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Author(s)	Mredha, Md. Tariful Islam
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学 位 論 文 内 容 の 要 旨
Abstract of Doctoral Dissertation

Degree requested Doctor of Life Science Applicant name Md. Tariful Islam Mredha

学 位 論 文 題 名
Title of Doctoral Dissertation

Designing biopolymer-based hydrogels with biomimetic superstructures

（バイオミメティック超構造を有する生体高分子ゲルの創製）

Nature is an advanced school to learn biomaterial designing, where various biopolymers are found in different organized forms to regulate cellular activity and various specific bio-functions. Hydrogels, a class of soft and wet materials, are considered to be the most promising smart biomaterials due to their similarity to soft biotissues. The scope of hydrogels is often prevented due to their amorphous structure, resulting in the absence of many functions. Collagen, alginate, cellulose and chitosan are the most widely used natural biopolymers for biomedical applications. Inspired from nature, this dissertation intends to develop different kinds of biomimetic superstructures in hydrogel network based on those biopolymers.

Collagen is the main component of connective tissues and is the main abundant protein in the mammals. Marine collagen has been attracting attention as a medical material in recent times due to the low risk of pathogen infection compared to animal collagen. The author has found that, type I collagen extracted from the swim bladder of Bester sturgeon fish (a hybrid sturgeon of *Huso huso* x *Acipenser ruthenus*) has excellent characteristics such as high denaturation temperature, high solubility, low viscosity and an extremely fast rate to form large bundle of fibers under certain conditions. Those specific characteristics of swim bladder collagen (SBC) have been utilized to develop different types of superstructures in hydrogel network. The author has created stable, disk shaped hydrogels with concentric orientation of collagen fibers, for the first time, by the controlled diffusion of neutral buffer through collagen solution at room temperature. However, traditionally used animal collagens, *e.g.* calf skin collagen (CSC) and porcine skin collagen (PSC), could not form any stable and oriented structure by this method. The mechanism of the superstructure formation of SBC by this *reaction-diffusion* (RD) method has been explored. This SBC hydrogel made from marine-based atelocollagen, having a macroscopic superstructure, self-standing capability and high thermal stability, will be suitable for cell culture and other biological applications. The details of this study are discussed in chapter 2.

In chapter 3, diffusion-induced superstructure forming capability of SBC has been utilized further for the emergence of functions. The author has developed a bio-inspired novel method to create stripe pattern with long-range hierarchical structure in hydrogel network. Ordered patterns are quite ubiquitous in nature, could be found in animal, fish, birds, plants and human. Inspired by the mechanism of cell patterning in developmental biology, the author has designed a method, where mechanical signals could be transferred through *pulsatile diffusion* process in a RD system to create periodic stripe pattern in hydrogel network. The author succeeded in controlling the stripe width and gap from micrometer to millimeter length scales. This novel method has been applied universally for other bipolymeric systems, such as chitosan, carboxymethyl cellulose and alginate; however, the sensing capability of diffusion pulse depends on the main chain rigidity of polymer, which ultimately affects the superstructure patterns. These interesting materials with periodical stripe pattern could be

used to mimic the cell alignment in 3D microenvironments.

In chapter 4, the author focused on how to trigger the superstructure forming ability of SBC for designing various kinds of ordered structures in collagen hydrogels. By tuning the diffusion kinetics of buffer ions through SBC solution, the author successfully developed both concentric and radial orientation pattern and their combination at different percentages in the disc-shaped SBC hydrogels. In another study, the author has created complex twisting superstructures in cylindrical shaped SBC hydrogel by *free injection* method. The twisted plywood structure similar to the bone architecture has been generated by the combination of two mutually orthogonal effects of injection shear and salt diffusion. The author has created tough composite hydrogel using double network principle by applying a second neutral polymeric network of poly(N,N-dimethylacrylamide) (PDMAAm) into the anisotropic SBC hydrogel. This novel anisotropic composite hydrogel has anisotropic swelling behavior, high compressive stress (~7 MPa at 90% compression) and modulus (~1.43 MPa) despite the gel having ~85 wt% water.

Hydrogels with biomimetic superstructures and robust mechanical properties are extremely important for applying those materials as a replacement of soft supporting tissues, such as ligament and tendon. In those natural bio-tissues, collagen molecules secrete from fibroblasts and assembled at the molecular level in a periodic staggered array into fibrils which can subsequently arrange laterally to form dense structural hierarchies from the nanoscopic to the macroscopic length scales. In chapter 5, inspiring by nature this work proposed a facile and novel strategy for creating tendon-like hierarchical superstructures in hydrogel network. The strategy is simply the drying of physical hydrogel under confined condition. Irreversible and permanent fiber formation occurred by the contraction of aligned polymer chains in hydrogels during drying process. By applying this strategy, the author succeeded to produce perfectly aligned fibrous structures with several orders of hierarchical sub-structures in alginate hydrogel. This hydrogel shows robust mechanical properties (elastic modulus > 400 MPa and fracture stress > 20 MPa) similar to the natural load-bearing tissues (ligament and tendon). The author is also succeeded to create highly aligned fiber in cellulose and collagen hydrogel by this method. This strategy could be general for other biopolymeric hydrogels providing some critical conditions. This study would open a new avenue of materials science for designing biopolymer-based perfectly aligned fibrous hydrogel with hierarchical structures.

In brief, this dissertation has successfully designed several novel biomaterials with different kinds of biomimetic superstructures. The author has introduced a new marine collagen with excellent characteristics. The author has utilized those superior properties smartly for creating novel biomaterials with excellent functionalities. The author has developed a novel universal method for creating periodic stripe pattern with orthogonally oriented superstructures in hydrogel network. At the end, The author has introduced another novel universal method for creating perfectly aligned fibrous hydrogel with hierarchical structures. The author believes that this study will make a tremendous impact on medical science with the possibility of applying those biomimetic hydorgels for biomedical applications.