Mesenchymal Stromal Cell Transplantation in the Regeneration of Articular Cartilage and Bone Using a Magnetic Cell Delivery System

Mitsuo Ochi, MD

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From Hiroshima University Hospital, Hiroshima, Japan.

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The term mesenchymal stromal cells (MSCs) refers to those undifferentiated cells isolated from adult tissue that have the capacity to differentiate into mesodermal lineages, such as bone, cartilage, fat, muscle, or other tissues.[1] In addition, MSCs are capable of expressing and releasing a variety of growth factors and bioactive molecules to promote regeneration of damaged tissue. Because of their function, the clinical use of MSCs for the repair of damaged tissue is very promising.

Although several studies have reported the successful local transplantation of MSCs for tissue regeneration, local injection of MSCs is often insufficient to accumulate transplanted MSCs effectively into the lesion, and a large number of cells are required to treat damaged lesions, such as chondral defects or fracture nonunions. Furthermore, it has been reported that injured cartilage could be repaired by intra-articular injection of MSCs in the rat knee; however, in the study by Agung et al,[2] the injected MSCs diffused throughout the joint, resulting in free bodies of scar tissue being formed in this region.

We therefore conceived of a new technique for accumulating transplanted MSCs to a desired lesion using magnetic force. This would allow tissue regeneration to be achieved using a relatively small number of cells, with the aim of avoiding side effects such as the formation of free bodies of scar tissue. In our technique, iron-labeled MSCs are accumulated and retained at the desired lesion under the direction of a magnetic force by applying a magnetic field generator outside the body. Considering its potential clinical application, we have developed a superconducting bulk magnet system as a magnetic field generator that generates a maximum magnetic flux density of 5.07 Tesla and that has been downsized for better portability.[3] To induce magnetic responsiveness in the MSCs, ferucarbotran suspension was used. Ferucarbotran consists of superparamagnetic iron oxide nanoparticles developed for contrast-enhanced MRI and has been safely approved for use in humans. With regard to the effect of iron labeling and magnetic force on cell differentiation, we confirmed that the ability of the MSCs to undergo osteogenesis and chondrogenesis was not influenced by magnetic labeling or by application of the magnetic force.

We have examined the effectiveness of this cell delivery system for the regeneration of cartilage and bone based on the behavior of the transplanted MSCs and curability. Regarding the behavior of transplanted MSCs, we previously reported that magnetically labeled MSCs accumulated onto osteochondral defects of the patella in the knee joints of rabbits by controlling the direction of the magnetic force, as observed macroscopically and histologically.[4] Furthermore, we applied this technique to the transplantation of MSCs via swine knee arthroscopy to mimic the clinical situation and success-

fully delivered magnetically labeled MSCs to an osteochondral defect of the patella with the aid of arthroscopy.[4] Another study used in vivo bioluminescence imaging to trace the behavior of magnetically labeled MSCs sequentially following cell transplantation; these authors demonstrated that transplanted MSCs not only accumulated in the short term but were also retained at the desired lesion in the long term.[5]

Regarding the effect of treatment, an in vitro study demonstrated that our technique of using magnetically labeled MSCs and an external magnetic device was able to form a cell layer of the transplanted MSCs that contained an extracellular matrix on the degenerated human cartilage 3 weeks following cell transplantation.[6] The authors of an animal study also reported that the regeneration of the articular cartilage in a rat knee joint was enhanced by accumulating magnetically labeled synovium-derived cells to the chondral defect; however, these authors used a magnet that was implanted intra-articularly.[7] This technique has been reported to accelerate bone formation in a rabbit large bone defect model[8] and a rat nonhealing fracture model.[5]

Our novel, less-invasive approach is applicable to human cartilage defects and fracture nonunions. The cell transplantation procedure can be performed using only an injection, with arthroscopic assistance for a chondral lesion or with a fluoroscopic guide for a fracture nonunion. Furthermore, we believe that this new system should be applicable not only to manage injuries of the cartilage and bone but also to manage several other tissue injuries, such as those involving the brain and spinal cord, as well as myocardial infarctions. The technique described in this study has a promising potential to improve clinical stem cell therapies in the near future.

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