学 位 論 文 の 要 約
Summary of Doctoral Dissertation

博士の専攻分野の名称 博士（生命科学） 氏 名 趙 昱
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学 位 論 文 題 名
Title of Doctoral Dissertation

Create Tough Hydrogels Using Biopolymer
（生体高分子を含有する強靭ゲルの創成）

Hydrogels are a class of soft and wet materials. Due to the similarity to biotissues, hydrogels are drawing great attention in the field of biomedical field as biomaterials, such as extra-cellular matrix, artificial tissue and drug carrier. However, conventional hydrogels are mechanically weak, which limited their use as load-bearing biomaterials such as artificial cartilage. To solve this problem, several tough hydrogels, such as double network (DN) hydrogels(Gong et al. Adv. Mat., 2003), nanocomposite (NC) hydrogels (Haraguchi et al, Adv. Mat. 2002), and microgel-reinforced (MR) hydrogels(Hu et al, Macromolecules, 2011), have been developed in past decade. These hydrogels showed dramatically improved mechanical properties in comparison with conventional hydrogels. However, in addition to the mechanical properties, biocompatibility and/or biofunction of these hydrogels are also indispensable as biomaterial. To fulfill these requirements, biopolymers targeting of specific application and biocompatible polymers should be used as constitutes for developing tough hydrogels. Biopolymers carry a large number of charges that are closely related to the function of life. For example, the high charge density of proteoglycan (PG) produces large osmotic pressure to resist compressive load and to protect the cells in cartilage. However, the existing approaches used to synthesize the tough hydrogels are limited to specific polymers or polymer combinations and could not be applied straightforwardly to these polymers. This study aims to develop tough DN hydrogels from biopolymers and biocompatible polymers. Two types of tough hydrogels using biopolymers have been successfully developed in this work.

The first type of tough hydrogel is developed based on the molecular stent method to synthesize tough DN gels (st-DN gels). Conventional tough DN hydrogels are synthesized by two-step sequential polymerization to form polyelectrolyte as the first network and neutral polymer as the second network. This specific combination of polyelectrolyte network and neutral network limits the applicability of this DN concept to various polymer species. Recently, A molecular stent method to toughen the neutral and weak polyelectrolyte gels based DN principle has been invented (Nakajima et al, Adv. Func. Mat. 2012). By trapping linear polyelectrolyte as molecular stent in the neutral first network, this method excellently solved the problem that the first network of DN gels should be polyelectrolyte, and even the neutral network could be used as the first network. Based on this method, I designed the bio-active and tough DN gels that consist of the biocompatible, neutral polymer (PDMAAm) as the first and second networks and polyelectrolyte biopolymers (PG, HA, CS) as molecular stent. In this system, biopolymer plays two important roles. First, the biopolymers with high negative charge density give the extra osmotic pressure to increase the swelling degree of the first neutral gel. As a result, the first neutral gel becomes rigid and brittle the same as polyelectrolyte gels. Then the tough DN gels are synthesized by introducing the second network. Second, biopolymers are expected to show important biological function in the cell morphogenesis, such as mediating cell adhesion and providing filtration barrier. The obtained St-DN gels show excellent mechanical properties originated from biopolymers (Fracture stress 0.96 MPa, fracture energy 3.7 J/m^3). The St (PGs)-DN gels also show better property as scaffold for cultivation of the Human coronary artery endothelial cells (HCAECs) than conventional DN gels without PGs.

One problem of St (PGs)-DN gels is that the toughness of DN gels is based on the sacrificial bond of brittle network. The damage of the covalent bonds of the first network cannot be recovered. In this study, the second type of tough and self-recovery hydrogel is developed based on the reversible sacrificial bonds by using ionic bonds. Recently a novel class of tough and viscoelastic hydrogels from linear polyampholytes (PA) has been developed (Sun et al., Nature Mat. 2013). When equal numbers of the negative and positive charges are contained, the PA gels shrunk to a water content of 50-70 wt%, which is much less than that of conventional hydrogels, and show high toughness (fracture energy of 4000 J/m^2), 100% self-recovery, and high fatigue resistance. In this hydrogels, there are two levels of ionic bonds: the

strong ionic bonds form primary network and the weak bonds form sacrificial network. While Sun et al. used synthetic polyampholytes for PA gels, in this study I created a class of novel polyion complex gels consisting of negatively-charged biopolymer chondroitin sulphate and positively-charged poly(acryloyloxyethyltrimethylammonium chloride) (PDMAEA-Q), which are cross-linked by the ionic bond. The hydrogels have a high toughness (Fracture stress 0.66 MPa, fracture energy 2.84 J/m^3,) and self-recovery ability(90% recovery). For medical application, by changing the composition, the gels can show the anti-fouling to protein adhesion.

These tough and bio-active hydrogels using biopolymers have the potential use in medical field, such as artificial skin and cartilage. The developed methods are general and can be applied to other biopolymers, such as protein, polysaccharide, and DNA based on their polyelectrolyte nature.