조직공학에서 생체역학의 역할

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The Role of Biomechanics in Tissue Engineering

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Key Words : Tissue engineering (조직공학), cell mechanics (세포역학), substrate elasticity (표면탄성), mechanical signal (기계적 신호)

Abstract

Tissue engineering is an interdisciplinary field that utilizes the principles of engineering and life sciences toward the creation of biological substitutes. Traditionally, major components of tissue engineering are cells, scaffolds, growth factors and recently biomechanical aspects have been given much attention. A large number of studies have reported that mechanical signals are of particular interest in either encouraging or inhibiting cellular responses. In tissue engineering, cell adhesion is a very important step, because quality of adhesion may determine a cell fate in the future. Elasticity of cell-adhesive substrate is found critical in regulating stem cell differentiation. Cells exert different contractile forces for cell migration, depending on substrate mechanics. Though tissue engineering is very interactive with diverse expertise, for a breakthrough, principles of biomechanics in tissue and cell level needs to be fully understood.

1. 서 론

Tissue engineering is an interdisciplinary field that applies the principle of engineering and life sciences toward the development of biological substitutes that restores, maintains or improves tissue or organ function.[1] Primary duty of scaffold is to deliver specific cells into target sites in the body. An ideal scaffold should encourage the production of cell-specific extracellular matrix (ECM) by the transplanted cells and gradually be degraded with the growth of regenerating tissue. Due to the limited cell sources and dedifferentiation of tissue cells, mesenchymal stromal cells (MSCs) are extensively harnessed in tissue engineering. Growth factor, a chemical cue, is also essential in directing and regulating cellular behavior. In addition, mechanical cues are of particular interest in upregulating cell signaling pathway. For example, ultrasound has shown its positive effect not only on bone fracture healing but on cartilage metabolism. In another study, substrate mechanics was found to be a critical factor in eliciting different responses of stem cells. In this article, biomechanical aspects in tissue engineering are reviewed, focusing mainly on the effects of mechanically-induced biological cues and on the influences of substrate elasticity on cell behavior.

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2. Mechanical Cues on Cell Behavior

2.1 Therapeutic ultrasound on cartilage disease

A low-intensity ultrasound (LIUS) was examined for its possible therapeutic effects on degenerative osteoarthritic cartilage. For in vitro OA model, an engineered 3D neocartilage construct was treated daily with interleukin-1β (IL-1β) for 5 days. Followed by 24 hr pre-incubation with the first dose of IL-1β, the constructs were given ultrasonic stimulation (frequency: 1.5 MHz and SATA: 30 mW/cm^2) once a day for the pre-

determined time. Fresh IL-1β was added before the stimulation. The difference in the cell number and viability was insignificant between control (US-/IL+) and LIUS-stimulated groups. While the gene expression level of aggrecan was similar between control and LIUS (50 min) group, the ratio of collagen type II to I was higher in the control. The gene expression of matrix metalloproteinase (MMP)-1 was substantially down-regulated in the stimulated construct and that of MMP-13 was comparable between control and stimulated one (Fig. 1). From the histological analysis, the cartilage matrix, glycosaminglycan (GAG) was more intensely stained with the LIUS-treated constructs. This study hints that LIUS may be a mechanically-induced chondroprotective signal for osteoarthritic cartilage.

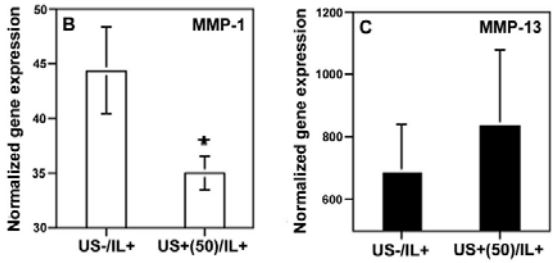

Fig. 1 Gene expression of MMP-1 and MMP-13 with or without ultrasound treatment.[2]

2.2 Ultrasound on stem cell differentiation

In this study, hypothesis is that LIUS preconditioning of MSCs in vitro can be effective in the chondrogenic differentiation of MSCs in vivo. Once rabbit MSCs were seeded onto the PGA scaffold, the PGA-MSC constructs were divided into four groups: untreated control, LIUS, transforming growth factor (TGF) and LIUS/TGF. The chondrocytes-seeded PGA construct was a positive control. For a week before implantation, LIUS group received ultrasound for 20 min daily at the intensity of 200 mW/cm^2. The TGF group was treated with 10 ng/ml TGF-β1. The samples were then implanted into the nude mouse subcutaneously for 6 weeks. Substantial size reduction and blood invasion were found much earlier in the non-LIUS groups than in the LIUS and LIUS/TGF groups. From the biochemical and mechanical analysis, the LIUS and LIUS/TGF group were significantly better in forming a hyaline cartilage-like tissue by 4 weeks than the non-LIUS groups. Presented by von Kossa staining, the development of bone matrix was highly suppressed until 4 weeks in the LIUS-treated groups (Fig. 2). In fact, before the implantation, the mRNA levels of Sox-9, aggrecan and TIMP-2 were higher in the LIUS-treated groups, while those of type I and type X collagens, and MMP-13 were stronger in the non-LIUS groups. The present results thus strongly indicated that the LIUS preconditioning in vitro could be an effective cue in up-regulating chondrogenic differentiation of MSCs in vivo.

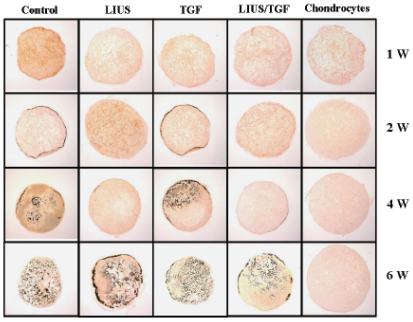

Fig. 2 Histologic features of von Kossa staining for the implanted constructs (original magnification x 10).[3]

3. Substrate Elasticity on Cell Response

It is believed that microenvironments in cell and tissue level seem to be vital in stem cell differentiation, along with the signaling molecules. Nascent MSCs can be directed to specific lineages and committed to certain phenotypes with extreme sensitivity to substrate elasticity. While soft matrices that simulate brain tissues could have a neurogenic potential, stiffer matrices that mimic muscles turned myogenic. Comparatively rigid matrices that are similar to collagenous bone were found to be osteogenic. During the initial week in culture, reprogramming of these lineages is possible with the addition of soluble growth factors, but after several weeks, the cells were reoriented and committed to the lineage specified by matrix elasticity. These results have great implications in understanding and in taking advantage of physical and mechanical aspects of in vivo

microenvironment for therapeutic uses of stem cells.

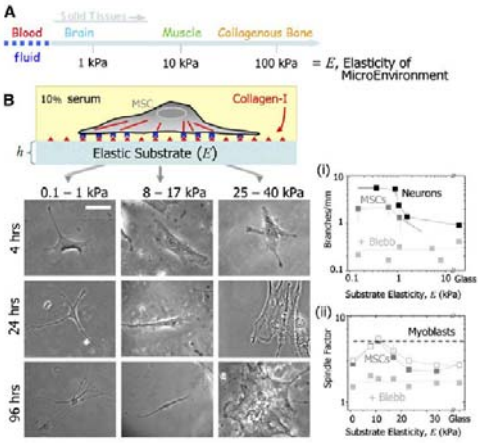

Fig. 3 Tissue elasticity and differentiation of naive MSCs.[4]

4. 결 론

It is well recognized that a mechanically-induced external signal is a critical factor in regulating cellular responses. Cell-adhesion substrates also intrinsically presented a huge potential in determining the fate of stem cells. Along with the study of traditional elements of tissue engineering, the creation of dependable tissue replacements should come with the in-depth knowledge of biomechanical principles and their applications in tissue engineering.

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