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REVIEW ARTICLE

The role of mesenchymal stem cells in osteoarthritis development and treatment

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Summary As the most common form of joint disorders, osteoarthritis (OA) imposes a tremendous burden on health care systems worldwide. Without effective cure, OA represents a unique opportunity for innovation in therapeutic development. In contrast to traditional treatments based on chemical drugs, proteins or antibodies, stem cells are poised to revolutionize medicine as they possess the capacity to replace and repair tissues and organs such as OA joints. Among different types of stem cells, mesenchymal stem cells (MSCs) are of mesoderm origin and have been shown to generate cells for tissues of the mesoderm lineage, thus, raising the hope for them being used to treat diseases such as OA. However, given their ability to differentiate into other cell types, MSCs have also been tested in treating a myriad of conditions from diabetes to Parkinson's disease, apparently of the ectoderm and endoderm lineages. There is ongoing debate as to whether MSCs can differentiate into lineages outside of the mesoderm and consequently their effectiveness in treating conditions from the ectoderm and endoderm lineages. In this review, we will discuss the developmental origin of MSCs, their differentiation potential and immune-modulatory effects, as well as their applications in treating OA. We suggest further investigations into new therapies or combination therapies that may provide more effective treatment for bone and joint diseases. Furthermore, cell-based therapy and its associated safety and effectiveness should be carefully evaluated before clinical translation. This review will provide updated information on recent approvals of its clinical trials and related applications, and discuss additional efforts on cell-based therapy for treating OA and other joint and bone diseases.

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Introduction

Osteoarthritis (OA) is the most common form of joint disorder, characterized by degeneration of articular cartilage [1] and reactive new bone formation at the articular margins, causing pain and stiffness of the affected joints [2]. The macroscopic features of OA could be revealed by radiograph and magnetic resonance images (Figure 1) and the microscopic features by way of histology (Figure 2). OA can affect all synovial joints, with the hip and knee being the most common sites that often lead to physical disability [2]. Currently, OA is the leading cause of disability among the elderly population and this is often associated with depression and sleeping disorder [3]. It is estimated that 10—15% of adults aged older than 60 years suffer from OA around the world [1]. As the population ages worldwide, it has been forecast that over 20% of world population will be suffering from OA and over 40 million people will be severely disabled by 2050 [1]. Unfortunately, without effective treatment [4], OA represents a significant economic burden for both the patients and the society at large [1,3,5—7].

Currently there is no effective therapy that can reverse the progressive nature in OA. However, one promising therapy may rely on the use of stem cells as therapeutics. The majority of the current stem cell therapies involve using mesenchymal stem cells (MSCs) due to their multilineage differentiation towards cell types in the joint and their immunoregulatory function. This could be efficacious in repairing the damaged joints in OA, not only for cartilage repair but also for subchondral bone remodelling. However, the safety and effectiveness of the new cell-based therapies must be carefully evaluated before any clinical application. Thus, significant challenges remain and will be addressed in this review.

Risk factors of OA

OA can be classified into primary and secondary forms [8]. Primary OA is a chronic degenerative disease related to aging [1] and heredity [2]. The exact aetiology of primary OA remains unknown [2], although genetic predisposition have been implicated [1]. Secondary OA can occur in any synovial joints and at any age due to articular injury [2], for instance, fracture, repetitive joint use, obesity [9—11], or metabolic disease such as diabetes [12,13]. The aetiology of the primary and secondary of OA is different, however patients' symptoms and signs are very similar [1]. Detailed risk factors for primary and secondary OA are summarized in Table 1.

Age has been well accepted as an independent risk factor for the development of OA [17], increasing the chance of total hip replacement in this group of patients [18]. Recently, more emphasis has been placed in genetic predisposition as another independent cause for OA. Genes such as those for the vitamin D receptor gene, insulin-like growth factor I, cartilage oligomeric proteins, and the human leukocyte antigen region have all been associated with OA [19]. Post-traumatic OA could develop in joints after sustaining fractures or contusion [14]. These injuries invariably accelerate the nature OA development and progression [2].

The development of OA also showed sex-specific prevalence and ethnic differences. Zhang et al [20] compared the prevalence of OA in Chinese from Beijing and Caucasians from Framingham, MA, USA. They reported that the prevalence of radiographic knee OA was higher in women than men of both Chinese and Caucasians aged $>$ 60 years [20]. Furthermore, ethnic variation also shown that Chinese women have a higher prevalence of knee OA than their Caucasian counterpart.

Higher body mass index is associated with higher risk of developing knee OA [24] and hip OA. Studies have shown that the risk of knee OA increases about 15% for each additional kg/m^2 $>$ 27 kg/m^2 [16,25]. However, development of OA in obesity does not confined to just the lower limb. Reports of upper limb involvement are just as common in OA of the hands and wrist [10]. Weight reduction and controlling obesity is the single patient control variable that can reduce the risk of OA development [18,24].

Oestrogen deficiency might be a risk factor for developing of OA as women has high incidence of OA after menopause [14]. Lower prevalence of OA was observed in women under oestrogen replacement therapy [2,14].

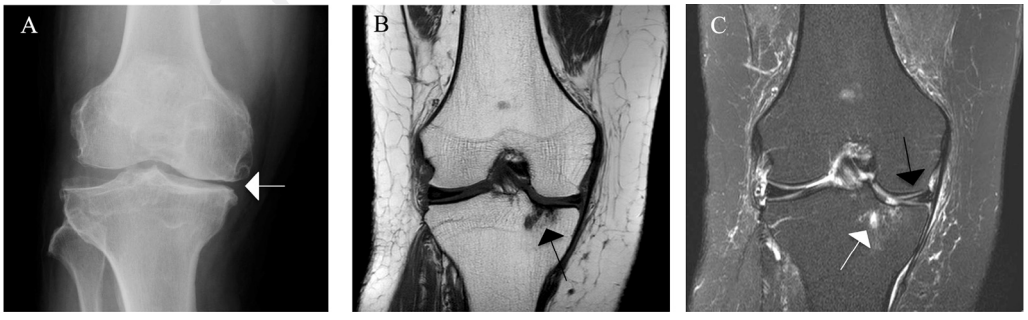

Figure 1 Radiograph and magnetic resonance images of a Kellgren—Lawrence Grade 3 knee illustrating the features of osteoarthritis. (A) Anteroposterior radiograph: joint space narrowing and definite marginal osteophytes at both the distal femur and tibia plateau (white arrow). (B) Corresponding coronal T1 weighted image: diffuse cartilage loss at the tibia plateau and subchondral cysts (black arrow). (C) Corresponding coronal T2 weighted image: a subchondral cyst with bone marrow oedema of the medial tibial plateau (white arrow), which cannot be visualized by radiography. Partial maceration and oedema of the body of the medial meniscus and extrusion of the body of the medial meniscus (black arrow), both factors contributing to radiographic joint space narrowing.

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