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Stem cell-based therapeutic strategies for cartilage defects and osteoarthritis

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The gold standard cell therapy for repair of articular cartilage defects is autologous chondrocyte implantation, with good outcomes long-term. Mesenchymal stromal/stem cells (MSCs) from bone marrow or connective tissues such as fat are being pursued as alternatives for cartilage repair, and are trialled via intra-articular administration in patients with knee osteoarthritis. Early-phase clinical studies concur on safety and provide some promising insight into efficacy, but the mechanism of action remains unclear. Recent studies implicate extracellular vesicles as important mediators of MSC action, offering exciting therapeutic prospects. Our increasing understanding of the mechanisms underlying intrinsic articular cartilage maintenance and repair fosters hope that novel/repurposed therapeutics could elicit repair through activation of endogenous stem/progenitor cells to maintain healthy joints and prevent osteoarthritis.

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Introduction

Osteoarthritis (OA) is a common degenerative joint disease, characterised by progressive cartilage breakdown, subchondral bone sclerosis and aberrant bone outgrowths (osteophytes). Traumatic joint lesions increase the risk of OA. Advances in the regenerative treatment of early cartilage lesions could help to prevent OA. This review discusses cell-based approaches for the repair of cartilage lesions and the treatment of OA (Figure 1).

Cartilage repair

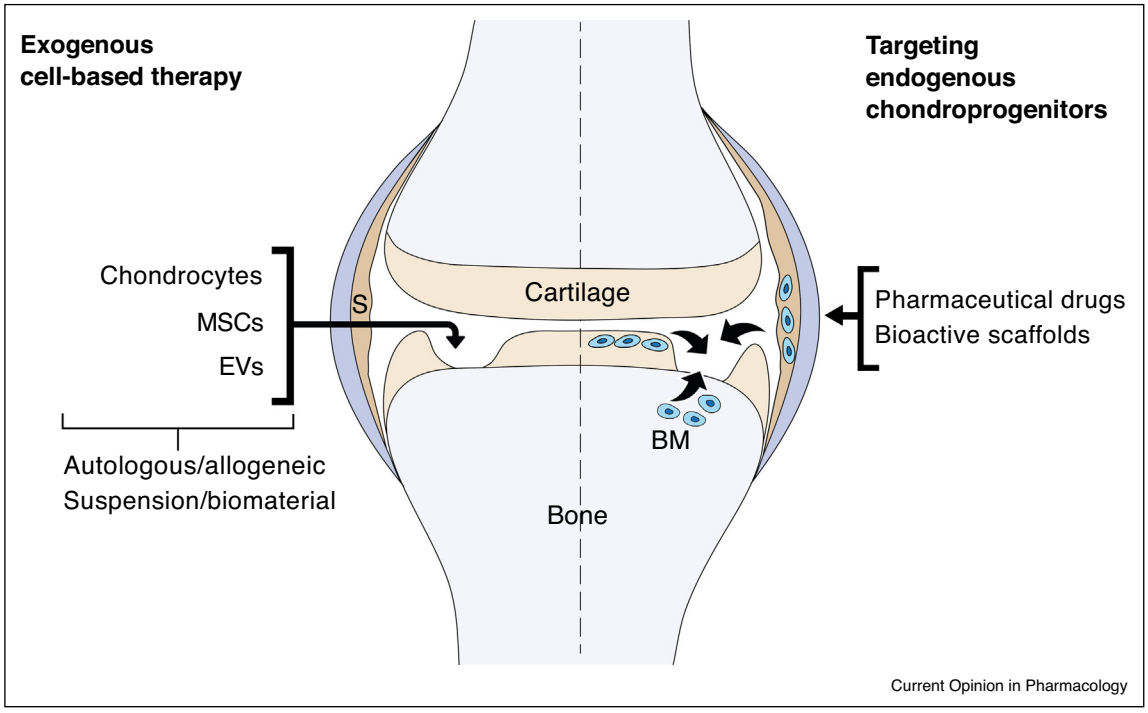
A commonly performed surgical procedure is microfracture, a marrow stimulation technique that allows communication between the joint space and subchondral bone marrow to release mesenchymal stromal/stem cells (MSCs) from the marrow that form a repair tissue. However, particularly in defects larger than 2 cm^2, the repair tissue with microfracture frequently undergoes degeneration over time with the formation of scar-like fibrous tissue or even replacement with bone [1].

Autologous chondrocyte implantation (ACI) was first described in 1994 by Brittberg and colleagues, who reported symptomatic relief in 14 out of 16 patients with lesions of the femoral condyle at 2 years follow-up [2]. A cartilage biopsy is obtained from a healthy area of the patient's articular cartilage, chondrocytes are isolated and expanded in culture, and are implanted in the cartilage defect either in suspension under a periosteal flap or synthetic membranes, or in three-dimensional matrices [3]. Clinical trials have confirmed the good clinical outcome of ACI. In 118 patients at 12 and 18 months following either ACI or microfracture, clinical outcome was similar in both groups but ACI was associated with increased structural repair [4]. At 5 years, clinical outcomes were again comparable [5]. However, ACI was more effective in a subgroup of patients who had undergone the procedures close to presentation of symptoms [6]. Results from up to 20 years follow-up have demonstrated that ACI is an effective and durable solution for the treatment of large joint surface lesions of the knee [7,8•].

However, variability in structural outcome after ACI has been reported, with some patients showing repair tissue consisting of disorganised fibrocartilage [9]. Chondrocytes dedifferentiate during culture-expansion to a fibroblast-like phenotype and lose their capacity to form stable hyaline cartilage *in vivo* [10], which may underpin the variability in structural outcome. The use of chondrocytes expanded under conditions that preserve their cartilage-forming potency may enhance joint surface regeneration with the formation of hyaline-like cartilage repair tissue [11]. Of interest, chondrocytes derived from the nasal septum, with known capacity to generate hyaline-like cartilage, have been successfully used for knee cartilage defect repair in ten patients [12••], but large controlled trials are warranted to assess efficacy.

MSCs are easy to grow in culture and have chondrogenic ability, and are therefore considered an alternative cell source for cartilage repair. MSCs have been isolated from bone marrow [13,14], and most connective tissues including periosteum [15,16], synovium [17,18], and adipose tissue [19]. Numerous preclinical studies have supported

Figure 1



Regenerative therapeutic strategies for cartilage defects and osteoarthritis. Exogenous cell-based therapy entails delivery of autologous or allogeneic cells such as chondrocytes or mesenchymal stromal/stem cells (MSCs), or extracellular vesicles (EVs), either in suspension or seeded in a biomaterial. Alternatively, endogenous chondroprogenitors, which reside in synovium (S), bone marrow (BM) and cartilage itself, could be targeted with pharmaceutical drugs or bioactive scaffolds to trigger or enhance intrinsic repair.

the use of MSCs in joint resurfacing [20], and studies in humans revealed a variable structural outcome, ranging from hyaline-like cartilage to fibrous tissue [21]. Notably, autologous bone marrow MSCs were shown to be non-inferior to chondrocytes in clinical outcomes at 24 months in an ACI-like procedure [22], although longer-term follow-up and more robust assessment of structural outcome are needed to draw definitive conclusions.

An important consideration is the tissue source of MSCs for cartilage repair, and whether MSCs from non-joint environments such as the stromal vascular fraction of visceral fat would be comparable to MSCs derived from joint tissues. MSCs from bone marrow appear to have high propensity to undergo chondrocyte hypertrophy and bone formation [23,24] and thus may not be ideal for the repair of articular cartilage. Superiority of MSCs from synovium for cartilage formation *in vitro* when compared with MSCs from other tissues including bone marrow and periosteum has been reported [25]. The differences in potency could be related to MSC ontogeny and distinctive molecular programmes of embryonic formation of the native tissues from which the MSCs are obtained. Lineage tracing studies in mice have demonstrated that articular cartilage and synovium have a common developmental origin from the Gdf5-expressing cells of the embryonic joint interzone. Gdf5-traced MSCs resident in the adult knee were found to display joint progenitor activity and ability to repair articular cartilage [26••,27••]. Promising data using synovium-derived MSCs have been reported in preclinical and clinical studies [28•,29,30].

Notably, chondroprogenitors derived from the surface zone of articular cartilage using differential adhesion to fibronectin, showed ability to maintain chondrogenic potency upon extensive expansion [31], and formed a cartilage-like repair tissue in a chondral defect in a goat model [32]. Human studies are awaited.

Interventions consisting of implantation of stem/progenitor cells seeded in smart biomaterials, with the addition of cartilage-promoting growth factors, are also being pursued to support adequate repair [33], but such combinations render the path to clinical application complex.

Osteoarthritis

Intra-articular injection of bone marrow MSCs in goats, in which the medial meniscus was excised and the anterior cruciate ligament was resected, resulted in regeneration of the medial meniscus and decreased development of secondary OA compared with untreated animals [34]. This and many other subsequent preclinical studies