Acta Biomaterialia 8 (2012) 3210–3217

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Polymer micelles with pyridyl disulfide-coupled antigen travel through lymphatics and show enhanced cellular responses following immunization

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ARTICLE INFO

Article history:
Received 29 February 2012
Received in revised form 3 May 2012
Accepted 6 June 2012
Available online 12 June 2012

Keywords:
Micelle
Self-assembly
Copolymer
Nanoparticle
Immunostimulation

ABSTRACT

Poly(ethylene glycol)-stabilized poly(propylene sulfide) core (PEG-PPS) nanoparticles (NPs) smaller than 50 nm efficiently travel to draining lymph nodes and interact with antigen-presenting cells (APCs) to induce potent immune responses following intradermal immunization. To determine if a similar system could be developed that could be more easily and reproducibly prepared and eliminated faster in vivo, we created block copolymers of PEG-bl-PPS capable of self-assembling into 25–35 nm micelles (MCs). Biodistribution studies showed that these MCs were able to travel to draining lymph nodes, where they preferentially interacted with APCs. To couple cysteine-containing antigens to the surface of the MCs, a new polymer was synthesized with a terminal pyridyl disulfide (PDS), forming PDS-PEG-bl-PPS-benzyl. When mice were immunized in conjunction with free CpG as an adjuvant, ovalbumin-conjugated MCs (MC-Ova) generated more (2.4-fold) Ova-specific $CD8^+$ T cells in the blood and higher (1.7-fold) interferon-gamma levels from splenocytes upon restimulation than in mice immunized with free Ova and CpG. When comparing this MC platform to our PEG-PPS NPs with disulfide-linked Ova, no significant differences were found in the measured responses. These results indicate that PDS-functionalized MCs are efficient antigen delivery vehicles that enhance immune responses compared to immunization with free protein.

1. Introduction

The ideal prophylactic vaccine uses the smallest amount of antigen possible to induce an appropriate, strong and long-lasting immune response without harmful side effects to the recipient. For the past 200 years, vaccination has primarily relied on simulating infection using attenuated or highly homologous pathogens to provide this protection. Such a strategy has shown only modest performance, though, against pathogens that are highly infectious, are difficult to culture outside of a host or expose few antigens for the immune system to recognize. As an alternative, subunit vaccines using isolated recombinant protein or synthetic peptide antigens delivered with an adjuvant have been pursued. These have also been shown to have shortcomings in terms of the number and type of pathogens against which they can protect. Therefore, a new strategy is necessary to enhance the host response to prevent diseases like malaria and dengue fever, which have not yet benefited from the protection of a vaccine [1].

One such strategy has been to target the most potent antigen-presenting cells (APCs) – dendritic cells (DCs) – using antibodies, special delivery techniques or ex vivo stimulation [2–4]. These strategies also require the DCs to be activated, usually by a pattern-recognition receptor (PRR) agonist, in order to initiate the immune response [5,6]. To maximize the effect of targeting in vivo, different conjugation and encapsulation strategies have been used to combine DC targeting with danger signal and antigen delivery [7,8].

Polymeric delivery systems offer advantages for vaccine design due to their flexibility in chemical and biological properties, as well as ease of manufacture. We have recently described a nanoparticle (NP) system composed of a poly(propylene sulfide) (PPS) cross-linked core with a poly(ethylene glycol) (PEG) corona, provided by using Pluronic F127 as an emulsifier, capable of targeting APCs within draining lymph nodes in a size-dependent manner [3]. These particles have also been functionalized on the PEG corona with pyridyl disulfide (PDS) groups to allow for antigen conjugation by disulfide bonding [9]. Depending on their surface

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http://dx.doi.org/10.1016/j.actbio.2012.06.007