

Editorial

# Stem Cell-Based Therapies for Cartilage Repair and Regeneration

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## Editorial

Articular cartilage is a tough, flexible connective tissue that covers the ends of bones. Articular cartilage comprises of abundant extracellular matrix and an aggregate-forming proteoglycan with embedded chondrocytes [1], which is responsible for frictionless joint movement. However, articular cartilage is vulnerable to damage from trauma and degenerative diseases such as Osteoarthritis (OA). People with cartilage damage commonly experience joint pain, stiffness, inflammation, even complete loss of joint function. Due to its a vascular status, articular cartilage has a very limited capacity for healing. Restoration of hyaline cartilage is a real challenge for the orthopaedic surgeon [2]. This motivates the development of new technologies for cartilage repair. So far, significant efforts have been made in the development of therapies for cartilage repair. Cell therapy has been shown to be the ideal way of repairing cartilage defects to native tissue. Available or promising options to treat cartilage defects include chondrocytes, Mesenchymal Stem Cells (MSCs), Embryonic Stem Cells (ESCs), Induced Pluripotent Stem Cells (iPSCs), reprogrammed chondrogenic cells from somatic cells by defined factors through transdifferentiation.

Autologous Chondrocyte Implantation (ACI) has been used for treatment of osteoarticular lesions for over two decades. This technique involves the excision of healthy cartilage from the joint, expansion of cells in vitro and implantation of expanded cells into chondral defects. It was showed that 88% of patients had excellent or good results after ACI [3]. However, chondrocytes tend to dedifferentiate into fibroblasts during in vitro expansion and result in fibrocartilaginous repair with a mixture of fibrous tissue and cartilaginous tissue. There is therefore significant interest in preserving the phenotype of the primary chondrocytes during in vitro expansion and improving surgical techniques to increase the success rate of ACI.

There has been an increasing interest in recent years in the development of stem cell-based therapy for cartilage repair. Stem cells are mainly classified into two kinds of cells: adult stem cells and pluripotent stem cells. MSCs are multipotent cells which are capable of differentiating into mesenchymal tissues including cartilage. MSCs are easily accessible from various tissue sources including bone marrow, adipose tissue, umbilical cord blood, skin, synovial tissue, muscle, periosteum and other tissues. Due to multilineage

differentiation capacity [4] and immunomodulatory properties [5], MSCs represent one of the most promising stem cells for regenerative medicine. MSC-based therapy has proven effective in the treatment of various cartilage degenerative diseases and injuries [6-10]. There is no difference between bone marrow-derived MSCs (BMSCs) and ACI in terms of clinical outcome [6]. Some disadvantages with MSCs need be considered when MSCs are used for clinical application. First, primary MSCs have limited proliferative potential during in vitro expansion, which limit large-scale production of MSCs. Second, MSCs from various tissues tend to differ in expansion capacity and differentiation potential. For example, BMSCs are superior to adipose tissue-derive MSCs in chondrogenic potential [11,12], suggesting that bone marrow-derived MSCs are better cell source for cartilage repair compared with adipose tissue-derive MSCs. Third, the quality of MSCs is also donor dependent, variance exists from donor to donor. Fourth, aging significantly decreases the survival and differentiation potential of MSCs[13].

Human ESCs represent one promising cell source for regenerative medicine due to their unlimited self-renewal and differentiation potential toward any types of cells. However, the direct use of hESCs for cartilage repair is greatly hampered by low differentiation efficiency and the propensity to form tumour in vivo. The pluripotency of hESCs need be attenuated by differentiation toward MSCs or chondrocytes [14,15]. Human ES-derived MSCs (hES-MSCs) represent a highly valuable, unlimited cell source for cartilage repair and regeneration. hESC-derived chondrogenic cells were able to repair cartilage defect with good surface regularity and complete integration with the adjacent host cartilage [16]. However, concerns with hESCs hinder their clinical application, such as immune rejection of cells derived from hESCs during transplantation and ethical issue regarding the use of human embryos for hESC derivation. Although hES-derived MSCs were reported [14,17,18], the problems with differentiation approaches greatly hamper the use of hESCs in clinical application, including cumbersomeness, low efficiency, the presence of unwanted differentiated types of cells and undefined medium components. The highly efficient, clinically compliant differentiation approaches need be developed for clinical application.

Since iPSCs were generated from fibroblasts by defined factors [19,20], iPSCs usher in a new era of personalized medicine. iPSCs resemble hESCs in morphology, gene expression, in vitro differentiation potential and tumorigenesis. As iPSCs have potential to generate patient-specific stem cells such as iPSC-MSCs or somatic cells such as chondrocytes for cartilage repair with minimal ethical concerns, iPSCs hold great promise for cartilage repair. There is no immune rejection with the clinical use of iPSCs, iPSCs therefore offer an unlimited autologous supply for therapeutic uses. Very interestingly, iPSC-MSCs have superior survival and engraftment to bone marrow derived-MSC [21]. Although iPSCs hold great promise for regenerative medicine, there are important safety issues to be considered before use for clinical trials, including tumorigenesis

from integrated oncogenes, insertion mutation causing cancers, epigenetic memories and genomic aberrations etc. To reduce the risk from transgene integrations, transgene-free strategies have been developed, including adenovirus [22] and small molecules [23]. iPSC technology is shifting into the realm of personalized medicine.

New strategies are being developed, which are promising to treat cartilage defects. Transdifferentiation, also lineage reprogramming, is a strategy for cartilage repair. It was shown that chondrocytes can be generated from human fibroblasts by a combination of five genes BCL6, T, c-MYC, MITF, and BAF60C [24]. This direct conversion from no cartilage tissue to cartilaginous tissue provides new insight into cartilage repair. In addition, gene therapy and small molecule also can improve the repair of damaged cartilage by enhancing the chondrogenic potential of cells. ZNF145 improves cartilage repair and regeneration earlier and better as an upstream factor of Sox9 [2]. Small molecule, kartogenin greatly enhances the cartilage repair and regeneration [25].

Many options have been made available for cartilage repair, adult stem cell therapies have proven good efficacy in some clinical trials, pluripotent hESCs have enormous potential for regenerative medicine, iPSCs provide patient-specific stem cells for personalized medicine. However, each has its own advantages and disadvantages, the clinical benefits of stem cells for cartilage repair are still being investigated or evaluated. There is still some way to go in widespread use of stem cells for cartilage repair. To obtain robust and reproducible results, the comprehensive strategies combined stem cells with scaffold, growth factor, gene therapy and small molecules need be developed.

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