Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of MMP-related genes in nucleus pulposus cells in rabbits

INTRODUCTION:
Synovial mesenchymal stem cells (MSCs) have high proliferative and chondrogenic potentials (1), and MSCs transplanted into the articular cartilage defect produce abundant extracellular matrix (2). Because of similarities between the articular cartilage and the intervertebral disc cartilage, synovial MSCs are a potential cell source for disc regeneration. Here, we examined the effect of intradiscal transplantation of synovial MSCs.

MATERIALS AND METHODS:
The nucleus pulposus tissues of mature Japanese white rabbit’s intervertebral discs were aspirated to induce disc degeneration, and allogenic synovial MSCs were transplanted. To chase transplanted cells, DiI-labeled cells and cells derived from GFP-positive transgenic rabbits were used. At 2, 4, 6, 8, 16, 24 weeks postoperatively (n=10 each time point), we evaluated with imaging analyses such as X-ray or MRI, and histological analysis. Microarray analyses of rats were performed to investigate the closeness of the gene profiles between the nucleus pulposus cells and the synovial or bone marrow MSCs. Furthermore, to investigate interaction between synovial MSCs and nucleus pulposus cells, human synovial MSCs and rat nucleus pulposus cells were co-cultured, and species specific microarray were performed.

RESULTS:
We confirmed survival of graft up until 24 weeks (Fig. 1). X-ray analyses demonstrated that intervertebral disc height in the MSC group remained higher than that in the degeneration group up until 24 weeks (Fig. 2A). T2 weighted MR imaging showed higher signal intensity of nucleus pulposus in the MSC group (Fig. 2B). Histological analyses revealed that nucleus pulposus of the MSC group were maintained. Higher expression of type II collagen around nucleus pulposus cells in the MSC group compared with even that of the normal group (Fig. 3). A hierarchically clustering analysis of microarray showed that the gene profile of the nucleus pulposus cells was different from that of the synovial and bone marrow MSCs equally (Fig. 4A). In co-culture of rat nucleus pulposus cells and human synovial MSCs, species specific microarray revealed that gene profiles of nucleus pulposus were altered markedly (Fig. 4B) with suppression of MMP-related genes such as matrix degradative enzymes and inflammatory cytokines (Table 1).

DISCUSSION:
After aspiration of the nucleus pulposus, intervertebral space rapidly decreases. Transplanted synovial MSCs promoted the remaining nucleus pulposus cells to synthesize type II collagen. Also, synovial MSCs affected the remaining nucleus pulposus cells by inhibiting their expressions of degradative enzymes and inflammatory cytokines, resulting in maintaining the structure of the intervertebral disc.

CONCLUSION:
Intradiscal transplantation of synovial MSCs prevented intervertebral disc degeneration in vivo. Co-culture assay in vitro revealed that nucleus pulposus cells dramatically changed their gene profile by interaction with synovial MSCs to inhibit expressions of the MMP-related genes.

REFERENCES: