Polysaccharide-nanogel engineering for DDS

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Introduction: Polymer hydrogels have been widely used as functional materials in biotechnological and biomedical applications. Control of the network structure of gels and the design of hydrogels with a well-controlled nano-domain structure are still challenging problems.
We designed tailor-made functional nanogels and hydrogels for a novel polymeric drug delivery system by self-assembly of functional associating polymers. In particular, hydrophobized polysaccharides such as cholesterol-bearing pullulans(CHP) formed physically cross-linked nanogels by their self-assembly[1]. The nanogels can trap hydrophobic molecules, proteins, and nucleic acids. Therefore, they are useful for artificial chaperone [2] or polymeric nanocarriers in protein delivery and immune therapy [3], respectively.
We report here polymerizable CHP nanogels as functional cross-linkers for preparing hybrid hydrogels.

Methods: Methacryloyl group-bearing CHPs (CHPMAs) were prepared by the reaction of CHP (M_W = 1.0 x 10^5) (1.2 cholesteryl groups per 100 glucose units) with glycidyl methacrylate (GMA). The degree of substitution was 6.2 per 100 glucose units (CHPMA6). Free radical polymerizations in water were performed in the presence of CHPMA nanogels and 2-methacryloyl-oxyethyl phosphorylcholine (MPC) using VA-044 as an initiator. Acryloyl group-bearing CHP (CHPA) was synthesized by DCC-mediated condensation of CHP and acrylic acid. The degree of substitution was 28 (CHPA28). CHPA nanogel in suspension and thiol-group modified poly (ethylene glycol, PEGSH) solution were mixed at the volume ratio of 4:1.

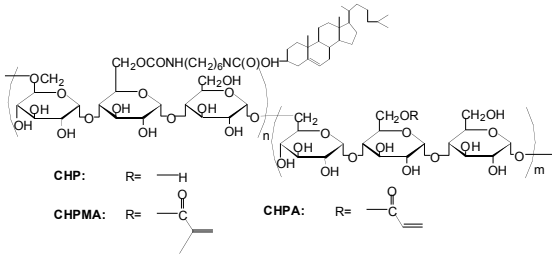

Fig.1 Structures of polymerizable CHP

Results/Discussion

CHPMAs formed nanogels (Rg 14-17nm) by self-assembly in water. The association number of CHPMA6 molecules per nanogel was 4-5 as determined by the SEC-MALS method. The numbers of methacryloyl groups per nanogel were calculated to be 170 (CHPMA6). The hybrid hydrogel was prepared by radical polymerization in water with CHPMA nanogel (10-30mg/mL) and MPC(10-30 mg/mL). CHPMA nanogels acted as effective cross-linkers for gelation [4]. TEM observation showed that the nanogel structure was retained after gelation and that the nanogels were well dispersed in the hybrid hydrogel.

FITC-insulin was spontaneously trapped in the hydrogels upon the addition of an aqueous FITC-insulin solution to swollen hybrid hydrogels. The number of trapped FITC-insulin molecules increased with an increase in the amount of CHPMA nanogel. The release profiles of the FITC-insulin from the gels were examined after the addition of 0.1 M phosphate-buffered saline to the hydrogels. Hybrid hydrogel stably kept FITC-insulin. The rate of release was less than 10% over 60 min. Moreover, circular dichroism of the released insulin from hybrid hydrogels was almost the same as that of native insulin. The hybrid hydrogels kept chaperon-like activity.

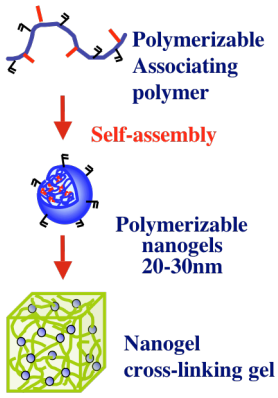

Fig.2 Nanogel engineering

We cross-linked CHPA nanogels with PEGSH to prepare a biodegradable hydrogel (CHP-PEG). CHPA molecules self-assembled to form a monodisperse nanogel with a diameter of 27 nm in water. CHPA nanogel and PEGSH were mixed in phosphate buffered saline. Galation occurred within 10 minutes when the final concentration of CHPA nanogels were 30 mg/ml in hydorgel. The nanogel structure was maintained after gelation and nanogels distributed homogeneously in the hydrogel. The hydrogel gradually swelled and degraded within 1 week in 10% serum. The CHP-PEG hydrogel delivery system was an efficient delivery system of bone anabolic agent, PGE_2[5].

Conclusions: New hybrid hydrogel with nanogel domains were prepared by polymerizable nanogel as cross linker. The immobilized nanogels retained their ability to encapsulate proteins. In addition, the trapped proteins can be released form hydrogel in an active form (chaperon like activity). Nanogel-based delivery system is expected to serve as a preferable hydrogel with the efficient drug-loading capacity for tissue engineering.

References:

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