, *HSC* hematopoietic stem cells, *ISCT* International Society for Cellular Therapy, *MSCs* mesenchymal stem cells, *SVF* stromal vascular fraction

marrow aspirate concentrate. Most cells are $CD34^+$ heme progenitors, and very few (0.01–0.001 %) are multipotent MSCs [17]. A subpopulation that only retains chondrogenic potential has also been identified, making them particularly attractive for joint conditions [18].

Because of the huge interest in using BMC as 'therapy', the performance of different commercial systems is compared in terms of cell recovery, stem/progenitor cells ($CD34^+$), and colony-forming units (CFU-F); that is, MSCs [19].

Alternatively, mononuclear cells can be isolated by density gradient centrifugation, and cultured on plastic surfaces to remove hematopoietic mononuclear cells. Adherent MSCs are then expanded for several generations.

Since cells are isolated from the niche that controls their phenotype (i.e., other cells, cytokines, extracellular matrix [ECM], molecular forces, and so on), following substantial manipulation, both bone marrow-derived mesenchymal stem cells (BM-MSCs) and ASCs are therefore considered an ATMP as ruled in the EU Directive no. 1394/2007 [20]. Similarly, in the USA, ATMPs are regulated by CBER (the Center for Biologics Evaluation and Research). These treatments are only allowed via an IRB approval protocol.

2.1.1.3 Peripheral Blood Progenitor Cells Peripheral blood progenitor cells (PBPCs) are $CD34^+$ cells collected in apheresis procedures typically after treating the patient with a granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF) [21]. Currently, PBPCs are used as a source of stem cells in the hematopoietic reconstitution. In addition, PBPCs can be harvested and cryopreserved. This product is injected within tendons and in the joint cavity to enhance tissue healing.

2.1.2 Platelet-Rich Plasma Technologies

PRP is a plasma preparation with a number of platelets above the normal level in blood, generally obtained after centrifugation of peripheral blood. PRP contains a complex molecular mixture including signaling and adhesive proteins. At present, it is evident that the therapeutic effect of PRPs in tissue healing is not only attributed to growth factors, but also to a myriad of chemokines and other cytokines actively involved in tissue-repair processes, including cell proliferation, differentiation, migration, angiogenesis, and the synthesis of ECM [22]. Importantly, PRPs also trigger synthesis of neurotrophic and angiogenic factors by local cells, thereby amplifying the initial effect [23].

Combining PRP with cell therapies provides a controlled milieu for cells. In addition, PRPs can function as both cell carriers and cytokine delivery systems. In fact, upon plasmatic fibrinogen cleavage and polymerization by thrombin action, the newly developed fibrin constitutes a suitable adhesive scaffold for cell delivery [24]. Platelets embedded within this fibrin scaffold slowly release the molecular pool stored in the alpha granules as well as other small molecules contained in dense granules [25]. What makes PRP attractive is the delivery system embodied by fibrin that confines molecules and cells to the chosen site.

The molecular characterization of PRPs is challenging and varies quantitatively from one individual PRP to another and from one formulation to another [26]. Up to now, it has been impossible to establish quality criteria for PRP products, because there is not enough information about which are the main molecules responsible for the therapeutic effect in each specific tissue condition. Although the initial paradigm of PRP actions was based on platelet number, currently we know that most PRP effects are the consequence of activation of migratory and local cells [27].

More research is necessary to describe how PRP influences the regenerative actions of MSCs. For example, it was recently shown that PRP could favor stemness, and prolongs survival of transplanted cells [28–30]. In addition, PRP can control secretory function [31] in different manners depending on PRP formulation and cell phenotype. Van Pham et al. [32] studied the behavior of the mixture of human ASCs obtained from SVF of ten individuals and expanded with PRP. In addition, ASCs were re-suspended in 3 mL of human PRP, after which the product was implanted into a cartilage injury in immunodeficient mice. This study showed that PRP efficiently stimulated ASC proliferation, and does not change the marker expression of ASCs, but it modifies the expression of SOX-9 (SRY [sex determining region Y]-Box 9), collagen type 2, and aggrecan. Also, PRP reduces vascular endothelial growth factor (VEGF) expression by ASC [32].

2.1.3 Conditioned Media

A less investigated product to be used for regenerative purposes is the conditioned culture media (CM). While growing in vitro, cells release to the extracellular milieu a pool of cytokines, chemokines, growth factors (including transforming growth factors [TGF-α, TGF-β], hepatocyte growth factor [HGF], epidermal growth factor [EGF], fibroblast growth factor [FGF-2], insulin growth factor [IGF-1], VEGF, angiopoietin [ANGPT-1], among others), as well as matricellular proteins, enzymes, microvesicles/exosomes, messenger RNAs (mRNAs), and microRNAs [33] (Fig. 1c). The source of CM is cells cultured in vitro under specific consistent protocols. CM is composed from the soluble molecular components of cell secretome, which can be tailored for specific therapeutic actions. Actually, the therapeutic potential of CM is based on one of the paradigms of MSC actions: the trophic and paracrine effects on local cells.

A major advantage of CM is that it can be easily manufactured, sterilized, packaged, and stored, and thus can constitute an 'off-the-shelf' stem-cell product.

The therapeutic value of the stem-cell CM is under research [34, 35]. Numerous patent applications have been filed in recent times (i.e., US2012/0276215A1). For example, an ongoing clinical trial [36] in OA is assessing the safety and feasibility of trophic factors from umbilical cord mesenchymal stem cells.

2.2 The Mechanism of Action of Regenerative Medicine Products

There are a number of conditions in which regenerative medicine products, in particular MSCs, have been investigated, and thousands of articles have been published on this topic. Consistent with the complexity of these products, extensive literature from the past decades indicates that regenerative medicine products modulate almost every facet of repair mechanisms (Fig. 3).

When injected systemically, the assumption that MSCs home to the relevant tissue and replace injured cells was based on both their migratory and differentiation capacities [37, 38]. Site-directed implantation (i.e., cells loaded in collagen membranes [or other scaffolds] placed within chondral or osteochondral defects) can also influence cell fate. In addition to tri-lineage differentiation capacity (i.e., bone, cartilage, and fat), adult MSCs further differentiate to tendon or ligament in the presence of environmental molecular cues including ligament/tendon-derived matrix [39].

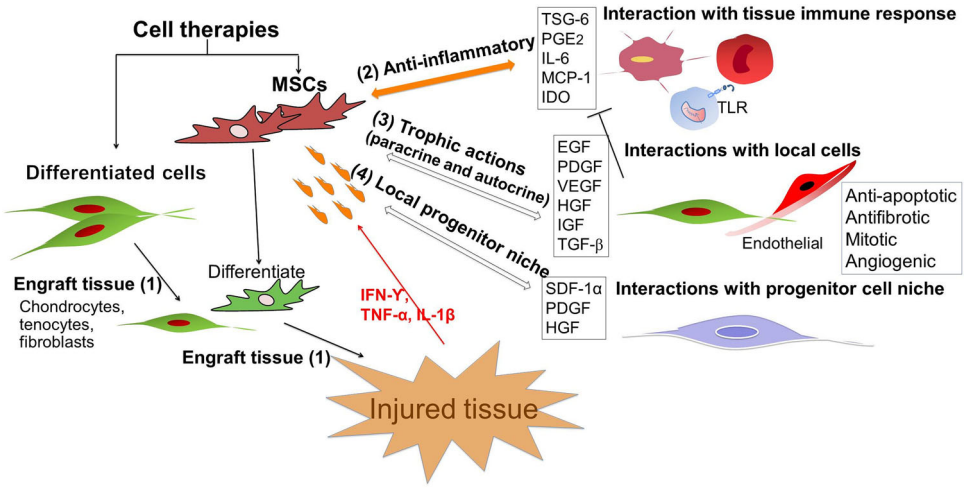

Fig. 3 Mechanism of action of cell therapies: while still unclear, several hypotheses have been proposed. Differentiated cells are injected or implanted within tissue lesions to (1) engraft, synthesize ECM molecules, integrate with the surrounding tissue, and return tissue to homeostasis conditions and full functional capabilities. MSCs can (1) engraft the tissue provided that the conditions of the host tissue are favorable for differentiation; (2) modulate the inflammatory response; (3) provide trophic and antiapoptotic factors; (4) interact with the progenitor niche. *ECM* extracellular matrix, *EGF* endothelial growth factor, *HGF* hepatocyte growth factor, *IDO* indoleamine 2,3-dioxygenase, *IFN* interferon, *IGF* insulin growth factor, *IL* interleukin, *MCP* monocyte chemotactic protein, *MSCs* mesenchymal stem cells, *PDGF* platelet-derived growth factor, *PGE_2* prostaglandin E_2, *SDF* stromal cell-derived factor, *TGF* transforming growth factor, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *TSG-6* TNFα-stimulated gene 6, TNFα-inducible protein 6, *VEGF* vascular endothelial growth factor

Why tissue engraftment rarely occurs after the local injection of cells is unknown. Several authors [40, 41] speculate that cell engraftment is hindered because the host tissue is not adequately conditioned, and does not provide normal trophic signals to implanted cells. This can happen especially in degenerative diseases such as OA or tendinopathy, in which the microenvironment could be deprived of nutrients and exposed to high concentrations of proteases such as A disintegrin and metalloprotease with thrombospondin (ADAMTS), metalloproteinases (MMPs) [42], and detrimental pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor (TNF-α) [43].

An alternative hypothesis currently being investigated focused on the trophic paracrine and autocrine actions of MSCs. Secreted growth factors, chemokines, and cytokine factors include TGF-α, TGF-β, HGF, IL-6, EGF, FGF-2, IGF-1, and VEGF [44, 45]. Cells can also limit tissue destruction and enhance repair by means of anti-apoptotic, proliferative, and angiogenic actions [46–48].

The therapeutic potential of MSC secretome is the reason to believe that CM may mimic the effects of cells. Similar trophic actions are advocated for the pool of growth factor and cytokines delivered by PRP [49]. A potential role for MSCs is the mobilization and activation of the local niche. Similarly, PRP can optimize the local niche, and progenitors within a tendon can be stimulated to proliferate and differentiate [50].

Recent literature has emphasized the role of MSCs as modulators of excessive inflammation [51, 52]. MSCs activated by local inflammatory molecules (i.e., TNF-α, IL-1β, and interferon gamma [IFN-γ]) secrete immunomodulatory factors including inducible nitric oxide synthase (iNOS), monocyte chemotactic protein 1 (MCP-1), interleukin 1 receptor antagonist (IL-1Ra), and prostaglandin E_2 (PGE_2) [53]. PGE_2 favors macrophage transition from M1 to M2 and the synthesis of anti-inflammatory IL-10 [54, 55]. Interestingly, when MSCs are activated by inflammatory cytokines present in the local milieu, they secrete TNFα-stimulated gene 6, TNFα-inducible protein 6 (TSG-6) that suppresses inflammation through a negative feedback loop on inflammatory toll-like receptor/nuclear factor kappa-b DNA-binding subunit (TLR/NF-κb) pathways [56, 57]. Actually, TSG-6 has been proposed as a marker of MSC quality and functional efficacy in modulating sterile inflammation [54].

Whether a single allogeneic MSC product can be used for all musculoskeletal conditions, and have similar efficacy to autologous MSCs, is unknown. But, assuming that aging of MSCs reduces their regenerative capabilities [58, 59], allogeneic MSCs may overcome this limitation. Ready-to-use MSCs are a feasible option because they escape immune recognition as they do not express HLA class 2 antigens and express moderate detectable levels of HLA class 1 antigen [60, 61]. However, once implanted,

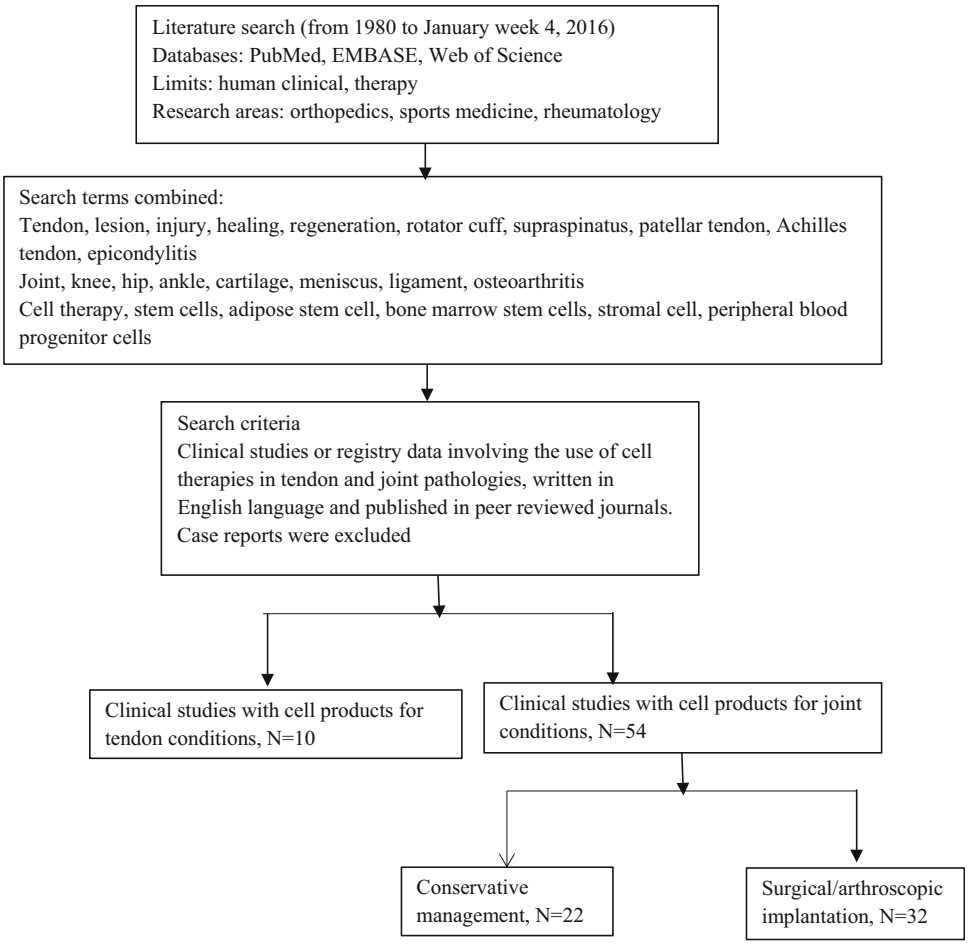

Fig. 4 Review methodology for cell therapies in tendons and joints

allogeneic MSCs can differentiate into local cells, and can activate the host immune response [62]. The presence of immunogenicity after cell differentiation can decrease their therapeutic effect. Current knowledge supports the theory that MSCs are immune evasive and not immune privileged, an issue that requires further scientific clarification.

Efficacy doses of regenerative medicine products are unknown. Regenerative medicine products are biological response modifiers in contrast to pharmaceutical agents or recombinant proteins. This means that they induce further cellular and molecular changes over time. However, because of their perception as drugs, MSC doses for expanded cells are measured in the millions or billions of cells, and initially calculated based on the recipient's body weight for systemic or intrathecal routes of administration [63]. Intralesional delivery compared with systemic administration has the advantage that cells arrive directly at the target tissue, avoiding cell losses that may occur during migration. Doses of PRP are measured as concentration of platelets or multiples of platelets relative to the number in peripheral blood.

3 Regenerative Therapies in Clinical Practice

To obtain more precise information about the clinical outcomes following cell therapies, we conducted a narrative review, categorizing the studies included in the review by target tissue and underlying pathology. We excluded studies examining the efficacy of autologous chondrocyte implantation (ACI) because they have been recently reviewed [64]. For the same reason, we did not review PRP studies [2, 65, 66].

3.1 Search Strategy

The review methodology is shown in Fig. 4. Articles were categorized according to condition, and whether the experimental cell product was applied by injection or at surgery. Additionally, studies were categorized according to whether fresh 'stem-cell-based products' (same-day procedures) or laboratory-expanded cells for 3–4 weeks were used. Data relating to experimental design, condition, patient population, as well as specific cell product,

Table 1 Tendinopathies conservatively treated with cell therapies [67–76]

Study (year)	Study design, *N*/patient population	Intervention/follow-up	Outcome measurements/follow-up/results
Epicondylitis ($N = 4$)			
Connell et al. (2009) [67]	Case series, $N = 12$	Injection, skin-derived cells, expanded	6 months: 11/12 patients had satisfactory outcomes Decrease in tear number, new vessels and tendon thickness
Moon et al. (2008) [68]	Case series, $N = 26$, lateral and/or medial, recalcitrant to conservative treatments	BMC + pucaine after arthroscopic debridement	8 weeks, 6 months: VAS, MEPS, no complications. Pain reduction, improvement in MEPS at 8 weeks and 6 months
Singh et al. (2014) [69]	Case series, $N = 30$ patients, first episode tendinopathy	BMC, 4–5 mL + 1 mL 2 % lidocaine	PREE, 2, 6 and 12 weeks, significant improvement in functional outcome at all time points
Wang et al. (2013, 2015) [70, 71]	Case series, recalcitrant patients, $N = 20$	Injection, autologous expanded tenocytes 2–5 $\times$ 10^6 cells	1 year, VAS decrease, quick DASH improvement, UEFS decrease and grip strength improved, MRI improved. Effect maintained at 4.5 years
Shoulder ($N = 2$)			
Centeno et al. (2015) [72]	Case series, 115 shoulders in 102 patients, tears <1.5 cm and shoulder OA	Preinjection with hypertonic dextrose, BM-MSCs 4.7 $\times$ 10^8 cells	DASH, NPS, MCID defined as 2 point reduction in NPS and 10 points in DASH
Ellera Gomes et al. (2012) [73]	Cases series, complete rotator cuff tears	Conventional rotator cuff repair plus PBMN cell injection into tendon borders	Significant increase in UCLA at 12 months, MRI integrity in all tendons 14/14, one patient relapsed after 2 years
Patellar tendon ($N = 2$)			
Clarke et al. (2011) [74]	RCT, $N = 46$ patients, 60 patellar tendons	Expanded dermal fibroblasts (2 mL) + PRP versus PRP + medium without cells (2 mL)	Improvement VISA-P, 6 weeks, 3 and 6 months. Reduction of hypoechogenicity and tear size in both groups at 6 months. Increased thickness in cell group
Pascual-Garrido et al. (2012) [75]	Case series, $N = 5$ patients, refractory patellar tendinopathy	Non-expanded BMC	5 years: significant improvement in Tegner and KOOS (all sub-scales). 7/8 patients would have the procedure again
Achilles tendon ($N = 1$)			
Tate-Oliver and Alexander (2013) [76]	Case series, $N = 3$, partial thickness interstitial tears	US-guided percutaneous infiltration of (SVF + PRP >4×)	Patients returned to full activities after12 weeks, US at 12 months showed restoration of normal tendon structure, improvement maintained at 3–4 years. Increase in discomfort 3–4 days after infiltration

BMC bone marrow concentrate, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *DASH* Disabilities of the Arm, Shoulder and Hand, *KOOS* Knee injury and Osteoarthritis Outcome Score, *MCID* minimal clinically important differences, *MEPS* Mayo Elbow Performance Score, *MRI* magnetic resonance imaging, *NPS* Numeric Pain Scale, *OA* osteoarthritis, *PBMN* peripheral blood mononuclear cells, *PRP* platelet-rich plasma, *PREE* Patient-Rated Elbow Evaluation, *RCT* randomized controlled trial, *SVF* stromal vascular fraction, *UCLA* UCLA Shoulder Rating Scale, *UEFS* Upper Extremity Functional Scale, *US* ultrasound, *VAS* visual analog scale, *VISA-P* Victorian Institute of Sports Assessment–Patellar

intervention type, and clinical outcomes were extracted and tabulated (Tables 1, 2, 3).

3.2 Results

Nine clinical studies used autologous cells obtained from different sources to treat tendon conditions [67–76] (Table 1). In addition, we identified 22 studies in which laboratory-expanded MSCs ($n = 11$) [77–88] or stem-cell-derived products ($n = 11$) were injected intra-articularly [89–99] (Table 2). Thirty-two studies performed arthroscopic/surgical delivery of cells [24, 101–133]; nine of these studies used laboratory-expanded cells [100–108] while stem-cell-derived products were used in 23 studies [24, 109–133] (Table 3).

3.2.1 Tendon Conditions

Studies examining the efficacy and safety of cell therapies in tendon conditions are shown in Table 1 [67–76]. Cell therapies consisted of culture-expanded tenocytes [70, 71] or skin fibroblasts [67, 74]; also, BMC [68, 69, 72], SVF [76], and PBPC [73] have been used in five case series.

A pioneer study was conducted in Australia by Wang et al. [70, 71], who implanted 2–5 $\times$ 10^6 autologous tenocytes, obtained from patellar tendon biopsies and further expanded in vitro, within the lateral epicondyle by ultrasound-guided injections with no peppering in 20 patients with recalcitrant tendinopathy. No donor-site complication was found at follow-up. Outcome scores included visual analog scale (VAS), decreasing from 5.73

Table 2 Conservative management: injections of cell products in joint conditions

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Injection of expanded mesenchymal stem cells ($N = 11$) [77–88]			
Centeno et al. (2015) [77]	Case series, ACL tears, $N = 10$, grade 1, 2, 3 tears	Injection, pre-injection of 3–5 mL of 12.5 % dextrose + 0.1 % lidocaine in normal saline into the ACL 2–5 days prior to 694 × 10^6 BM-MSCs/2.7 mL injection	1, 3, 6, and 12 months, VAS decrease 1.7, $p = 0.25$, LEFS increase 23.3, $p = 0.03$, self-rated improvement 86.7 %, 7/10 patients showed improvements in at least 4/5 measurements (VAS, LEFS, FRI, subjective % improvement and MRI)
Centeno and Freeman (2014) [78]	Controlled study, severe carpometacarpal OA, $n = 6$ patients treated and $n = 10$ untreated controls, chronic	Injection of 5.76 × 10^6 BM-MSCs	11.8 months after cell infiltration improvement of 60 %, whereas 19 % in the control group. VAS reduction 63 % and frequency and duration of pain decreased by 41.7 % and 83.3 %. No complications among treated patients
Centeno et al. (2011) [79]	Controlled study, knee OA, $n = 6$ experimental, $n = 10$ controls. Setting: interventional pain practice	Injection, 5.76 × 10^6 BM-MSCs expanded with platelet lysate	At 12 months, 60 % improvement in treatment group (95 % CI 22–99) and 19 % in the control group (95 % CI −110 to 73); $p = 0.003$, pain decrease, frequency, and duration
Davatchi et al. (2011) [80]	Case series, knee OA, $N = 4$	Injection, autologous expanded BM-MSCs 8–9 × 10^6 cells	VAS, walking time to pain improved in ¾ patients, number of stairs they were able to climb improved significantly
Emadedin et al. (2012) [81]	Case series, knee OA, $N = 6$ females requiring prosthesis	Injection, 20–24 × 10^6 BM-MSC, suspended in saline serum and injected under fluoroscopy	No adverse events, pain, functional status, and walking distance improved at 6 months but the effect slightly decreased at 12 months. MRI showed increase in cartilage thickness, extension of the repair tissue over the subchondral bone and decrease in the size of subchondral edema in 3/6 patients
Jo et al. (2014) [82]	Case series, knee OA, $N = 18$	Injection, Ad-MSCs three different doses, 1 × 10^7 cells; 5 × 10^7 cells; 1 × 10^8 cells	Improvement VAS, WOMAC at 6 months, clinical, radiological, arthroscopic, and histological evaluations showed results in the high-dose group. The size of cartilage defect decreased in the medial femoral condyles and tibial plateau on the high-dose group. Hyaline cartilage on histology
Kim et al. (2015) [83]	Cohort study, $n = 20$ patients treated with MSCs + PRP injection vs $n = 20$ matched patients implanted arthroscopically with MSCs + PRP	MSCs isolated from SVF and expanded. Arthroscopic implantation vs injection	At 28.6 months IKDC and Tegner better in the implantation than injection group. ICRS grade assessed arthroscopically, better in the implantation group, $p = 0.041$
Orozco et al. (2013), (2014, 2-year follow-up) [84, 85]	Case series, knee OA, $N = 12$	Injection, autologous 40 × 10^6 BM-MSC	MRI at 1 year, 27 % decrease of poor cartilage areas, 68–78 % improvement in algofunctional index
Soler Rich et al. (2015) [86]	Case series, knee OA, K-L: II–IV, $N = 50$ patients	Injection autologous 40 × 10^6 BM-MSC	Lequesne, WOMAC, VAS, MRI, significant reduction in pain at 6 and 12 months post-treatment. VAS decreased significantly. Total WOMAC decrease at 12 months but not significant. Poor cartilage index used to quantify T2 mapping showed promising outcomes in 74 % of patients at 12 months

Table 2 continued

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Vangsness et al. (2014) [87]	RCT, surgically removed meniscal tissue, $N = 55$ patients, injections 7–10 days after partial medial meniscectomy	Single knee injection, 50×10^6 allogeneic MSCs, 150 $\times 10^6$ allogeneic MSCs with HA as vehicle, control group HA injection	No ectopic tissue formation, at 12 months increased meniscal volume (up to 15 %) in 24 % patients in group A (lower dose) and 6 % patients in group B (higher cell dose) $p = 0.022$), no patient in the control group. Significant reduction in pain as measured by VAS. Evidence of meniscus regeneration in patients who received cells
Vega et al. (2015) [88]	RCT, knee OA severity II–IV K-L, $n = 15$ per group	Injection/allogeneic 40×10^6 BM-MSCs vs HA (60 mg single dose)	VAS, Lequesne, WOMAC, 6 and 12 months. No differences in pain between groups except for VAS at 12 months, Lequesne and WOMAC decreased only in experimental group. 77 % patients satisfied in the cell group and 38 % in the control group. No serious adverse events. MRI T2 relaxation measurements showed cartilage quality improvement in the MSC group
Injection of SVF and/or BMC ($N = 11$) [89–99]			
Bui et al. (2014) [89]	Case series, knee, $N = 21$	SVF + PRP	8.5 months, improvement in VAS, function, and MRI
Centeno et al. (2014) [90]	Case series, knee OA, $N = 424$ knees, early stage	Injection BM-MSCs two doses $n = 185$ dose $>4 \times 10^8$ and $n = 224$ dose $<4 \times 10^8$	IKDC, VAS; 1, 3, 6 months and 1 year; better with higher dose, $p < 0.001$
Centeno et al. (2014) [91]	Registry data, knee OA, 840 procedures	Injection, 616 BMC and 224 BMC + adipose	LEFS increase, NPS decrease, addition of adipose tissue no benefit. Adverse events 6 % in BMAC group and 8.9 % in BMC + adipose
Fodor and Paulseth (2016) [92]	Case series, knee OA (K-L I–III), $N = 6$ patients, 8 knees	Injection SVF, 14.1×10^6 nucleated cells	3 months and 1 year improvement in WOMAC and VAS. MRI at 3 months, no detectable differences
Gibbs et al. (2015) [93]	Case series, knee OA, $N = 4$ patients, $N = 7$ joints	Injection, SVF + PRP	2, 3, 6, 8, and 12 months, KOOS, get up and go test, stair climbing test returned to normal
Kim et al. (2014) [94]	Case series, knee OA K-L I–IV, $N = 41$ patients (75 knees)	Injection, BMC + fat	3, 6, 12 months. Significant improvement in VAS, IKDC, SF-36, more effective in early OA
Koh et al. (2013) [95]	Case series, knee OA, $N = 18$	SVF from infrapatellar pad injected (1.18×10^6) with PRP, two injections PRP 1.28×10^6 platelet/μL	3 months, 1 and 2 years, WOMAC, Lysholm, VAS. Improvement in MRI and clinical scores. Improvement related to number of injected cells
Koh and Choi (2012) [96]	Knee cartilage defects, retrospective comparative study	SVF + PRP versus PRP (SVF is from infrapatellar pad)	16.4 months VAS, Lysholm, Tegner better in SVF + PRP
Oliver et al. (2015) [97]	Case series, knee OA, $N = 70$ patients, K-L: II–IV	3 mL BMC + 2 ml lipoaspirate in 0.00125 % lidocaine	3 and 6 months, KOOS sub-scores improved but not significantly
Pak et al. (2013) [98]	Chondromalacia patellae, $N = 3$	SVF + PRP	3 months, VAS, FRI, ROM, MRI pain and function improvement, and MRI evidence of cartilage regeneration

Table 2 continued

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Pak et al. (2013) [99]	Case series, OA, $N = 91$ patients. Hip $n = 22$; knee $n = 74$; ankle $n = 2$; low back $n = 2$	SVF + HA + activated PRP + three injections of activated PRP weekly within a month	Mean follow-up 26 months, significant decrease in VAS at 1 and 3 months. Pain and swelling 1 day after SVF + HA + activated PRP in 37 % of patients. Safety assessment: infection 0 %, tumor 0 %, tenosynovitis/tendonitis 22 %, neurologic 1 % hemorrhagic stroke 2 weeks after the procedure

ACL anterior cruciate ligament, *Ad-MSCs* adipose-derived mesenchymal stem cells, *BMAC* bone marrow aspirate concentrate, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *BMC* bone marrow concentrate, *CI* confidence interval, *FRI* Functional Rating Index, *HA* hyaluronic acid, *ICRS* International Cartilage Research Society, *IKDC* International Knee Documentation Committee, *K-L* Kellgren-Lawrence score, *KOOS* Knee injury and Osteoarthritis Outcome Score, *LEFS* Lower Extremity Functional Scale, *MRI* magnetic resonance imaging, *MSC* mesenchymal stem cell, *NPS* Numeric Pain Scale, *OA* osteoarthritis, *PRP* platelet-rich plasma, *RCT* randomized controlled trial, *ROM* range of movement, *SVF* stromal vascular fraction, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

to 1.21, and the shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick DASH questionnaire), improving from 45.88 to 6.61, after 1 year. In addition, the Upper Extremity Functional Scale (UEFS) decreased significantly from a mean value of 31.73 to 9.21, and grip strength improved from a mean value of 19.85 to 46.60. The cell treatment was unsuccessful in one patient who opted for surgery after 3 months. Magnetic resonance imaging (MRI) score improved significantly at 1 year compared with baseline ($p < 0.001$). Durability of the therapeutic effects was maintained at a mean 4.5-year follow-up [71].

Connell et al. [67] studied the effect of autologous fibroblasts, prepared from skin biopsies, on recalcitrant epicondylitis in 12 patients. Six months after cell injections, 11 of 12 patients showed decreased tear number and tendon thickness as assessed by ultrasound (US) [66]. Moon et al. [68] investigated the effect of BMC in 26 patients with medial or lateral epicondylitis, and reported a reduction in pain and enhanced functionality at 6 months. Centeno et al. [72] reported the effects of BMC injection for the treatment of supraspinatus tears and shoulder OA in a prospective multi-site registry study. Eighty-one rotator cuff tears and 34 patients with shoulder OA followed needle injection treatment with BMC containing PRP and platelet lysate; the nucleated cell count in BMC was an average of 4.7×10^8 cells. Of note, tendons were previously treated with hypertonic dextrose in order to condition the host tissue. DASH scores decreased by an average of 52.6 % ($p < 0.001$) and numeric pain scale decreased by 44.2 % ($p < 0.001$). The reduction of disability and pain started at the first month after treatment. Improvement continued for up to 2 years.

The efficacy of autologous fibroblast injections combined with PRP was examined in a randomized clinical trial (RCT) involving 46 patients and 60 patellar tendons [74]. The experimental group showed better functional outcomes than the control group treated with PRP injections. A reduction of hypoechogenicity and tear size was reported in both groups, but tendons treated with cells displayed increased thickness. In a case series, Pascual-Garrido et al. [75] injected eight patients with refractory patellar tendinopathy with BMC and followed them for up to 5 years. Seven of the eight patients were satisfied with the procedure, and significant improvements were seen in Tegner and Knee injury and Osteoarthritis Outcome Score (KOOS).

Significant improvements were reported except for patients with bilateral pathology. SVF combined with PRP was injected in three patients with partial thickness interstitial tears in their Achilles tendon [76]. Restoration of a normal tendon structure was reported after 12 months, and the improvement was maintained for 3–4 years.

Table 3 Surgical (arthroscopy/arthrotomy) implantation of cell products in joint conditions

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Surgical/arthroscopic implantation of expanded MSCs ($N = 9$) [100–108]			
Akgun et al. (2015) [100]	Prospective randomized pilot study, $N = 14$, knee, full thickness chondral lesions >2 cm^2	Mini-arthrotomy m-AMI vs m-ACI. MSCs harvested from synovia and expanded/chondrocytes harvested and expanded	6, 12, and 24 months, m-AMI group better for all KOOS sub-scales than m-ACI (pain, symptoms, ADL, sport/rec). MRI at 24 months m-AMI excellent and m-ACI group good. Bone marrow edema signal decreased to normal in m-AMI. No complications
Haleem et al. (2010) [101]	Case series, knee chondral lesions $N = 5$ patients full-thickness defects, 3–10 cm^2	Arthroscopy 15×10^6 BM-MSCs + PR-fibrin glue (7.7×10^8 pts/mL) 2×10^6 cells/cm^2 covered with periosteal flap	All patients improved ICRS score at 6, 12 months, second look arthroscopy in 2 patients showed nearly normal joints; MRI of 3 patients showed complete defect fill, 2 patients showed incomplete congruity
Koh et al. (2014) [102]	Case series, $N = 37$ knees, chondral lesions 2.3–8.9 cm^2	2.5–6.1 $\times 10^6$ MSCs from SVF	Improved IKDC, Tegner. ICRS grading at 2nd look 76 % of knees rated abnormal
Lee et al. (2012) [103]	Prospective cohort study, knee chondral lesion	$N = 35$ patients arthroscopic microfracture + outpatient injection of 10^7 BM-MSCs + 2 mL HA versus $N = 35$ MSCs implanted in open surgery	VAS, IKDC, Lysholm, significant improvements in both groups at 24 months
Nejadnik et al. (2010) [104]	Observational cohort study, knee chondral lesions, $N = 72$	Arthrotomy to implant cells $N = 36$ patients ACI vs $N = 36$ BM-MSC, 2-stage procedure. BM-derived MSCs and chondrocyte expansion	IKDC, ICRS, SF-36, Lysholm, Tegner. No differences between groups
Saw et al. (2013) [105]	RCT, knee, grade 3–4 chondral lesions $N = 50$ patients, 25 per group	Subchondral drilling and 5 injections of HA vs PBPC + HA (once per week) at serial visits post-surgery 6 months after surgery 1 injection per week for 3 weeks	No differences between groups at 24-month IKDC. No notable adverse effects. 16 patients per group had histology and 2nd look arthroscopy ICRS histologic score, MRI scans at 18 months, significantly better in the experimental group
Sekiya et al. (2015) [106]	Case series, knee, single cartilage lesion of the femoral condyle, $N = 10$ (5 patients underwent concomitant ACL reconstruction among whom 2 had meniscus suturing)	Expanded synovial MSCs with autologous serum for 14 days, arthroscopic implantation on the defect	MRI improved from 1.0 ± 0.3 to 5.0 ± 0.7 $p = 0.005$, histology performed on 2nd look arthroscopy on 4 patients showed hyaline cartilage in 3 patients and fibrous cartilage in 1 patient, Lysholm no change, Tegner 76 ± 7 before and 95 ± 3 after. Average follow-up 52 months
Teo et al. (2012) [107]	Case series, patellar OCD, adolescent patients, mean age 16.8 years	$N = 20$ autologous chondrocytes, $N = 3$ patients cultured BM-MSC	6, 12, and 24 months. Mean IKDC score, Tegner-Lysholm outcomes, and Lysholm-Gillquist scale improved from 45, 2.5, and 50, respectively at surgery to 75, 4, and 70, respectively, at 24-month follow-up. Complications include periosteal hypertrophy observed in 2 patients
Wong et al. (2013) [108]	RCT, unicompartmental knee OA and genu varum, $n = 28$ patients cells + HA vs $n = 28$ controls	HTO + microfracture + BM-MSCs (injected post-op) vs HTO + microfracture. Expanded BM-MSCs were injected after 22 days	MOCART adjusted by age, at 1 year better in the cell group. Tegner, Lysholm, IKDC cell treatment added improvement
Arthroscopic implantation of non-expanded cells ($N = 23$) [24, 109–133]			
Buda et al. (2016) [109]	Case series, osteochondral lesions of the talus and ankle OA, $N = 56$	BMC + PRF, arthroscopic or open-field surgery, bone filling with demineralized bone matrix in selected cases	12, 24, and 36 months' follow-up, clinical improvement assessed by AOFAS at 3 time points. MRI in 22 patients, MOCART revealed complete degree of filling with bone edema in most patients. 16/56 required another intervention (failures) another treatment

Table 3 continued

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Buda et al. (2015) [110]	RCT, ankle, osteochondral lesions of the talus, $N = 80$, 40 per group	ACI vs BMC + PRP arthroscopic debridement	48 months MRI, MOCART similar in both groups, clinical outcomes similar in both groups
Buda et al. (2015) [111]	Retrospective study, knee, hemophiliac patients, $N = 5$	BMC transplantation, synovectomy, arthroscopic debridement	24 months, AOFAS improvement and MRI MOCART signs of cartilage regeneration
Buda et al. (2014) [112]	Case series, ankle, $N = 64$ patients, post-traumatic type II focal lesions talar dome	BMC + [porcine collagen powder + PRP] or BMC + [HA membrane + PRP]	6, 12, 18, and 24 months, final follow-up 72 months, AOFAS improvement no differences between both scaffolds. 60/64 patients participate in low-impact sports at 4.8 months and 49/64 patients in high-impact sport at 11.9 months
Buda et al. (2010, 2013) [113, 114]	Case series, knee osteochondral lesions, $N = 30$ patients, 28 with post-traumatic lesions, Grade II-IV and 2 patients with osteochondritis dissecans	BMC, concentrated from 60 to 6 mL soaked into HA membrane, implanted arthroscopically and covered with PRP	6, 12, 18, 24, 36 months, IKDC, KOOS significant improvement. MRI, MOCART score (6 and 12 months) showed association with KOOS score, regeneration of subchondral bone and cartilage, histology in 2 patients showed type II collagen and proteoglycans
Enea et al. (2015) [115]	Case series, knee, focal chondral lesions, 2.5 cm^2	Microfracture with collagen immersed in BMC	12 months, macroscopic assessment, all repairs appear almost normal. Clinical improvement. No adverse effects
Giannini et al. (2009, 2013) [116, 117]	Case series, osteochondral lesions of the talus, $N = 49$ patients	BMC + scaffold	2, 3, and 4 years AOFAS improved and correlated with MRI findings
Gobbi et al. (2011) [118]	Case series, knee, grade IV chondral lesions, size 9.2 cm^2, $N = 15$ patients, 6/15 had multiple chondral lesions	BMC + collagen I/III matrix	6, 12, and 24 months, improvement in IKDC, KOOS, Lysholm, Tegner, SF-36. MRI showed cartilage-like tissue covering lesions
Kasemkijwattana et al. (2011) [119]	Case series, $N = 2$, grade 3–4 ICRS classification	Arthroscopic implantation BM-MSCs + 3D collagen	30 months, no complications, significant improvement KOOS, IKDC. Defect fill, stiffness and incorporation to adjacent cartilage as assessed in arthroscopy
Kim et al. (2015) [24]	Retrospective cohort study, knee $N = 54$ patients (56 knees) isolated full thickness cartilage lesions K-L 1–2	37 patients (39 knees) SVF without scaffold, 17 patients = knees, SVF + fibrin glue	28.6 months IKDC and Tegner improved, no differences between groups. At 2nd look arthroscopy, better ICRS grade in group 2
Kim et al. (2015) [120]	Retrospective case series, knee $N = 49$ patients (55 knees) isolated full thickness cartilage lesions K-L 1–2	SVF	Significant differences in clinical outcomes among the age and lesion size group. Age >60 years and lesion size >6 cm^2 showed poor outcomes
Kim et al. (2016) [121]	Case series, isolated knee chondral lesions, K-L grade 1–2, $N = 24$ patients	Arthroscopic debridement SVF + fibrin glue	24 months, IKDC and Tegner significant improvement, MRI MOCART significant improvement
Kim et al. (2013) [122]	Case series, $N = 45$ patients >50 years ankle, osteochondral lesions of the talus	Arthroscopic marrow stimulation, $N = 35$ patients (37 ankles) vs BMC injection + arthroscopic marrow stimulation	21.8 months, Roles and Maudsley better without BMC, Tegner better in BMC group
Kim et al. (2014) [123]	Cohort study, $N = 49$ patients, 50 ankles, osteochondral lesions of the talus	Arthroscopy $N = 26$ OC stimulation, $N = 24$ OC stimulation and SVF	All clinical outcomes (VAS, AOFAS, Tegner, MOCART) improved in MSC group compared with controls

Table 3 continued

Study (year)	Study design, condition, *N*/patient population	Intervention/cell product	Outcome measurements/follow-up/results
Koh et al. (2016) [124]	Prospective randomized trial ICRS grade III/IV, symptomatic cartilage defect >3 cm^2 on the femoral condyle	ADSC + fibrin glue + microfracture vs microfracture	MRI at 24 months, complete cartilage coverage in 65 % of experimental group vs 45 % in the control group. KOOS better in experimental group but no differences in sub-scores, 2nd look arthroscopy and histology showed no differences between groups
Koh et al. (2015) [125]	Case series, knee chondral lesions $N = 30$ patients >65 years	Arthroscopic lavage and injection of 4.2×10^7 SVF cells with 3 mL PRP	2 years, VAS and function improvement, 16/30 patients followed 2nd look arthroscopy: 3 knees normal cartilage, 7 new cartilage partially covered the defect, 4 knees uncertain change, and 2 knees failed healing. 5/30 worsened K-L degree at 2 years
Koh et al. (2014) [126]	Prospective comparative study, knee	Surgery HTO + PRP vs HTO + PRP + MSC	Lysholm, KOOS, VAS. Greater improvement in VAS and KOOS for pain and symptoms in the MSC + PRP group. Arthroscopic evaluation showed fibrocartilage coverage in 50 % of MSCs + PRP and 10 % of the patients in PRP group
Krych et al. (2016) [127]	Cohort study, knee, full thickness cartilage defects $N = 46$	Scaffold + BMAC, $N = 12$; scaffold + PRP, $N = 23$; scaffold control $N = 11$	12 months, MRI scaffold + BMAC improved maturation with greater fill and T2 values closer to hyaline cartilage
Michalek et al. (2015) [128]	Case series, multicenter, osteoarthritis, 1128 patients, 1856 joints (hips and knees), 503 patients candidates for total joint arthroplasty	SVF + PRP	3, 6, 12 months KOOS/HOOS. 80.6 and 91 % of patients improved >50 % at 3-month and 12-month follow-up. 4/503 patients required total hip replacement
Saw et al. (2015) [129]	Case series, knee, $N = 8$ patients, ICRS Grade 4 lesions	Open wedge HTO and 5 weekly injections of PBSCs + HA (8:2), 3 additional injections at intervals 6, 12, and 18 months	Histology at 2nd look arthroscopy, ICRS visual assessment scale mean 1274 (1340 is normal cartilage). No infections
Skowroński et al. (2013) [130]	Case series, ICRS grade III–IV cartilage lesions in the knee, $N = 54$ patients	BMC + collagen	1 and 5 years, Lysholm, KOOS, VAS. At 1 year, 25 points improvement in KOOS and 35 points in Lysholm
Silva et al. (2014) [131]	RCT, tendon–bone attachment, ACL reconstruction, $n = 20$ experimental group, $n = 23$ control group	Arthroscopy, ACL reconstruction, 3 mL BMC, 1.5 mL injected in the graft and 1.5 mL injected within the bone tunnel, without irrigation	MRI at 3 months, no differences between groups in SNR in the upper and lower interzones
Wakitani et al. (2002, 2011) [132, 133]	Case series, knee, $N = 41$ patients, 45 knees, cell transplantation performed in 1988	BM-MSC	Safety: 11 years and 5 months follow-up, no tumors, no infections

ACL anterior cruciate ligament, *ACI* autologous chondrocyte implantation, *AMI* autologous mesenchymal stem-cell implantation, *AOFAS* American Orthopedic Foot and Ankle Score, *ADSC* adipose stem cells, *BMAC* bone marrow aspirate concentrate, *BMC* bone marrow concentrate, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *HA* hyaluronic acid, *HOOS* Hip Injury and Osteoarthritis Outcome Score, *HTO* high tibial osteotomy, *ICRS* International Cartilage Research Society, *IKDC* International Knee Documentation Committee, *K-L* Kellgren-Lawrence severity score, *KOOS* Knee injury and Osteoarthritis Outcome Score, *MOCART* magnetic resonance observation of cartilage repair tissue, *MRI* magnetic resonance imaging, *MSCs* mesenchymal stem cells, *OA* osteoarthritis, *OCD* osteochondritis dissecans, *PBPC* peripheral blood progenitor cells, *PBSCs* peripheral blood stem cells, *PRF* platelet-rich fibrin, *PRP* platelet-rich plasma, *RCT* randomized control trial, *SF-36* Short Form-36, *SNR* signal-to-noise ratio, *SVF* stromal vascular fraction, *VAS* visual analog scale

Cell replacement treatment associated with PRP can be useful in severe degenerative cases in which PRP alone is insufficient to reverse the progression. Moreover, PRP is a good adjuvant to cell therapies, as it enhances cell survival and proliferation, and helps to confine cells at the delivery site. Clarke et al. [74] have compared dermal fibroblasts + PRP versus PRP alone. A reduction in hypoechogenicity and tear size was found in both groups, though increased thickness was more evident in the cell group.

Further research to identify the best cell source and treatment regimens is needed. Moreover, design of cell therapies should be tailored according to anatomical area; that is, the main body of the tendon or the enthesis. Precise needle delivery is important. As novel cell tracking systems are developed, we will be able to visualize whether cells integrate in the host tissue, and thus the ultimate fate of the implanted cells can be clarified [134].

Table 4 shows a summary of advantages and disadvantages of the different types of cells being examined in clinical studies, and the development stages in tendon and joint conditions following the IDEAL framework. The latter includes four stages of therapy development described as idea, exploration, assessments, and large data sets [135].

3.2.2 Joint Conditions

Peeters et al. [136] assessed the safety of intra-articular delivery of MSC products either by injection or surgical implantation. They analyzed 844 interventions, and reported two related adverse events, one infection and one pulmonary embolism, and two non-related adverse events, one prostate cancer and one Schwannoma. Minor events included pain, swelling, and dehydration. Most clinical studies do not refer explicitly to adverse events, but when these were considered, minor self-resolving adverse events were reported. Follow-up as long as 11 years has been maintained in one study including 41 patients (45 knees) treated with BMC, and no tumors have been reported [132, 133]. Moreover, a multicenter analysis of adverse events in 2372 patients undergoing adult autologous stem-cell therapy corroborated the safety of MSC-based therapies [137].

We have classified clinical studies into needle injection delivery (Table 2), or surgical/arthroscopic delivery (Table 3). In addition, we have grouped studies according to regulatory criteria as expanded MSCs (i.e., more than minimal manipulation), 'advanced therapy' or fresh cell products, interventions performed on the same day (i.e., SVF [qualified as ATMP]), or BMC. Based on current clinical studies, there is equal interest in freshly isolated mixed-cell populations (BMC, SVF), and culture-expanded mesenchymal stromal/stem cells.

3.2.2.1 Needle Injection Delivery

3.2.2.1.1 Intra-Articular Injections of Culture-Expanded Mesenchymal Stem Cells. *Anterior Cruciate Ligament* Intraligamentous injection of BM-MSCs improved the integrity of anterior cruciate ligament (ACL) with grade 1–3 tears in seven of ten patients, as determined by analysis of images using Image J software [77].

Meniscus An RCT by Vangsness et al. [87] reported the safety and efficacy of two doses of cells: 50 and 150 million allogeneic BM-MSCs suspended in hyaluronic acid (HA), and injected intra-articularly 7–10 days following meniscectomy. According to outcome data, surgically removed meniscal tissue was regenerated, cartilage surface protected, and joint damage decreased. The number of patients with increased meniscal volume was five of 54 patients (four from the group that received the lower dose of cells, and one from the higher dose group) at 12 months post-procedure. Only three patients maintained the increased meniscal volume at 2 years (mean percentage 18; 95 % CI 4.0–45.6). Other ongoing trials are examining the efficacy of autologous MSCs in meniscus injury grade 3 [138], and also autologous BMC injection in patients undergoing partial or complete meniscectomy [139].

Cartilage Lesions and Osteoarthritis The needle injection technique (intra-articular cell injection) was used in 22 studies [77–99] (Table 2). Eleven studies examined the effect of intra-articular injections of in vitro expanded MSCs. Cell doses ranged from 5.76×10^6 to 400×10^6 cells.

Both RCTs [87, 88] used donor-derived (allogeneic) BM-MSCs and used the cell vehicle, HA, as control. Vega et al. [88] included 30 patients who were randomized to either allogeneic BM-MSCs ($n = 15$), or a single high-molecular weight HA injection ($n = 15$).

Overall, all case series that evaluated injections of culture-expanded MSCs involved few patients and showed moderately good results, with no safety problems.

3.2.2.1.2 Needle Injection Delivery of Stromal Vascular Fraction or Bone Marrow Concentrate. Freshly prepared SVF combined with PRP was injected in 113 knees, 22 hips, two ankles and two lower backs, and outcomes reported in five cases series [89, 93, 95, 96, 98], and the combination PRP + HA in one study [99]. In addition, one registry data study [91] reported outcomes after 840 knee injections, 616 knees injected with BMC, and 224 knees with a mixture of BMC and fat. The addition of fat to BMC showed no benefit [91]. Mean reported improvement was 46.8 % in patients receiving BMC and 39.3 % in patients receiving BMC plus lipoaspirate. There were no differences between patients undergoing bilateral versus unilateral procedures. Kim et al. also injected BMC and fat in 75

Table 4 Summary of advantages and disadvantages of the different types of cells being examined in clinical studies

Cell-based product	Tissue source	Procedure	Regulation	Advantages	Disadvantages	IDEAL framework
Tenocytes	Tendon	Tissue biopsy Laboratory expansion	ATMP	Easy and minimally invasive access. Very proliferative cells	Limited information about functionality of transplanted cells. High cost	2a
Dermal fibroblasts	Skin	Tissue biopsy Laboratory expansion	ATMP	Easy and minimally invasive access. Very proliferative cells	No information about phenotypic changes towards tenocytic lineage. High cost	2a
Chondrocytes	Cartilage	Tissue biopsy Laboratory expansion	ATMP	FDA approved. Carticel® commercially available	Unavailability of tissue. Low yield. Dedifferentiation. High cost	4
BMC	Bone marrow	Aspiration Centrifugation	Tissue	Delivery of nucleated cells (minimally manipulated). Point of care processing technology same day	Heterogeneous product. Low MSC number. Better results if matrix supported and arthroscopic implantation	2b
SVF	Adipose tissue	Lipoaspiration Digestion Centrifugation	ATMP	Fresh product. Point of care processing technology same-day procedure	Heterogeneous product. Limited understanding of mechanism of action	2d
Fat graft	Adipose tissue	Tissue harvest Separation from oil and liquid	Tissue	Used to augment BMC tissue graft prepared at point of care	Inflammatory effects when mixed with BMC	2a
PBPC	Peripheral blood	G-CSF or GM-CSF treatment Apheresis procedure	Blood product	Can be harvested and cryopreserved	Very few studies. Insufficient information on mechanism of action	2a
BM-MSCs	Bone marrow	Aspiration Centrifugation Cell selection Cell expansion	ATMP	Can be cryopreserved. Allogeneic or autologous. Well characterized	Age-related changes in cells lead to regenerative decline. BM-MSC yield depends on harvesting procedure. High cost. Ectopic bone formation in tendon	2a
ASCs	Adipose tissue	Lipoaspiration Digestion Centrifugation Cell selection Cell expansion	ATMP	MSC potentiality independent of the harvest site. Can be cryopreserved	Different cell sub-populations. High cost	2a

IDEAL framework [136]: stage 1, idea; 2a development, small number of reports; 2b exploration, increased number of reports and patients per report, registries; 3 assessments, RCTs, multicenter studies, analysis of large data sets

ASCs adipose stem cells, *ATMP* Advanced Therapy Medicinal Product, *BMC* bone marrow concentrate, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *FDA* Food and Drug Administration, *G-CSF* granulocyte colony-stimulating factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *MSCs* mesenchymal stem cells, *PBPC* peripheral blood precursor cells, *RCT* randomized clinical trial, *SVF* stromal vascular fraction

knees, and reported better outcomes in patients with early OA [94]. Pak et al. [99] reported on 100 joints (74 knees, 22 hips, 2 lower backs, and 2 ankles) in 91 patients injected with SVF (10 mL) combined with PRP (2 mL buffy coat) + HA (1 mL 0.5 %). Patients returned for four additional PRP injections (freshly prepared, one injection per week), and the treatment lasted 1 month. Patients were followed for up to 30 months (by phone). VAS improved significantly at 1 and 3 months after treatment. Complications included pain and swelling secondary to injection in 37 % of joints and 22 % of patients reported tendonitis/tenosynovitis; no infections were reported. One patient suffered a hemorrhagic stroke 2 weeks after the procedure, but this was considered not related to the procedure, as the frequency of this event in the general population is 1 %. No tumors were found.

Gibbs et al. [93] treated four patients (seven joints) with SVF and PRP, followed by rehabilitation for 4 months. Pain and quality of life, as measured using KOOS, improved significantly; mobility returned to normal.

As an alternative to bone marrow and subcutaneous fat, Koh et al. [95] used the infrapatellar pad as a source for MSCs and injected a mean of 1.18×10^6 cells with 3 mL of PRP; patients experienced a significant reduction in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (from 49.9 to 30), an improvement in Lysholm score, and significant pain reduction (VAS). Improvements in MRI scores were also reported ($p < 0.001$).

3.2.2.2 Surgical/Arthroscopic Delivery

3.2.2.2.1 Culture-Expanded Mesenchymal Stem Cells. Tendon–bone healing following ACL reconstruction remains an unresolved issue of ACL surgery. Filling the bone tunnels with PRP does not speed up tendon-to-bone integration [140]. Recently, a randomized trial was performed to assess the suitability of fresh BMC in tendon–bone healing [131]. However, there were no differences between cell-treated patients and controls, as assessed by MRI.

Ten studies described the implantation of culture-expanded MSCs during arthroscopy or open surgery for chondral lesions or OA [96, 100–108] (Table 3). Interestingly, Kim et al. examined the potential differences between arthroscopic implantation of cells, and site-directed delivery by injection: arthroscopic implantation was more accurate and produced better clinical and imaging results [83].

Intra-articular delivery of MSCs with arthroscopic procedures was performed in debridement, microfractures [103], management of patellar osteochondritis dissecans (OCD) [107], or microfracture with high tibial osteotomy [108]. MSCs were in some studies just implanted in the defect using periosteal flaps or embedded in scaffolds such as collagen [112], HA [103, 105], PRP-fibrin [102], or fibrin glue [24].

One controlled study [100] used ACI as control for AMI (autologous mesenchymal stem cell implantation), with better results in the AMI group. In five case series, joints were treated with synovium-derived MSCs [106], infrapatellar-derived MSCs [96], and BM-MSCs [101, 107, 108].

3.2.2.2.2 Stem-Cell-Based Products: Arthroscopic Delivery of Stromal Vascular Fraction, Bone Marrow Concentrate or Peripheral Blood Progenitor Cells. Surgical implantation of non-expanded cells has been performed in 23 studies (Table 3). Of these, seven studies involved osteochondral lesions of the talus [109, 110, 112, 116, 117, 122, 123] and seven studies used SVF [24, 120, 121, 123–125, 128]; another study [129] used PBPCs and the other 15 studies used BMC [109–119, 122, 126, 127, 130–133]. In several studies, cells were used as an adjuvant to surgical interventions including microfracture or subchondral drilling [115, 122–124], arthroscopic debridement with or without synovectomy [110, 111, 121], arthroscopic lavage [125], and open-wedge high tibial osteotomy [126, 129].

Histology and second-look arthroscopies after cell intervention have been evaluated in several studies [125, 126, 141]. Koh et al. examined 16 knees after arthroscopic lavage combined with injection of SVF [125]. On second look, three knees were considered very positive (normal cartilage appearance), seven were rated positive (new cartilage partially covered the defect), four knees were rated neutral (uncertain change), and two patients experienced failed healing. Moreover, 37 knees were examined after MSC intervention by the same authors, and were evaluated using International Cartilage Research Society (ICRS) grading. Results showed that 2/37 were normal, 7/37 were nearly normal (grade II), 20/37 were abnormal (graded III), and 8/37 were severely abnormal (graded IV). High bone mass index (BMI) and large lesions were predictors of poor clinical outcomes. The same authors [126] evaluated at second look (median 19.8 months post-surgery) patients that followed high tibial osteotomy (HTO) with SVF + PRP or HTO + PRP, and results revealed that patients in the SVF + PRP group showed more regenerative changes as assessed by the Kanamiya grading system [126]. In four of the five patients treated with 7–8 mL of PBPC + 2 mL HA, Saw et al. [141] found regenerated cartilage integrated with surrounding tissue. Histology showed predominance of type II collagen, particularly in deeper layers with collagen type I in the superficial layer. These findings, together with the columnar morphology of cells, could reveal features of hyaline cartilage [141]. However, to date, control of the fate of adult MSCs within the joint is far below expectations, with the regenerated tissue having features of fibrocartilage and a lack of architectural organization [142].

4 Conclusions

This review of the recent literature indicates that several different cell phenotypes, including tendon, skin, or mesenchymal stem cells, can be suitable for tendon conditions, with applications performed most often with ultrasound-guided percutaneous injections. Indeed, the complexity of articular conditions has shifted research from autologous chondrocyte implantation to the use of a variety of mesenchymal stromal cell products. MSCs are applied not only for the treatment of chondral defects, but also for those of ligaments and the meniscus, and to reduce joint degeneration and reduce the burden of OA. Cells can engraft joint tissues especially at lesion sites. However, multipotency

may not be the major determinant of success, and repair may rely on a combination of differentiation ability and paracrine effects able to stimulate the ability of exogenous cells to promote endogenous healing mechanisms. A moderate amount of basic science work shows that the approach may work, and a sizeable amount of animal work shows that MSCs and other biological interventions seem to have some effect. However, translational work in human medicine is lacking, and the small volume of well performed work in humans shows that essentially these therapies, though based on sound basic science findings, do not seem to work particularly well for clinical purposes.

It is likely that opportunities for developing effective treatment for musculoskeletal tissues will arise only after the secrets of MSCs have been unveiled. When transplanting cells, the conditions of the host tissue are of high functional importance as differentiation into suitable cell phenotypes can be inhibited by inflammatory factors produced by the host tissue/organ. The anti-inflammatory properties of PRP can help prevent environmental hostility.

Numerous hurdles need to be overcome as cell therapy progresses. On the one hand, technical challenges associated with robust cell manufacturing at reduced costs are mandatory. On the other hand, use of these technologies will require identifying and understanding the heterogeneity of stem-cell products as well as specific features of disease stage and progression. In this context, identification of biomarkers can serve not only to assess changes in tissue quality, but also to subgroup patients and tailor biological interventions according to specific pathological processes.

Compliance with Ethical Standards

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