Therapeutic Strategy of Third Generation Autologous Chondrocyte Implantation for Osteoarthritis

Introduction

Knee osteoarthritis (OA), a clinical syndrome with low-grade inflammation caused by abnormal wearing of the articular cartilage that covers joints and acts as a cushion, results in pain, destruction of the joints or decrease of synovial fluid that lubricates the joints. Because of the limited capacity for repair when damaged, abnormal wearing of the articular cartilage is a major clinical problem. Various therapeutic strategies including bone marrow stimulation and transplantation of osteochondral autograft or allograft have been developed to restore articular cartilage and produce a permanent repair. Among those, autologous chondrocyte implantation (ACI) is one of the promising choices for cartilage repair. The classical ACI was first described in 1994 and approved by the USA Food and Drug Association in 1997. The first generation ACI provided significant and long-term benefits for patients in terms of diminished pain and improved function. However, hypertrophy or ossification of patched periosteum and complex operative technique developed in the second generation ACI, where bioengineered bi-layer collagen membranes were used without a periosteal flap. In addition, further technological advances have led to the third generation ACI, where biomaterials seeded with chondrocytes were used as carriers and scaffolds for cell growth. These “all-in-one” grafts do not need a periosteal cover or fixing stitches and can be trimmed to exactly fit the cartilage defect. Although the advantages of this new technique exist in its technical simplicity, shorter operating time, and the possibility to perform the surgery via a mini-arthrotomy or arthroscopy, the availability to OA is unknown and the effect is still controversial. Several clinical studies of the third generation ACI for partial cartilage injury have reported its potential, but there is no study of the third generation ACI applying for OA like change. Therefore, the purpose of this study is to evaluate the efficiency of the third generation ACI for the rat knee osteoarthritides produced by transaction of anterior cruciate ligament.

Materials and Methods

Animal model: The institutional animal care and committees of RIKEN Center for Developmental Biology approved all animal procedures. Athymic nude rats (F344/N Jcl nu/nu) aged 8 to 10 weeks were subjected to anterior cruciate ligament transaction. Two weeks after the operation, we confirmed the degeneration of articular cartilage by macroscopic assessment and histology of toluidine blue staining.

ACI procedure: Following materials were transplanted at the part of cartilage injury with defect shape in patella groove after regulation by a micro drill. We set three groups: ACI group (human chondrocytes derived from human specific collagen type 2 and SOX 9), collagen group (collagen alone), and sham group (no transplantation; negative control).

Contribution of transplanted chondrocytes: To examine human cell derived chondrogenesis, mRNA expression by RT-PCR analysis for chondrogenic markers (human specific collagen type 2 and SOX 9) and double immunofluorescence staining for human specific collagen type 2 and HLA-ABC were performed at week 4.

Morphological healing of OA: To confirm the recovery from OA-like arthritis, we performed macroscopic and histological evaluation at week 0, 4, 8, 20. We evaluated OA repair semi-quantitatively using a grading and staging system. In this system, there are six histological grades and four histological stages. The total score (score= grade x stage) ranges from 1 point (normal articular cartilage) to 24 points (no repair).

Results

Contribution of transplanted chondrocytes: RT-PCR analysis using regenerated tissue samples from transplanted site demonstrated that the expressions of human specific collagen type 2 and SOX 9 were detected in the ACI group, suggesting that regenerated cartilage was derived from transplanted human chondrocytes. However, there were no expressions in collagen and sham groups. Double immunofluorescence staining for human specific collagen type 2 and HLA-ABC at week 4 demonstrated that double stained cells were seen in the ACI group, but not in the collagen and sham groups.

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