

Modes of intra-articular injection of Mesenchymal Stem Cells for treatment of Osteoarthritis

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Abstract

Despite the high prevalence and morbidity of osteoarthritis (OA), an effective treatment for this disease is currently lacking. Restoration of the diseased articular cartilage in patients with OA is, therefore, a challenge of considerable appeal to researchers and clinicians. Techniques that cause multipotent adult mesenchymal stem cells (MSCs) to differentiate into cells of the chondrogenic lineage have led to a variety of experimental strategies to investigate whether MSCs instead of chondrocytes can be used for the regeneration and maintenance of articular cartilage. MSC-based strategies should provide practical advantages for the patient with OA. These strategies include use of MSCs as progenitor cells to engineer cartilage implants that can be used to repair chondral and osteochondral lesions. Delivery of MSCs might be attained by direct intra-articular injection or by graft of engineered constructs derived from cell-seeded scaffolds. Promising experimental and clinical data are beginning to emerge in support of the use of MSCs for regenerative applications

Key points: osteoarthritis, MSCs, intra-articular injection.

Introduction:

Osteoarthritis (OA), the most common form of joint disease, is characterized by degeneration of the articular cartilage and, ultimately, joint destruction.⁽¹⁾ Currently, OA is a major cause of disability in the elderly; the prevalence of this disease is expected to increase dramatically over the next 20 years with an increasingly aged population.⁽²⁾ The burden of OA is exacerbated by the inadequacies of current therapies. Non-pharmacologic and pharmacologic treatments are used for early and moderately early cases of OA, but protection of articular cartilage has so far not been convincingly shown.^(3, 4) Surgical intervention is often indicated when the symptoms cannot be controlled and the disease progresses.⁽⁵⁾ Whether arthroscopic lavage and/or debridement can provide symptomatic relief is unclear.⁽⁶⁾ Methods for the repair of articular cartilage lesions

include the transplantation of osteochondral grafts, micro fracturing, and autologous chondrocyte implantation, with or without the assistance of a scaffold matrix to deliver the cells;⁽⁷⁻¹²⁾ however, all of these techniques are limited to the repair of focal lesions.⁽¹³⁾ Consequently, patients with OA are currently excluded from these treatments. The challenge for researchers to develop disease-modifying OA treatments is, therefore, of paramount importance. Adult mesenchymal stem cells (MSCs), which have the ability to differentiate into cells of the chondrogenic lineage, have emerged as a candidate cell type with great potential for cell-based articular cartilage repair technologies. MSCs can be isolated from a variety of adult tissues, readily culture-expanded without losing their multilineage differentiation potential, and have been induced to undergo chondrogenic differentiation *in vitro* and *in vivo*.⁽¹⁴⁾

patient with OA differ functionally from those of healthy individuals, in terms of their chondrogenic capacity and longevity. The proliferative, chondrogenic and adipogenic capacities of MSCs obtained from patients with OA are reportedly reduced.⁽²⁵⁾ Perhaps the altered activity status of these MSCs is related to their exposure to elevated levels of proinflammatory cytokines and/or anti-inflammatory drugs. Whether susceptibility to OA might result from reduced mobilization or proliferation of MSCs remains to be ascertained.⁽²⁴⁾ Several studies have described an age-dependent reduction in the number of progenitor cells isolated from human bone marrow,^(26,27) although others could not find any such inverse relationship between age and MSC numbers.^(25, 27) Also, an age-dependent decline in the differentiation capability of MSCs has been reported by several investigators.⁽²⁵⁻²⁹⁾ In this context, however, researchers and clinicians should note that sufficient numbers of MSCs with adequate chondrogenic differentiation potential can be isolated from patients with OA, irrespective of their age or the etiology of their disease.^(30, 31, 32) These results, therefore, suggest that the therapeutic use of MSCs for the regeneration of cartilage in patients with OA is feasible.

Delivery Modes for Mesenchymal Stem Cells

A crucial requirement for MSC-based OA therapy is the delivery of the cells to the defect site. Direct intra-articular injection might be possible in early stages of the disease when the defect is restricted to the cartilage layer, whereas a scaffold or matrix of some kind would be required to support the MSCs in cases where the subchondral bone is exposed over large areas.

Direct Intra-articular Injection of MSCs

Direct intra-articular injection of MSCs is, technically, the simplest approach to their

use in OA therapy. Following injection, MSCs would be distributed throughout the joint space, and would interact with any available receptive cells and surfaces. The highly cellular synovial lines all the internal surfaces of the joint space, except for the cartilage and meniscus, so it is likely to be a primary tissue for MSC interaction.⁽³³⁾

Direct intra-articular injection of MSCs has only been carried out in a few numbers of studies. In one study, autologous MSCs in a dilute solution of sodium hyaluronan (hyaluronic acid) were directly injected into the knee joints of goats, in which OA had been induced by a total medial meniscectomy and resection of the anterior cruciate ligament.⁽³³⁾ Joints exposed to MSCs showed evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Articular cartilage degeneration, osteophytic remodeling, and subchondral sclerosis were also reduced in the treated joints. There was no evidence of repair of the ligament in any of the joints.⁽³¹⁾ Whether the changes observed in MSC-treated joints resulted from direct tissue repair by the transplanted cells or from their interaction with host synovial fibroblasts at the site of injury is still unclear.

Delivery by Cell Suspension

Following delivery of cell suspensions, the aim is for transduced MSCs to release therapeutic proteins that interact with all available tissues, including cartilage. Considerable progress has been made towards defining the parameters that prolong intra-articular transgene expression, an approach that was originally developed for the treatment of rheumatoid arthritis (RA).⁽³⁴⁾ Furthermore, insulin-like growth factor I 'administered' by intra-articular delivery partially reversed matrix degradation in OA.^(35, 36, 37) Other cell types were initially investigated, but MSCs have

the potential to be at least as beneficial when used in *vivo* approaches.^(13, 15, 38)

A growing body of literature indicates that many of the pleiotropic gene products considered necessary for cartilage repair and regeneration are compatible with intra-articular delivery in suspension. However, delivery of transforming growth factor β 1 or bone morphogenetic protein 2 to the synovial resulted in severe swelling, fibrosis, and osteophyte formation within joints.^(40, 41) Candidate complementary DNAs for synovial gene transfer should, therefore, be carefully chosen, safety-tested and validated.

Delivery within a Matrix

The above-mentioned anti-inflammatory treatments for RA and OA are, in principle, useful for preventing disease progression, but might not be able to restore damaged cartilage. An alternative strategy uses genetically modified MSCs in matrix-guided approaches to cartilage regeneration.^(38,41) MSCs are first stimulated to undergo chondrogenic differentiation, stabilized as chondrocytes, then introduced on a matrix to the defect site, with the aim of establishing a cartilage phenotype without progression to hypertrophy or differentiation.⁽¹³⁾ As already mentioned, however, this approach has been used mainly to treat focal cartilage defects. Future studies will show whether such technology will be suitable for repairing large areas of eroded cartilage, as occurs in advanced OA.⁽⁴²⁾

Conclusions

Direct intra-articular injection of cells is considered a technically simple approach to treatment of advanced OA, whether this approach can elicit beneficial effects (such as minimizing further cartilage damage) in human OA joints remains to be seen -- and, if so, to what extent and under which conditions. The use of MSCs in combination with bioactive substrates, natural or

synthetic, also has significant clinical potential and is likely to be important in future, MSC-based, cartilage-repair technologies. In this context, MSCs might also offer promise in the future as vehicles for therapeutic gene delivery. In the long term, MSC-based technologies might be able to permit the engineering of cartilage not only for repair of focal lesions but also as a treatment option for OA joints, to realize the ultimate goal of a fully biological prosthesis.

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