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Editorial

Fish Collagen as a Scaffold

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Background

The regenerative medicine consists of three components, cell, nutrient (growth factor), and scaffold. The combinatory usage of these components is important for successful results. For the scaffold manufacturing, bioactive natural organic material such as fish collagen originated from marine products have been widely investigated because the severe inflectional problems (zoonosis); bovine spongiform encephalopathy, avian and swine influenzas, and tooth-and-mouth disease in bovine, pig, and buffalo occur all over the world still now. Although the exact examination methods for zoonosis are established for preventing infections in human, the collagen originated from species except mammalian and avian is now needed for expanding medical choices.

Biochemical and Physical Characteristics

Biochemical properties of marine collagen are different from those of mammalian collagen. Fish type I collagen is unique in its extremely high solubility in dilute acid [1,2] compared to avian and mammalian collagen. Furthermore, as the solubility of fish (tilapia) type I atelocollagen is low at 4°C and neutral pH, a higher salt concentration is necessary to solve and preserve it (unpublished data). For biochemical analyses, the strict condition for sample preservation is important and indispensable before collagen extraction. This means that the hydroxyproline content in relation to collagen stability strongly depends on these sampling procedures [3]. Amino acid composition of fish collagens is almost similar to that of mammalian collagens [4]. Glycine was the most abundant amino acid and accounted for more than 30% of all amino acids. The degree of hydroxylation of proline was calculated to be 35-48%, which was also similar level to that of the mammalian (approximately 45%) [4]. The linear relationship between collagen stability and hydroxyproline content was recognized. Furthermore, it is very interesting that the degree of hydroxylation of proline of fishes in cold sea, for example chum salmon, was reported low level (35-37%) [5,6], compared to that of fishes in relatively warm sea, which is related to the denaturation temperature (Td) of fishes. The physical and structural properties of fish (tilapia) Type I atelocollagen (TAC) were investigated and evaluated as a scaffold on a sponge form. Different concentrations {0.5%, 1.0%, and 2.0% (v/v)} of TAC solution were evaluated for the physicochemical analyses. Differential scanning calorimetry showed that the Td of fish collagen was 35-36°C. The scanning electron microscopy indicates that the pore size (90-160 μm) of TAC sponges is acceptable for cell seeding and cell proliferation. The tensile strength of porous sponges was in the range of 0.01-0.07 MPa. These findings [7] indicate that the TAC sponge prepared from tilapia skin is one of candidates as a scaffold in regenerative medicine due to its physical and structural properties. The 1.0% (v/v) concentration of fish collagen-produced form sponge is especially recommended to be advantageous for preparing and handling the solution, and for sponge formation.

Preclinical Tests

Collagen composition is well known to affect growth and cell behavior such as adhesion, proliferation, and differentiation. Especially, the RGD sequence in collagen contributes to the cell adhesion property. Compared to bovine collagen, low levels of isoleucine, leucine, hydroxylysine, and lysine in fish collagen can bring a rapid biodegradation, because these amino acids support the stiffness of collagen. This smooth biodegradation process might also accelerate tissue regeneration. The extract of fish collagen gel was examined to clarify its sterility. Furthermore, biological tests of a low concentration of fish collagen solution were conducted in accordance with the standards of the International Standards Organization (ISO). All sterility tests concerning bacteria and viruses (including endotoxin) yielded negative results, and all evaluations of cell toxicity, sensitization, chromosomal aberrations, intracutaneous reactions, acute systemic toxicity, pyrogenic reactions and hemolysis were negative according to the criteria of the ISO and the Ministry of Health, Labour and Welfare of Japan. These data [8] strongly demonstrated that atelocollagen prepared from tilapia is a promising safe biomaterial for use as a scaffold in regenerative medicine.

Biomedical Applications

Fish (tilapia) type I collagen is enzymatically and sufficiently treated to become an atelocollagen with ultra-low antigenicity. Furthermore, the antigenicity of this enzyme is also treated to the clinically safe level. We have already confirmed that the above-mentioned treated fish collagen showed no immunological rejection in a large animal experiment (unpublished data).

The scaffold functions are to a) provide structural integrity and to define a potential space for the engineered tissue, b) guide the restructuring that occurs through the proliferation of the donor cells and in-growth of the host tissue, c) maintain distances between the parenchymal cells that permit diffusion of the gas and nutrients and possibly, the in-growth of vasculature from the host bed, and d) transimit the tissue-specific mechanical forces to cue the behavior of the cells within it [9]. Based on these functions as a scaffold, the sponge form may be suitable and reasonable for the scaffold structure [10]. There are mainly three methods for injecting cells into sponge form; the injection using micropipette tip or syringe with needle, and the direct agitation of sponge and cells. Furthermore, in addition

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to transplanted cells, cell-free method has been recently receiving an attention. The new cell-free method is mediated by exsomes (extracellular vesicles), which are predominantly released from the endosomal compartment and contain a cargo that includes miRNA, mRNA, and proteins from the original cells [11]. The application of exsomes together with scaffold has a strong possibility for the future alternative, cell-free therapy including regenerative medicine.

Besides sponge form, the fish collagen is useful as a liquid solution, which is convenient for pouring into the narrow space and easily becomes a gel state for 15 minutes at 37°C. As an interesting project (principal representative: Dr. Nakashima M, Director, National Center for Geriatrics and Gerontology, Japan) using collagen scaffold for dental pulp regeneration is introduced and outlined in the end. This clinical practice is to pour three tissue engineering components (pulp stem cells, granulocyte-colony stimulating factor, and collagen solution) into the empty pulp space. After 1-2 months, the pulp regeneration occurs. Small numbers of clinical cases have been completed. Multi-institutional joint clinical research is now planning for confirm the efficacy of this method. The final role of our department in this project is to evaluate the safety and stability of an alternative biomaterial, fish collagen in place of conventional bovine collagen.

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