Novel Techniques in Arthritis & Bone Research
ISSN: 2575-8888

Juniper Publishers
key to the Researchers

Short Communication
Volume 1 Issue 2 – May 2017
DOI: 10.19080/NTAB.2017.01.555557

Nov Tech Arthritis Bone Res

Cartilage Tissue Engineering-A Novel Biomaterial for Cartilage Repair Generated by Self- Assembly: Creation of a Self-Organized Articular Cartilage-like Tissue

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Submission: April 25, 2017; **Published:** June 02, 2017

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Summary

For successful articular cartilage tissue engineering, three-dimensional biomaterials created in vitro by cultivation of autologous chondrocytes or mesenchymal stem cells with a collagen gel have been implanted to replace defective or degenerative parts of the articular cartilage in limited cases with joint trauma or arthritis. However, several passages of chondrocyte culture are required to obtain a sufficient number of cells for tissue engineering. Several other problems arise including dedifferentiation of chondrocytes during cell culture.

The purpose of our study is to create a novel biomaterial possessing functions and structures comparable to native hyaline articular cartilage by utilizing the physicochemical properties of the cartilage matrix components themselves, in other words, employing a self-assembly technique instead of using chondrocytes, to produce cartilage matrices eventually leading to articular cartilage tissue formation. We demonstrate that self-assembly of cartilage components including type II collagen, proteoglycan and hyaluronic acid could construct self-organized cartilage-like material, which is characterized by nano-composite structure comparable to articular cartilage and by elasticity and low friction coefficient as small as those of native cartilage.

Introduction

For the treatment of advanced joint destruction and degeneration, reconstruction of joints using new technologies such as tissue engineering are now attracting attention. Biomimetic hydroxyapatite scaffolds for bone tissue engineering have already been so well devised that they have sufficiently high affinity to the bone and enough rigidity similar to bone to be usable for the treatment of bone defects [1]. Since bone itself has superb ability of remodeling, grafted bone is replaced by the host bone tissue through self-organization over a period of several weeks to months. In contrast, materials suitable for cartilage repair still remain to be created which have perfectly cartilage-specific tissue qualities represented by properties of high elasticity and high lubrication [2,3].

Problems of Cartilage Tissue Engineering-Limitation of Cell Source

For the cartilage tissue engineering, chondrocytes are cultured in vitro in collagen or agarose gel to fabricate a three-dimensional material that can be implanted in a limited number of cases where subjects have a small posttraumatic cartilage defect of less than 3cm3 in volume [3]. Some researchers are trying to obtain cell resources for cartilage tissue engineering by induction of differentiated chondrocytes from mesenchymal stem cells derived from the bone marrow. However, using current techniques, 2~5x106 mature chondrocytes are supposed to be required to fill a 1cm3 cartilage deficit with cartilage-like tissue [2,4]. This requires continuous cell culture over several passages to obtain enough cell resources (number of cartilage cells).

Many problems therefore remain to be solved from the viewpoint of cellular resources, since cultured cells may lose properties specific to the chondrocyte and may dedifferentiate during passages in culture. Moreover, it takes several months for the tissue engineered cartilage like tissue to survive and become organized even when grafted in the defect site, since articular cartilage has less capacity for repair.

Our Novel Biomaterial for Cartilage Repair Generated by Self-Assembly-Creation of a Self-Organized Articular Cartilage-like Tissue

For the purpose of creating the articular cartilage-like tissue applicable to clinical use and overcoming the problem about "cell resource" in cartilage repair, we have been focusing on a novel biomaterial formed by self-assembly [5]. Recently, new materials and devices have been developed through self-assembling various molecules at the nanometer scale by manipulating the intermolecular relations [6].

Theory of self assembly

Molecules move randomly (Brownian motion) according to thermal motion and they may form a self-organized structure based on certain rules depending on the conditions of physicochemical properties such as inter-molecular avidity, surface modification, directions of covalent bonds, and ion arrangements.

Self assembled biomaterial for cartilage tissue engineering

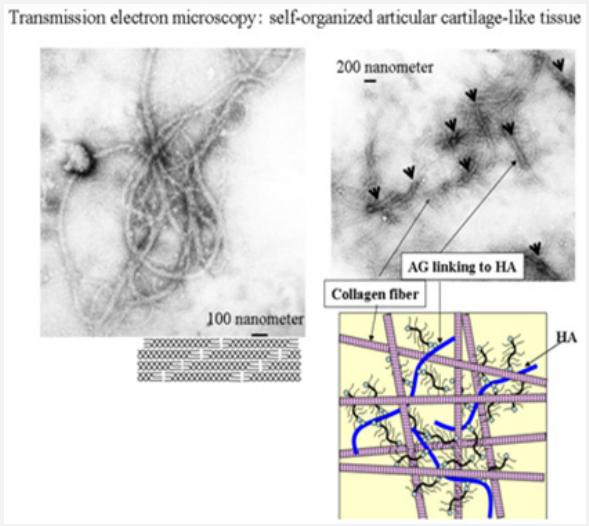

Figure 1: A self-assembled cartilage like complex from hyaluronic acid (HA), aggrecan (AG), and type II collagen.

We demonstrated that it is possible to create a novel biomaterial for cartilage repair with high performance as well as microstructures comparable to hyaline articular cartilage (Figure 1). The analysis by transmission electron microscopy showed that the self-organized collagen polysaccharide complex had a nano-composite structure in which the fibrous collagen was bound to AG linking to HA (arrow head), resembling cartilage tissue. This figure was modified from our previous study [4]. We have developed a technology for creation of cartilage-like tissue not by cultivating chondrocytes to produce cartilage tissue via cartilage matrices, but by self-assembly of the cartilage matrix components, without using cells (Figure 2). Our self assembled cartilage tissue showed high elasticity (0.5~3.0MPa).

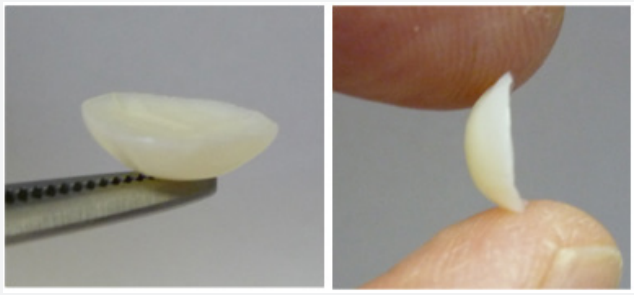

Figure 2: Self assembled cartilage like tissue with high elasticity.

Transplantation of the self-assembled cartilage like tissue into the knee joints of experimental animals

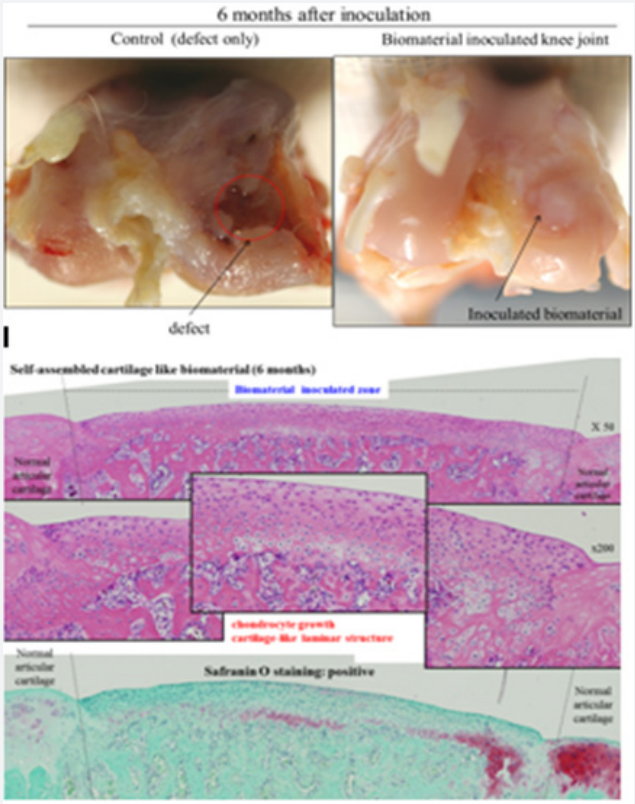

Figure 3: Representative images: transplantation of the self-assembled cartilage like tissue into the knee joints of experimental animals.

We transplanted the self-assembled cartilage-like tissue into the OA model animal, partially defecting the articular cartilage tissue of the joint, and examined histologically the transplanted tissue over time (6 weeks after transplantation). The self-organized complex was found even at 6 months to maintain the same tissue structure as was initially observed. In cartilage tissue engineering, an environment suitable for the long-term

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survival of chondrocytes is needed (Figure 3). We prepared the site of articular cartilage defect in each knee joint by drilling the surface of lateral condyle. The self-assembled biomaterial was then transplanted into the pit. As a control group, the defect was not treated. Even after 24 weeks, the transplanted self assembled cartilage tissues were maintained in the joint.

Conclusion

Our self-organized cartilage-like tissue has a nano-composite structure and is composed of components equivalent to native articular cartilage. It can, moreover, be manufactured in a short time of only a few hours. Our final goal is to develop a biomaterial most suitable for cartilage production. We emphasize the originality of this study, in which we do not need cellular resources like chondrocytes but only cartilage matrix components in order to produce cartilage-like tissue by the self-organization process.

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