Synovial Stem Cells in Musculoskeletal Regeneration

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The synovium is a thin layer of connective tissue that lines the joint surface, tendon sheaths, and bursae at freely moving articulations in the body. Embryologic origin of the synovial tissue is the mesenchymal layer, which also gives rise to bone, cartilage, ligament, and muscle tissue. The synovium has several functions, including lubrication of the articulating surfaces, nutrition of articular cartilage, and regulation of immune response within the joint.

Synovial Cells

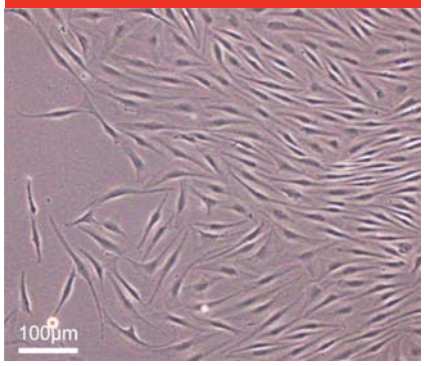
The synovium contains two main cell types: type A and type B synoviocytes. Type A synoviocytes are tissue macrophages and have phagocytic functions. Type B synoviocytes are fibroblast-like cells and function in the formation of synovial fluid.[1] In 2001, De Bari et al[2] isolated mesenchymal stem cells (MSCs) from the synovium (Figure 1). Type A synoviocytes can be characterized and eliminated from mixed synovial cell populations through a selective culturing process. However, type B synoviocytes and synovial-MSCs have similar phenotypic features, and specific characteristics to clearly differentiate these two cell types from each other have not been determined yet.[1]

In terms of immune phenotype, there are many similarities between synovial-MSCs and MSCs of other origins. Both cell types are positive for surface markers such as CD44, CD90, and CD105. However, cells derived from synovium, including synovial-MSCs, have higher expression of CD44 (a hyaluronan receptor) and can express uridine diphosphoglucose dehydrogenase, which is a vital enzyme involved in hyaluronan synthesis.[3] In vitro studies have shown that synovial-MSCs have superior potential to differentiate into chondrocytes and to produce cartilage compared with MSCs of other origins.[4] Moreover, synovial-MSCs have greater proliferation and colony-forming capacity than do other stem cell sources.[4]

Synovial-MSCs and Cartilage Regeneration

Based on the promising results from in vitro studies, investigators have launched animal model studies to evaluate the effects of synovial-MSCs in vivo. In a rabbit model with full-thickness articular cartilage defect, Koga et al[5] demonstrated that local transplantation of synovial-MSCs results in extensive cartilage matrix formation at the defect site. These authors also observed that in the deeper zone of the defect, synovial-MSCs differentiated into bone cells, whereas synovial-MSCs at the superficial zones differentiated into chondrocytes. This observation supported the multilineage differentiation potential of synovial-MSCs according to local microenvironments in vivo. In a pig model, transplantation of synovial-MSCs into a full-thickness articular cartilage defect promoted cartilage regeneration based on arthroscopic, MRI, and histologic analysis as early as 3 months after the procedure.[6] Bilge et al[7] used a rabbit knee model as an in vivo culture medium to evaluate the effects of synovium on chondrocyte growth. These authors observed that cartilage grafts

Figure 1



Histologic appearance of human synovial mesenchymal stem cells under the phase contrast microscope 14 days after initial plating.

that are in direct contact with the synovium produce more chondrocytes compared with cartilage grafts that are not. Studies of animal meniscal defect models demonstrated that transplanted synovial-MSCs adhere to sites of meniscal injury, differentiate into cells resembling meniscal fibrochondrocytes, and enhance meniscal regeneration.[8,9]

Sporadic human studies have reported that the number of synovial-MSCs in synovial fluid increases in knees with degenerated cartilage and osteoarthritis and following intra-articular ligament injury.[10,11] This observation raises the question whether the number of synovial-MSCs that are mobilized from synovium into synovial fluid increases according to the degree of cartilage degeneration as part of the reparative process. Human trials investigating the effects of intra-articular synovial-MSC transplantation to promote cartilage regeneration and/or to prevent osteoarthritis should answer this question.

Application of Synovial-MSCs for Bone, Tendon, and Muscle Regeneration

Synovial-MSCs may offer an alternative cell-based treatment strategy for bone, tendon, and muscle regeneration. In a rabbit bone defect model, Matsusaki et al[12] demonstrated that using tissue-engineered construct derived from synovial-MSCs with hydroxyapatite accelerates osteoinduction. In a rat Achilles tendon graft model, synovial-MSC implantation into bone tunnel accelerated early remodeling of tendon-to-bone healing.[13] Another rat model study showed that synovial-MSCs have myogenic potential and contribute to skeletal muscle regeneration in vivo.[14] In spite of these reports, there is not sufficient evidence regarding osteogenic and myogenic potential of synovial-MSCs compared with bone marrow– and muscle-derived MSCs.

Future Perspectives

In vitro and animal model studies support the use of synovial-MSCs in cartilage regeneration as an important, arguably superior, cell-based treatment alternative. Further investigations in the near future should help in our understanding the complexity of synovial-MSC biology in terms of isolation, characterization, culturing, distinguishing from, and interacting with other cell types before this promising cell-based therapy can be translated into clinical practice.

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