

Nanogel-based Materials For Drug Delivery System

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INTRODUCTION: There has been interest in applying nanogels to drug delivery systems, such as protein delivery and gene delivery. In general, chemically cross-linked nanogels are synthesized by microemulsion polymerization or a cross-linking reaction of intra-associated polymer molecules. We develop tailor-made functional nanogels to create novel nanobiomaterials (nanogel engineering) by the self-assembly of functional associating polymers as building blocks¹. In particular, nanogels of cholesteryl group-bearing pullulan (CHP) selectively interact with proteins as a host and are useful as artificial molecular chaperone² and drug carriers such as cancer immune therapy³. Various stimuli-responsive nanogels such as pH, temperature and light were also obtained by the self-assembly of functional associating polymers. Macrogels with well-defined nanostructures were obtained by using these nanogels as building blocks⁴. The self-assembling method using associating polymers is an efficient and versatile technique for preparing functional nanogels and hydrogels.

We report here recent advances of nanogel engineering for drug delivery system, especially polymerizable nanogels as functional cross-linkers for preparing hybrid hydrogels with nanosize domains for application to tissue engineering.

METHODS: Methacryloyl group - bearing cholesteryl pullulan (CHP) (CHPMA) was prepared by the reaction of CHP ($M_w = 1.0 \times 10^5$) (1.2 cholesteryl groups per 100 glucose units) with glycidyl methacrylate (GMA). For example, the degree of substitution was 6.2 per 100 glucose units (CHPMA6). CHPMA6 formed nanogels (~17nm) by self-assembly in water. The association number of CHPMA6 molecules per nanogel was 4-5 by SEC-MALS. The hybrid hydrogel was prepared by radical polymerization in water with CHPMA nanogel (10-30mg/mL) and MPC (10-30mg/mL). Acryloyl-group modified CHP (CHPA) molecules, for example, which have 28 acryloyl groups per 100 anhydrous groups, self-assembled to form a relatively monodisperse nanogel with a diameter of 27 nm in water. CHPA nanogel suspension and thiol-group modified poly(ethylene glycol) (PEGSH) solution were mixed as

the molar ratio of acryloyl group to thiol group was 1:1.

RESULTS: CHPMA nanogels acted as effective cross-linkers for gelation. TEM observation showed that the nanogel structure was retained after gelation and that the nanogels were well dispersed in the hybrid hydrogel. The immobilized nanogels retained their ability to encapsulate proteins. In addition, the trapped proteins can be released from hydrogel in an active form (chaperon like activity).

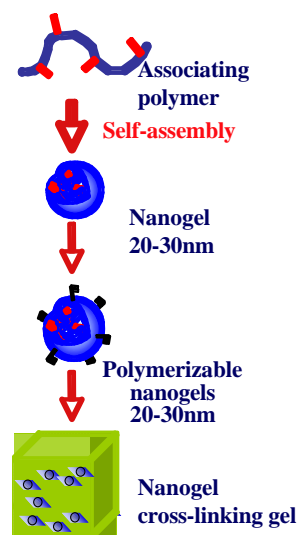


Fig.1 Nanogel engineering

CHPA nanogels were cross-linked with PEGSH to prepare a biodegradable hydrogel (CHP-PEG gel). Gelation occurred within 10 minutes when the final concentration of CHPA nanogels was 30 mg/ml in hydrogel. The nanogel structure was maintained after gelation and nanogels distributed homogeneously in the hydrogel. The CHP-PEG hydrogel was an efficient delivery system for bone anabolic agent, PGE₂⁵ and also cytokines.

DISCUSSION & CONCLUSIONS: Nanogel cross-linking hydrogel with chaperon-like activity can be used as a new hydrogel scaffold with isolated binding nanodomain (nanomatrix) of proteins or drugs for tissue engineering.

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