Editorial

Human somatic stem cell-based therapy for cartilage regeneration

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Clinical investigations using human somatic tissue derived stem cells for a variety of different diseases have been performed. Neural crest-derived stem cells exhibit somatic organization, can contribute to mesenchymal stem/stromal cells (MSCs) (1) and are used for cartilage treatment, bone reconstruction and anti-inflammatory treatments for diseases. The most common cell source for cartilage treatment is MSCs (2,3). Many clinical studies have used neural crest-derived stem cells (or MSCs) from different tissues and different methodologies. These differences in the generation of somatic tissue-derived stem cells have led to variable results in clinical studies. Although stem cell properties have been poorly characterized, human trials are presently under way.

In the recent investigative study by Pelttari *et al.* (4), the authors showed that HOX genes are differentially expressed in adult human neuroectoderm-derived nasal chondrocytes (NCs) and mesoderm-derived articular chondrocytes (ACs). The HOXC (C4, C5 and C8) and HOXD (D3 and D8) genes were consistently expressed in ACs. However, NCs did not express these genes. A comparison of MSCs from human bone marrow (BM-MSCs) and human dental pulp (DPSCs) demonstrated that HOX expression is higher in BM-MSCs and that low expression is exhibited in DPSCs. These data indicate that the expression pattern of the HOX genes distinguishes the developmental origin of tissues (neuroectoderm or mesoderm).

Four weeks after transplantation into a goat articular knee defect, GFP-positive goat NCs were identified in regions of the repaired tissue. Interestingly, transplanted NCs expressed HOX genes. The authors demonstrated that NCs (low amounts of HOX genes expressed *in vitro*) exhibited up-regulated HOX gene expression levels depending on the transplantation site. Furthermore, NCs activated HOX genes during co-culture with ACs and continued expressing these genes after further long-term culture *in vitro*. These data suggest that ACs trigger HOX gene expression by either paracrine signaling or direct clustering.

Next, a long-term study in goats was performed to obtain preclinical evidence of the effect of NCs on the repair of articular cartilage defects. These results show improved quality of tissue repair using NCs compared to ACs, which was confirmed by Alcian blue staining at 6 months. The pilot clinical trial using NCs also showed that these cells can be detected after 4 months and have an effect on cartilage regeneration.

The finding that the developmental origin of tissue (neuroectoderm or mesoderm) can be distinguished by HOX gene expression is also useful for the basic sciences. Neural crest cells originate at the neural folds during vertebrate development (5) and then migrate to various locations, where they differentiate into many types of cells. Previous reports have shown that MSC development partially originates in the neural crest (1,5,6). The normal MSC isolation method consists of an *in vitro* culture method, which is unavoidably contaminated by hematopoietic cells and the cellular heterogeneity of the cultures (7). In fact, depending on the study, cultured MSCs express a different subset of various cell lineage-specific surface antigens (7). Because MSCs consist of cells of mixed neural crest and mesoderm origins (1), HOX gene expression may become heterogeneous. The findings of this study may impact the elucidation of tissue-specific mechanisms in somatic tissues.

A previous study was conducted to investigate the

cartilage regeneration potential of embryonic stem cells (ESCs) (8). The authors identified the surface antigen of cartilage-committed cells at developmental stages. Isolation of cells with the surface antigen from differentiating human ESCs revealed a population of chondrocyte progenitors. The authors describe a developmental approach for the induction of highly purified chondrocytes from human ESCs that could enable substantial progress in cartilage tissue regeneration. Dr. Yamanaka and colleagues showed that the ectopic expression of a defined set of transcription factors, Oct4, Klf4, Sox2, and c-Myc, reprograms mouse and human fibroblasts into embryonic stem-like cells called induced pluripotent stem cells (iPSCs) (9,10). These iPSCs can become an ultimate transplant cell source, avoiding various ethical problems. Other researchers have shown that statin treatment can rescue patient-specific iPSC models [mouse fibroblast growth factor receptor 3 (FGFR3) skeletal dysplasia] (11). Recently, a study reported direct reprogramming of human fibroblasts into induced neural crest cells by overexpression of a single transcription factor, SOX10, in combination with environmental cues, including WNT activation (12). These studies could enable substantial progress in cartilage tissue engineering. Chondrogenic cells derived from induced somatic cells could promote and help to evaluate the treatment of cartilage lesions.

Worldwide, millions of patients suffer from osteoarthritis; unfortunately, the incidence is rising due to aging populations. Stem cell treatment attempts to regenerate cartilage using adult stem cells, and the methods for these treatments have been improving. It is important for clinical applications to determine whether the cells used are effective for therapy. The findings presented by Dr. Pelttari and colleagues identify neuroectoderm-derived NCs as a suitable resource for articular cartilage repair. It is important to identify a safe cell source that is suitable for therapy in different types of human tissue.

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