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MEETING REPORT

Tissue engineering (IBMS/JSBMR joint meeting 2013)

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It has been said that tissue engineering is based on three elements: cells, scaffolds and signaling molecules. Improving the properties of each of these elements and finding appropriate combinations of these elements are the purposes of many of the studies being performed today. Therefore, the papers on tissue engineering presented at the second *International Bone and Mineral Society* and the *Japanese Society for Bone and Mineral Research* (IBMS/JSBMR) meeting were classified into three categories: cells, scaffolds and signaling molecules, and are briefly described below.

Cells

There is a need for cells sources for tissue engineering. One approach is to induce osteoblasts or chondrocytes from mesenchymal stem cells (MSCs). MSCs were originally obtained from bone marrow, and later from other tissues, including adipose tissue, synovial tissue and so on. The gene expression profiles of MSCs from different origins (synovium, meniscus and cruciate ligament) were investigated.[1] Lists of genes that are uniquely expressed in each type of MSC will contribute to understanding the specific functions of MSCs from various tissues.

Since the development of induced pluripotent stem (iPS) cells, iPS cells have become new cell sources for the bone and cartilage tissue engineering. A keynote lecture on iPS cells was provided serially by Shinya Yamanaka and Kazutoshi Takahashi. Yamanaka described that, 50 years ago, only fertilized eggs and germ line cells were believed to have a full set of genes, and that somatic cells lost some of the genes during differentiation, and thus had specific sets of genes. However, nuclear transfer experiments performed by John Gurdon proved that somatic cells also have a full set of genes, because eggs that received a nuclear transfer become pluripotent. In addition, Takahashi introduced another important report showing that the transduction of fibroblasts with MyoD results in their conversion into muscle cells. These two important findings provided the foundation for the development of iPS cells, which could be generated by the transduction of somatic cells with a key set of transcription factors. He also explained the various applications of iPS cells, including disease modeling and the generation of iPS cell stocks for cell transplantation. For disease modeling, iPS cells are established from patients, followed by differentiation of the iPS cells toward cells of the diseased organ. The resultant cells may be used for investigating the pathomechanics of the disease and for drug screening. For regenerative medicine, the iPS cell stock is composed of iPS cells generated from individuals with homozygous human leukocyte antigen types. Cells derived from such iPS cells may be used promptly for allografting without the risk of inducing severe immunological rejection.

However, before the application of iPS cells for clinical use, methods for inducing the differentiation of iPS cells into specific types of somatic cells, including bone cells and cartilage cells, had to be developed. Several useful methods for differentiating embryonic stem (ES) cells have been reported so far. With regard to the differentiation of iPS cells into chondrogenic cells, the methods can be classified into several types.[2] These include (1) the coculture of ES cells with chondrocytes, (2) embryoid body formation followed by differentiation toward chondrocytes, (3) differentiation of iPS cells toward mesenchymal cell-like cells followed by differentiation into chondrocytes and (4) directed differentiation toward chondrocytes by the sequential addition of appropriate combinations of cytokines mimicking the developmental pathway. Koyama *et al.* initially formed embryoid bodies from human iPS cells.[3] Outgrown cells from embryoid bodies had MSC characteristics and were subjected to pellet culture to promote chondrogenic differentiation. Kanke *et al.*[4] reported a method for differentiating mouse ES cells toward osteoblasts using chemically defined conditions. They used small chemical compounds to modulate the Wnt and hedgehog signals sequentially, and succeeded in obtaining osteoblasts.

As a new cell source for cartilage tissue engineering, this author talked about chondrogenic cells generated directly from dermal fibroblast culture by the misexpression of a defined factor.[5] It is necessary to erase the fibroblastic characteristics,

in addition to inducing chondrogenic properties, in order to generate pure chondrocytes from dermal fibroblasts. As the transduction of fibroblasts with four reprogramming factors (c-Myc, Klf4, Oct3/4 and Sox2) results in the generation of iPS cells, and is associated with the complete erasure of the fibroblastic characteristics, this author and colleagues hypothesized that the transduction of fibroblasts with some of the reprogramming factors and chondrogenic factors may convert fibroblasts toward chondrocytes. As a result, misexpression of two reprogramming factors (c-Myc and Klf4) and one chondrogenic factor (Sox9) allowed for the generation of chondrocytes directly from mouse dermal fibroblast cultures.

Scaffolds

The usefulness of TiO_2 as a scaffold for osteoblasts derived from human MSCs has been demonstrated.[6] Xiangmei *et al.*[7] similarly demonstrated the usefulness of a nanofiber scaffold to deliver MSCs *in vivo*. They showed the anti-inflammatory effects of MSCs in a scaffold against arthritis. As a study related to tissue engineering, it was demonstrated that irradiated bone can be used to fill bone defects. The use of reduced radiation was shown to improve the bone quality, while still ensuring sterility.[8]

Signaling Molecules

Bone morphogenetic proteins (BMPs) induce both osteoblasts and adipocytes from MSCs. During the symposium, Baron[9] explained that specific zinc-finger proteins differentially mediate these BMP actions in each cell lineage. These findings will contribute to understanding how to direct MSCs to differentiate toward specific target types of cells at the molecular level.

O'Keefe *et al.*[10] explained the signals that regulate bone regeneration. For example, the COX-2 expressed in periosteal progenitors regulates stem cell populations and bone regeneration by affecting the balance between EP1 and EP2/EP4 signaling.

Kang *et al.*[11] reported that the addition of testosterone and BMP2 in the scaffold synergistically enhanced the repair of large bone defects created in mouse femurs. The androgen receptor mediates the effects of testosterone, because androgen receptor knockout mice did not show any effects of the application of testosterone in the scaffold.

Roberts *et al.*[12] identified the conditions that can efficiently create bone tissue *in vitro* by human periosteum-derived cells (hPDCs) on calcium phosphate-rich matrices (CPRM). A microarray analysis of the hPDCs on the CPRM *in vivo* revealed that pathways related to inflammation and development were involved in the development of the cells. Pretreatment of hPDCs-laden CPRM *in vitro* with growth factors that mediate the activation of these pathways promoted bone formation *in vivo*.

Complex actions of BMPs on osteoblasts were also reported. High-dose BMP2 reduces the cell proliferation and increases the apoptosis of periosteal cells through the elevation of DKK1 and SOST expression. The differential actions of the BMPs need to be considered when contemplating their use for clinical applications.[13]

Conflict of Interest

The author declares no conflict of interest.

References

1. Ezura Y, Hayata T, Notomi T, Noda M. Identification of differentially expressed genes in mesenchymal stem cells derived from synovium, meniscus and ligament. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P3004).
2. Oldershaw RA. Cell sources for the regeneration of articular cartilage: the past, the horizon and the future. *Int J Exp Pathol* 2012;**93**:389–400.
3. Koyama N, Miura M, Nakao K, Kondo E, Fujii T, Kanamoto N *et al.* The development of culture method for chondrogenic differentiation of human ips cells. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (Abstract no. YIS04).
4. Kanke K, Hojo H, Lichtler A, Chung U, Ohba S. Novel approach for the differentiation of embryonic stem cells into osteoblasts under a chemically-defined condition. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P2046).
5. Tsumaki N. Chondrocyte differentiation and direct conversion to chondrogenic cells. *IBMS BoneKEy* 2013;**10**:332 doi:10.1038/bonekey.2013.66 (Abstract no. IS16).
6. Gordeladze J. The use of microrna- and gene-assisted manipulation of mesenchymal stem cell (hMSCS) derived osteoblasts, optimally propagated and differentiated In TiO_2 scaffolds. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P1072).
7. Xiangmei Z, Yamaoka K, Sonomoto K, Kaneko H, Satake M, Yamamoto Y *et al.* Suppressive effect of mesenchymal stem cells with nano-fiber scaffold in collagen-induced arthritis. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P1070).
8. Forwood M, Nguyen H, Morgan D, Gineyts E. Reduced radiation sterilization dose of bone allografts improves bone quality and surgical outcomes, yet retains sterility assurance levels. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P2024).
9. Baron R. Coordinated regulation of bone remodeling and fat formation by the zinc finger protein 521 and its interactions with Ebf1. *IBMS BoneKEy* 2013;**10**:332 doi:10.1038/bonekey.2013.66 (Abstract no. IS17).
10. O'Keefe RJ, Huang C, Xie C, Zhang X. Stem cell populations and signals that regulate bone regeneration. *IBMS BoneKEy* 2013;**10**:332 doi:10.1038/bonekey.2013.66 (Abstract no. IS18).
11. Kang HY, Cheng BH, Chu TM. Testosterone is as effective as bone morphologic protein-2 in promoting the repair of critical-size segmental defect of femoral bone in mice. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (Abstract no. OC28).
12. Roberts S, Eyckmans J, Bolander J, Schrooten J, Chen C, Luyten F. Mapping early bone formation gene networks allows targeted osteoinduction of human periosteal progenitors *in vitro* and *in vivo*. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P1071).
13. Kamiya N, Kim H. High-dose BMP2 reduces cell proliferation and increases apoptosis via DKK1 and Sost in human primary periosteal cells. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (Abstract no. P3028).