Journal of Stem Cells Research, Reviews & Reports

Austin Publishing Group

Open Access Full Text Article

Editorial

Stem Cell-Based Therapies for Cartilage Repair and Regeneration

Tong Ming Liu*

Cancer Stem Cell Group, Genome Institute of Singapore

***Corresponding author:** Tong Ming Liu, Cancer Stem Cell Group, Genome Institute of Singapore, Singapore 138672, Tel: 65 68088229; Fax: 65 68088308; Email: dbsliutm@yahoo.com

Received: Aug 01, 2014; **Accepted:** Aug 02, 2014; **Published:** Aug 04, 2014

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 tumeriogenesis. 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 tumeriogenesis

Citation: Liu TM. Stem Cell-Based Therapies for Cartilage Repair and Regeneration. J Stem Cells Res, Rev & Rep. 2014;1(1): 1002.

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.

References

1. Poole AR. Cartilage in health and disease. Lippincott, Williams and Wilkins. In Arthritis and Allied Conditions: A Textbook of Rheumatology. 2005.
2. Liu TM, Guo XM, Tan HS, Hui JH, Lim B, Lee EH. Zinc-finger protein 145, acting as an upstream regulator of SOX9, improves the differentiation potential of human mesenchymal stem cells for cartilage regeneration and repair. See comment in PubMed Commons below Arthritis Rheum. 2011; 63: 2711-2720.
3. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. See comment in PubMed Commons below J Bone Joint Surg Br. 2003; 85: 223-230.
4. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. See comment in PubMed Commons below Science. 1999; 84: 143-147.
5. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. See comment in PubMed Commons below Blood. 2005; 105: 1815-1822.
6. Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. See comment in PubMed Commons below Am J Sports Med. 2010; 38: 1110-1116.
7. Xie X, Wang Y, Zhao C, Guo S, Liu S, Jia W, et al. Comparative evaluation of MSCs from bone marrow and adipose tissue seeded in PRP-derived scaffold for cartilage regeneration. See comment in PubMed Commons below Biomaterials. 2012; 33: 7008-7018.
8. Moriguchi Y, Tateishi K, Ando W, Shimomura K, Yonetani Y, Tanaka Y, et al. Repair of meniscal lesions using a scaffold-free tissue-engineered construct derived from allogenic synovial MSCs in a miniature swine model. Biomaterials. 2013; 34: 2185-2193.
9. Dahlin RL, Kinard LA, Lam J, Needham CJ, Lu S, Kasper FK, et al. Articular chondrocytes and mesenchymal stem cells seeded on biodegradable scaffolds for the repair of cartilage in a rat osteochondral defect model. See comment in PubMed Commons below Biomaterials. 2014; 35: 7460-7469.
10. Long T, Zhu Z, Awad HA, Schwarz EM, Hilton MJ, Dong Y. The effect of mesenchymal stem cell sheets on structural allograft healing of critical sized femoral defects in mice. See comment in PubMed Commons below Biomaterials. 2014; 35: 2752-2759.
11. Liu TM, Martina M, Hutmacher DW, Hui JH, Lee EH, Lim B. Identification of common pathways mediating differentiation of bone marrow- and adipose tissue-derived human mesenchymal stem cells into three mesenchymal lineages. See comment in PubMed Commons below Stem Cells. 2007; 25: 750-760.
12. Afizah H, Yang Z, Hui JH, Ouyang HW, Lee EH. A comparison between the chondrogenic potential of human bone marrow stem cells (BMSCs) and adipose-derived stem cells (ADSCs) taken from the same donors. See comment in PubMed Commons below Tissue Eng. 2007; 13: 659-666.
13. Roobrouck VD, Ulloa-Montoya F, Verfaillie CM. Self-renewal and differentiation capacity of young and aged stem cells. See comment in PubMed Commons below Exp Cell Res. 2008; 314: 1937-1944.
14. Lian Q, Lye E, Suan Yeo K, Khia Way Tan E, Salto-Tellez M, Liu TM, et al. Derivation of clinically compliant MSCs from CD105+, CD24- differentiated human ESCs. See comment in PubMed Commons below Stem Cells. 2007; 25: 425-436.
15. Oldershaw RA, Baxter MA, Lowe ET, Bates N, Grady LM, Soncin F, et al. Directed differentiation of human embryonic stem cells toward chondrocytes. See comment in PubMed Commons below Nat Biotechnol. 2010; 28: 1187-1194.
16. Toh WS, Lee EH, Guo XM, Chan JK, Yeow CH, Choo AB, et al. Cartilage repair using hyaluronan hydrogel-encapsulated human embryonic stem cell-derived chondrogenic cells. See comment in PubMed Commons below Biomaterials. 2010; 31: 6968-6980.
17. Villa-Diaz LG, Brown SE, Liu Y, Ross AM, Lahann J, Parent JM, et al. Derivation of mesenchymal stem cells from human induced pluripotent stem cells cultured on synthetic substrates. See comment in PubMed Commons below Stem Cells. 2012; 30: 1174-1181.
18. Wei H, Tan G, Manasi, Qiu S, Kong G, Yong P, et al. One-step derivation of cardiomyocytes and mesenchymal stem cells from human pluripotent stem cells. See comment in PubMed Commons below Stem Cell Res. 2012; 9: 87-100.
19. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. See comment in PubMed Commons below Cell. 2007; 131: 861-872.
20. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. See comment in PubMed Commons below Science. 2007; 318: 1917-1920.
21. Lian Q, Zhang Y, Zhang J, Zhang HK, Wu X, Zhang Y, et al. Functional mesenchymal stem cells derived from human induced pluripotent stem cells attenuate limb ischemia in mice. See comment in PubMed Commons below Circulation. 2010; 121: 1113-1123.
22. Stadtfeld M, Nagaya M, Utikal J, Weir G, Hochedlinger K. Induced pluripotent stem cells generated without viral integration. See comment in PubMed Commons below Science. 2008; 322: 945-949.
23. Hou P, Li Y, Zhang X, Liu C, Guan J, Li H, et al. Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. See comment in PubMed Commons below Science. 2013; 341: 651-654.
24. Ishii R, Kami D, Toyoda M, Makino H, Gojo S, Ishii T, et al. Placenta to cartilage: direct conversion of human placenta to chondrocytes with transformation by defined factors. See comment in PubMed Commons below Mol Biol Cell. 2012; 23: 3511-3521.
25. Johnson K, Zhu S, Tremblay MS, Payette JN, Wang J, Bouchez LC, et al. A stem cell-based approach to cartilage repair. See comment in PubMed Commons below Science. 2012; 336: 717-721.