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REVIEW ARTICLE

Cartilage repair by mesenchymal stem cells: Clinical trial update and perspectives

Wayne Yuk-wai Lee [a,b,c,*], Bin Wang [a,b,c]

[a] *Department of Orthopaedics & Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, PR China*
[b] *Stem Cells and Regenerative Medicine Laboratory, Li Ka Shing Institute of Health Sciences, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, PR China*
[c] *SMART Program, Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, PR China*

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Summary Osteoarthritis is a degenerative disease of joints with destruction of articular cartilage associated with subchondral bone hypertrophy and inflammation. OA is the leading cause of joint pain resulting in significant worsening of the quality-of-life in the elderly. Numerous efforts have been spent to overcome the inherently poor healing ability of articular cartilage. Mesenchymal stem cells (MSCs) have been in the limelight of cell-based therapies to promote cartilage repair. Despite progressive advancements in MSC manipulation and the introduction of various bioactive scaffolds and growth factors in preclinical studies, current clinical trials are still at early stages with preliminary aims to evaluate safety, feasibility and efficacy. This review summarises recently reported MSC-based clinical trials and discusses new research directions with particular focus on the potential application of MSC-derived extracellular vehicles, miRNAs and advanced gene editing techniques which may shed light on the development of novel treatment strategies.

The translational potential of this article: This review summarises recent MSC-related clinical research that focuses on cartilage repair. We also propose a novel possible translational direction for hyaline cartilage formation and a new paradigm making use of extra-cellular signalling and epigenetic regulation in the application of MSCs for cartilage repair.

* Corresponding author. Room 501, 5/F, Li Ka Shing Medical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong SAR, PR China.
E-mail address: waynelee@ort.cuhk.edu.hk (W.Y.-w. Lee).

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Introduction

Osteoarthritis (OA) is a condition of progressive erosion of articular cartilage characterised by worsening pain during movement of joints and decreasing ability of the joint to withstand mechanical stress, eventually limiting joint mobility and function. Any synovial joint can develop OA, but knees, hips and small hand joints are the most commonly affected sites [1]. It often severely impedes elderlies' daily activities. In the United States, data from 2010 to 2012 showed that 21.4%, or around 52.5 million adults reported doctor-diagnosed arthritis during that period; and 9.2% among them had arthritis-attributable activity limitations [2]. Damage to articular cartilage due to traumatic injury or other pathological conditions is traditionally considered to be the main cause of OA. Articular cartilage in diarthroidal joints is composed of hyaline cartilage with a specialised anatomical structure and composition facilitating low friction and painless movement. Articular cartilage is hyaline cartilage composed of chondrocytes residing in a dense extracellular matrix (ECM). The specialised composition of the ECM renders unique viscoelastic properties allowing smooth movement. Collagen is the major constitute making up to 60% of the dry weight. Type II collagen accounts for 90—95% of total collagen and the formed fibres are intertwined with proteoglycan aggregates [3]. Fibrocartilage and elastic cartilage are another two types of cartilage in the human body with different ECM and cell compositions [4,5]. Disruption of the articular cartilage severely affects the knee joint's load-bearing functions, restricting both the ease and range of movement thus highlighting the importance of chondrocytes for joint health. Chondrocytes originate from mesenchymal progenitor cells and contribute about 2% of the total volume of cartilage; their survival relies on a suitable microenvironment and mechanical stress. However, despite their importance, they have limited potential for replication, leading to a limited capacity of the cartilage to recover in response to injury. The exact pathophysiology of OA is still disputed, but a cardinal feature of OA is the thinning of articular cartilage associated with pain, inflammation, and radiologically observable changes such as sclerosis and osteophytes. Synovial irritation, inflammation and bone remodelling processes result in a more uneven joint surface which could further accelerate joint damage. Emerging evidence indicates that OA is not just a cartilage disease, but rather a dynamic pathological conditions of all of the whole joint tissues including the synovium and subchondral bone [6—9].

Current treatments for OA and their limitations

According to the OA Research Society International (OARSI) and the American Academy of Orthopaedic Surgeons, the main OA treatments can be categorised into physical measures, pharmacological therapy and surgery [10,11]. Physical measures help to reduce the mechanical imbalance and thus, the risk of OA. Drugs, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics are optional for moderate to severe pain, which are reported to be associated with considerable side effects, including liver toxicity, gastrointestinal complications like bleeding and perforated gastric ulcers, nausea, dizziness, constipation, tiredness, etc. Intra-joint injections of hyaluronic acid was one option for the treatment of cartilage lesions, but recent clinical studies showed that the use of hyaluronic acid did not significantly improve clinical outcomes compared with the placebo group [12]. Arthroscopic lavage and debridement have previously been recommended as treatment modalities up until the early 2000s [13]. Previous uncontrolled studies have signified pain improvement in more than half of the patients [14]. It was thought that the debridement procedure prevented further degradation of the joint during movement, delaying the progression of osteoarthritis and reducing pain. Studies later proved that both procedures performed no better than the placebo in improving knee pain and self-reported function [15], therefore this line of treatment was subsequently abandoned. Minimally invasive microfracture procedures had brought hope to patients, but growing evidence showed that the generated fibrocartilage-like repair tissue was less optimal for long-term benefits [16,17]. All these treatment solutions may benefit some subjects as reflected by symptom relief, but none of them can prevent the affected articular cartilage from progressive destruction. These patients would eventually need a surgical joint replacement surgery to regain joint function. Apart from the long waiting time in local public hospitals for this surgery, many of these patients who suffer from cartilage lesions are relatively young, and they would outlive the useful life of a total joint replacement [18], implying the need for a second joint replacement surgery. In view of these limitations, extensive efforts have been spent to search for alternative strategies to promote cartilage repair. In this Review, we discuss the rationale and recent clinical trial experiences of the use of mesenchymal stem cells (MSCs) for OA therapy, and summarise some novel research directions to facilitate the application and outcome of MSC-based therapy for the clinical management of OA.

Cell-based therapy for OA

Articular chondral or osteochondral lesions usually cannot regenerate into hyaline cartilage. It is speculated that the lack of vasculature within damaged cartilage might limit the infiltration of progenitor cells which are required for the tissue regeneration process [19]. Tissue engineering has come into the limelight of modern science since its introduction in the 1980s. In recent years, cellular components, engineered scaffolds and bioactive substances have been explored as an alternative to traditional surgical methods to facilitate functional tissue regeneration. Autologous chondrocyte implantation (ACI) is a typical example of tissue engineering widely accepted to treat small to moderate-sized osteochondral defects. The first arthroscopic operation is required to obtain a cartilage biopsy for the expansion of chondrocytes *in vitro*, which will be implanted into the debrided defect site and covered by a membrane in the second operation. This technique with autologous cells could avoid eliciting immune complications and minimise site morbidity when compared with autologous osteochondral implantation. The drawback of a lack of mechanical and biocompatible scaffolds to support chondrocyte