Amphiphilic Block Polymers based on Polypeptides as Versatile Drug Nanocarriers

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Abstract

Using polymers as drug delivery vehicles can increase the solubility of drug molecules, making it possible to deliver them systemically, can decrease generalized toxicity effects and provide enhanced circulation and residence times, and improve targeting within the body. Polymer-drug conjugates have demonstrated excellent potential in this regard, with several now in the marketplace or clinical trials as treatments for cancer and other medical conditions [1]. A step further into the development of the next generation of polymer conjugates for biomedical applications will be the design of self-assembled and multifunctional architectures from amphiphilic block copolymer conjugates which would provide several benefits over the use of single polymers [2,3]: (i) First of all, passive targeting (EPR effect) will be achieved since most of the self-assembled nanocarriers (micelles, vesicles) can be designed in the size range of 10 to 200 nm without compromising the biocompatibility/biodegradability due to the smaller nature of their self-assembling components; (ii) A modular and multifunctional architecture will allow to introduce in the design active targeting moieties, therapeutics, imaging probes, stimuli responsive cross-linkers, etc....; (iii) pharmacokinetics might be modulated through an additional trigger (aside from the cleavable conjugation bonds): the disassembly of the nanocarriers in response to physiological inputs (temperature, redox, pH, enzymes, ionic strength...); (iv) hybrid nanostructures might help to move the concept of combination therapy towards more sophisticated and tailored polymer therapeutics[4]. A number of new architectures based on poly-L-glutamic acid (PGA), Poly-L-leucine (PLeu) and Polyethylene glycol (PEG) including diblock and triblock (block and random) systems have been obtained by means of the ring opening polymerisation of the γ-benzyl-L-glutamic acid and L-Leucine N-Carboxyanhydrides (NCA) by nucleophilic PEG initiators [5]. Additionally, we have modified the PGA moieties introducing stimuli bioresponsive cross-linkers such as thiols and therefore providing a versatile platform for drug delivery. Preliminary characterizations of these systems through Dynamic Light Scattering, NMR-Diffusion Ordered Spectroscopy (DOSY), Transmission Electron Microscopy (TEM) and Fluorescence have shown the adjustable critical micelle concentration and size of the assembled micelles through the molecular architecture. Moreover, thiol-functionalized triblock copolymers have been designed for the encapsulation of a model hydrophobic drug and its release under reductive environment has been tested as a proof of concept.

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