Materials designs toward macrophage- and dendritic cell-targeted immunotherapeutics

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Statement of Purpose: Polymeric nanoparticles hold tremendous potential in medicine, especially if modes of biofunctionality can be incorporated into them. Here we consider different kinds of biofunctionality, focused on applications in macrophage- and dendritic cell-targeted immunotherapeutics. We consider functionality in pathways for degradation, in physiological routes of penetration of biological barriers for delivery, and in activation of dendritic cells for induction of adaptive immune responses.

Our laboratory has recently described a novel family of AB and ABA block copolymeric amphiphiles that are capable of forming micelles and vesicles [1, 2], as well as inverse emulsion-polymerized nanoparticles based on the B block using Pluronic emulsifiers [3, 4]. As a hydrophilic block A, we employ polyethylene glycol (PEG), because of its well known toxicological profile and its well-defined and low polydispersity. As a hydrophobic block, we have selected polypropylene sulfide (PPS), a low Tg polymer that can be synthesized by a ring opening living polymerization also with low polydispersity [5]. We have demonstrated that these polymers form mesoscopic aggregates that are sensitive to oxidative environments by conversion of the hydrophobic PPS to the hydrophilic polypropylene sulfone [2]; this provides a route of degradation of the micelle-forming amphiphile into a fully soluble low molecular weight polymer, sufficiently small for clearance by renal filtration. We have also sought to render these same structures sensitive to reduction, to allow destabilization of vesicles within the early endosome after endocytosis by linking the two blocks with a reduction-sensitive disulfide [6], for use in intracellular delivery, for example of adjuvant molecules targeting intracellular receptors (such as CpG DNA), antigens for targeted MHC 1 presentation, or antigen-encoding DNA. Thus, the redox sensitivity of these materials can be used to enable release of incorporated agents and ultimate elimination of the micelle-forming polymer.

With the micelle-forming AB and ABA block copolymers as well as the analogous materials formed by inverse emulsion polymerization of propylene sulfide using Pluronics as emulsifier, we are seeking nanoparticle forms that are sufficiently small as to pass barriers to efficiently access the targeted antigen-presenting cells. Of particular interest to us, is targeting dendritic cells resident in the lymph nodes after intradermal or subcutaneous injection [7]. We have shown that ultrasmall particles, ca. 25 nm, can target lymph node-resident dendritic cells very efficiently, being swept through the tissue interstitium by the slow flows that exist between the blood and lymphatic capillaries in the skin. Also with such small nanoparticles, we see very effective penetration of mucosal barriers in the nasal sinus and very efficient uptake by antigen presenting cells in the lung after instillation in the mouse.

Finally, we seek to be able to incorporate biofunctionality into these nanoparticles for activation of antigen presenting cells. In a first approach, we designed the nanoparticle surface for activation of complement by the alternative pathway, and we demonstrated that complement activation could serve as a very potent, particle-mediated danger signal for dendritic cell activation in situ [8]. Current work focuses on incorporation of additional danger signal molecules into the nanoparticle formulation, including engineered flagellin truncation variants, and CpG sequences incorporated into DNA encoding antigen to which an immune response is desired. For the latter, ABC block copolymers have been formed, of PEG and PPS as the A and B blocks respectively, and of linear polyethylene imine (PEI) as the C block, connected to the AB block copolymer by a reducible disulfide bond. These block copolymers can form polymer micelles that are also very small and capable of transfecting dendritic cells *in situ*. Finally, we have sought to incorporate small molecule immunomodulatory molecules, both adjuvants and immunosuppressants, into the hydrophobic domains within the micelle cores [9].

References:

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