Development of regenerative therapies using iPS cell-derived cartilage

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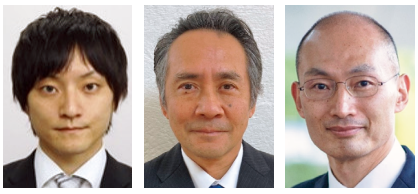

Abstract

Induced pluripotent stem cells (iPSCs) are a promising resource for allogeneic cartilage transplantation to treat articular cartilage defects that do not heal naturally. We showed that allogeneic iPSC-derived cartilage (iPS-Cart) survived and was integrated with the host cartilage without immune response in a primate model of chondral defects in the knee joints. Single-cell RNA-sequence (scRNA-seq) analysis indicated that iPS-Cart differentiated after transplantation, acquiring expression of PRG4 which is crucial for joint lubrication. We also investigated the application of iPS-Cart to diseases other than cartilage-related conditions and found that transplantation of human iPS-Cart into an immunodeficient rat model of intervertebral disc degeneration suppressed disc degeneration, and transplantation into a large bone defect model in immunodeficient mice resulted in a new bone formation.

Background & Results

Existing cell transplantation therapies for cartilage damages are considered to repair the damage by activating host tissue with factors transiently produced by the transplanted cells, and their repair ability is limited. Therefore, we are aiming to establish a curative regenerative therapy in which the graft itself constitutes the reparative tissue by transplanting iPS-Cart into the damaged tissue. Allogeneic cartilage transplantation into primate models had never been assessed. We therefore evaluated the efficacy and immune response of allogeneic iPS-Cart transplantation using a monkey model of knee joint cartilage defect. The allogenic iPS-Cart in chondral defects elicited no immune reaction and directly contributed to tissue repair for at least four months. iPS-Cart was integrated with the host native articular cartilage and prevented degeneration of the surrounding cartilage. ScRNA-seq analysis indicated that iPS-Cart differentiated after transplantation, acquiring expression of PRG4 which is crucial for joint lubrication.

Degeneration of nucleus pulposus of intervertebral disk is a major cause of low back pain. Because intervertebral disk degeneration is an irreversible condition, there is a need for regenerative treatments. The results of scRNA-seq analysis of the nucleus pulposus and cartilage showed that the gene expression profiles of the two were very similar. When iPS-Cart was transplanted into a nude rat model of caudal disc degeneration, disc degeneration was prevented for at least six months after the implantation indicating spatial and functional replacement of lost nucleus pulposus by iPS-Cart.

A large bone defect formed after surgical treatments of open fracture or bone tumor is difficult to be treated. iPS-Cart has properties of primordial cartilage. We transplanted iPS-Cart into a bone defect model of the femur of immunodeficient mice and found new bone formation in the bone defects.

Significance of the research and Future perspective

Transplantation of iPS-Cart could be applied to regenerative therapies for diseases that are difficult to heal naturally, such as cartilage damage, intervertebral disc degeneration, and severe bone defects. A clinical study is currently underway to transplant allogeneic iPS-Cart into cartilage-injured areas in patients with articular cartilage damage, and the acquisition of clinical proof of concept is expected to pave the way for social implementation.

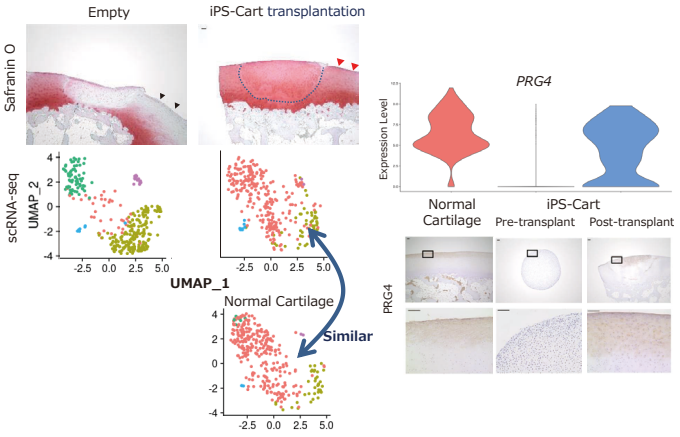

Fig.1. Evaluation of allogenic iPS-Cart transplantation into cartilage defects in primate models.
iPS-Cart survived and was integrated with the host cartilage. Chondral defects in the empty group were filled with non-cartilaginous fibrous tissues, while defects in the transplantation group were filled with cartilaginous tissue. Gene expression profiles of iPS-Cart after transplantation and normal articular cartilage were very similar, acquiring expression of PRG4 which is crucial for joint lubrication.

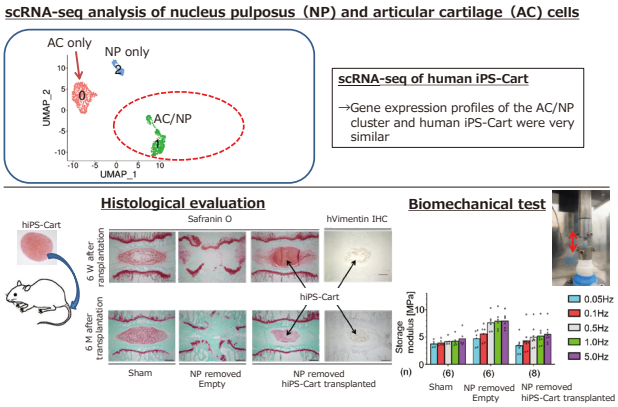

Fig.2. Effect of human iPS-Cart transplantation on intervertebral disc regeneration. Disc degeneration was prevented for at least six months after transplantation. The mean storage modulus of the hiPS-Cart group was significantly lower than that of the empty group and not significantly different from that of the Sham group.

Fig. 3. New bone formation after hiPS-Cart transplantation into femoral bone defects. iPS-Cart was transplanted into a bone defect model of the femur of SCID mice. New bone was formed in the defect 16 weeks after transplantation of iPS-Cart.

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Keyword articular cartilage damage, allogenic transplantation, intervertebral disk degeneration, bone defect, induced pluripotent stem cells