Biologically-active Nanostructures Derived from Functionalized Polymerization Initiators

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Introduction

Nanoscopic particulate materials present great promise for use as carriers and reporters for biomedical applications, for example as imaging contrast agents, drug delivery vessels, scavengers of toxins, etc. Although a significant amount of effort has been dedicated to the preparation and study of nanostructured materials for medical development, a key challenge toward directing the transport, delivery and clearance of these materials, i.e. their biodistribution, has not been solved. The distribution of materials in vivo is a complex process that relies upon interfacial interactions between the material and the variety of biological tissues, which requires understanding of the supramolecular and multivalent interactions at the molecular level over nanoscopic dimensions (the size of the nanostructured material) and control over the surface chemistry of the nanoscale material. Because this is a complex and dynamic process, there is much work, of fundamental and applied nature, to be done over the next many years.

One of the immediate challenges is the development of synthetic methodologies that allow for the preparation of well defined nanostructures having surface chemistry and internal structure, each of which can be controlled and modified accurately. We have focused over the past several years on shell crosslinked (SCK) polymer micelles, which are robust core-shell nanoparticles that allow for tuning of the internal core and external shell compositions and properties. In this presentation, several synthetic routes for the introduction of biologically-active surface moieties will be described, and the characterization of the materials will be detailed, from in vitro model studies to in vivo biodistributions. The development of SCKs for targeting to selective tissues will also be discussed.

Details of the Presentation

The preparation of well defined SCK nanostructured materials that present biologically-active moieties emanating from their surfaces has been accomplished by several synthetic approaches [1-5]. The focus of this presentation will be the diverse and unique synthetic approach that incorporates the biologically-active moiety at the initiator stage of the synthesis to ensure placement at a polymer chain terminus [3-5]. Supramolecular assembly and covalent crosslinking of the polymer chains then yields the SCK nanostructures.

As is illustrated in the scheme below, a functionalized initiator, in this case bearing a biotin unit, was utilized for the growth of block copolymers containing a functionalized chain terminus. In this example, atom transfer radical polymerization allowed for the polymerization subsequently of *tert*-butyl acrylate and methyl acrylate. Selective cleavage of the *tert*-butyl esters then produced the amphiphilic block copolymer having a biotin unit at the initiated chain terminus (which is at the end of the hydrophilic segment of the amphiphilic block copolymer). Assembly of mixed micelles in aqueous solution provided for control over the stoichiometry of the biotin units contained within the shell and presented from the surface of the polymer micelles. The stabilized SCKs, also presenting biotin surface groups, were then obtained by crosslinking *via* amidation of the acrylic acid residues upon reaction with diaminotriethylene glycol, promoted by the addition of a carbodiimide coupling agent. The biotinylated SCKs serve as a model system to conduct rigorous characterization of the surface accessibility and bioavailability of the functionalities [3]. Other examples, which provide for saccharide [4] or peptide functionalization [5] of the SCKs, will also be described. The peptide-functionalized initiators and polymers were produced upon a solid support, and this facilitated the rapid peptide synthesis and transformation into a peptidic-synthetic hybrid polymer structure. The motivations for each synthesis and thorough physicochemical and biological data will be discussed.

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