Preparation of Positively and Negatively Charged Nanogels Using Oligolactide-grafted Polysaccharides and Their Polyion Complex Formation

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Introduction: Recently, self-assembled nanoparticles have been extensively studied because of their unique characteristics and the variety of application in many areas including the biomedical fields. The spherical highly swelled gel-like nanoparticles known as "Nanogel" could be prepared from graft-copolymers composed of high-molecular-weight hydrophilic main-chain and short hydrophobic side-chains[1,2]. Such nanogels have attracted growing interests over the last decade, because of their potential utility in biomedical fields such as drug delivery systems (DDS) and bio-imaging. Akiyoshi and coworkers reported hydrophobized polysaccharides that can form physically crosslinked nanogels in aqueous solution[1] and entrap both of hydrophobic and hydrophilic molecules such as proteins. We also developed biodegradable oligo(L-lactide)(OLLA)-grafted dextran (Dex-*g*-OLLA) nanogels using biodegradable OLLAs as hydrophobic side-chains (Fig. 1). In addition, we succeeded the preparation of protein-loaded Dex-*g*-OLLA nanogels using lysozyme as a model protein and found that the lysozyme-loaded nanogels showed sustained release of lysozyme for 1 week without denaturation in PBS at 37 °C[3].

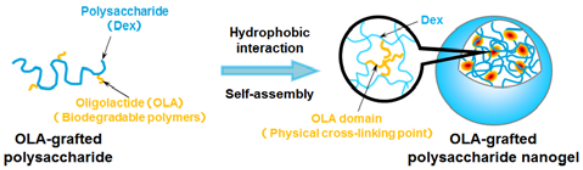

Figure 1. Schematic illustration of nanogel formation by oligo(L-lactide)-grafted dextran (Dex-*g*-OLLA).

Recently, Akiyoshi and coworkers proposed "nanogel tectonic engineering" for construction of functional hierarchical gels or interfaces through the bottom-up assembly of nanogels[4]. Hierarchical integration of individual components for controlling nanostructure is a novel strategy for construction of gel material and functional nano-/micro-soft gel interfaces. On the other hand, self-organized associations of various natural and artificial polymers by weak multiple non-covalent interactions such as electrostatic interaction, hydrogen bonding and hydrophobic interaction are of interest to develop materials for bottom-up type nanotechnology. Among them, we focused on polyion complex (PIC) formation by electrostatic interaction in polycation and polyanion. In this study, we prepared positively and negatively charged biodegradable nanogels from OLLA-grafted diethylaminoethyl dextran (DEAE-Dex-*g*-OLLA) and OLLA-grafted carboxymethyl dextran (CM-Dex-*g*-OLLA). Then, we mixed these nanogels in aqueous solution and investigated their electrostatic aggregation behavior and the properties of the aggregations (Fig. 2).

Methods: Hydroxy-terminated OLLA (OLLA-OH) was prepared according to literature. DEAE-Dex-*g*-OLLA and CM-Dex-*g*-OLLA were synthesized by the coupling reaction of DEAE-Dex (MW: 500,000) or CM-Dex (MW: 170,000) with OLLA using carbonyldiimidazole (CDI). Positively or negatively charged nanogels could be prepared by a solvent exchange method using dialysis membrane. Particle sizes and zeta potentials of the obtained nanogels were investigated on a Zeta Sizer (Malvern). After mixing of positively charged DEAE-Dex-*g*-OLLA nanogel solution and negatively charged CM-Dex-*g*-OLLA nanogel solution the aggregation behavior was monitored.

Results: DEAE-Dex-*g*-OLLA and CM-Dex-*g*-OLLA was successfully synthesized by the coupling reactions of DEAE- or CM-modified dextran with OLLA using CDI. The degree of polymerization of L-LA was 10. Average number of OLLA chains per DEAE-Dex molecule or CM-Dex molecule was was 29 or 3.7, respectively. The weight content of sugar unit for DEAE-Dex-*g*-OLLA and CM-Dex-*g*-OLLA were 92 and 97wt%, respectively. Positively charged DEAE-Dex-*g*-OLLA nanogel and negatively charged CM-Dex-*g*-OLLA nanogel could be prepared by a solvent exchange method. The sizes and zeta potentials were estimated to be about 379nm (+46.2 mV) for positively charged nanogel and 434 nm (−1.39 mV) for negatively charged nanogel.

Conclusions: In conclusions, positively charged DEAE-Dex-*g*-OLLA nanogel and negatively charged CM-Dex-*g*-OLLA nanogel could be successfully prepared. These nanogels having opposite charges could form polyion complex in aqueous solution.

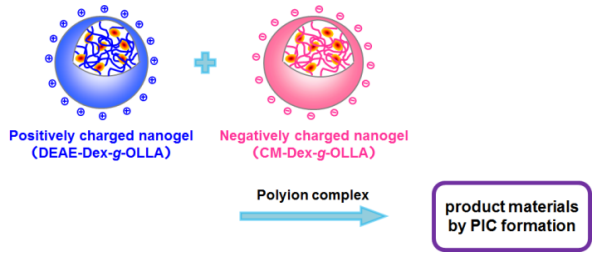

Figure 2. Schematic illustration of polyion complex formation by mixing positively charged nanogel solution and negatively charged nanogel solution.

References: (1) Akiyoshi, K. et al., Macromolecules 1993; 26:3062. (2) Nagahama K. et al., Biomacromolecules 2007; 8: 2135. (3) Nagahama, K. et al., Macromol Biosci 2008; 8: 1044. (4) Morimoto, N. et al., Biomacromolecules 2005; 6: 1829.