Chapter 11
Applications of Nanomaterials for Activation and Suppression of Immune Responses

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ABSTRACT

Evaluation of immuno-modulating properties of nanomaterials is important to develop new potential therapeutics for inflammatory diseases and cancer. Activation and suppressive effects of nanomaterials on immune responses occur through various interactions with different host proteins. They can also be engineered as carriers and/or adjuvants for different proteins or antigens. Particles, emulsions, and tubes/rods are the major formats of nanomaterials currently used in biomedical applications. Sometimes, nanomaterials induce side effects like undesired immunosuppression and toxicities, which are major concerns at present in designing optimal nanotherapeutics. This chapter summarizes different types of nanomaterials and their effect on immune responses.

INTRODUCTION

Nanomaterials comprise of small substances in the size range < 100 nm. Due to their smaller size they possess unique mechanical, functional, electrical and magnetic properties (Tao Gao, 2005). They could be made from different types of materials including metals, ceramics and polymers into various forms such as nanotubes, nanoparticles, nanoemulsions, nanoliposomes and quantum dots (Aitken et al., 2006). Low doses, site specificity and modifiable characteristics make them versatile materials for robust applications in medicine like drug delivery, cancer therapy, magnetic resonance imaging and in the delivery of antigens/immunogens (Lonkar & Dedon, 2011). In this context, fluorescent nanoprobe was used as a biomarker for detecting increased vascular permeability in cancer and arthritis disease models (Sandanaraj et al., 2010). Nanoparticle based delivery of biomolecules offers more advantages of sustained delivery for longer period of time with improved *in vivo* stability and minimum side effects over conventional methods. Generally, these materials come in contact with antigen presenting cells (APCs), for example macrophages and modulate

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the immune responses in both directions. Either, they can activate the immune responses with weak vaccines/antigens or suppress an undesirable immune response such as inflammation, autoimmune disorders or graft rejection (Dobrovolskaia & McNeil, 2007; Banu S. Zolnik, 2010).

BACKGROUND

Nanomaterials could be from either natural or designed synthetic materials for specific targeting of particular tissues. Hence, it is important to investigate the interactions between materials and the immune system to understand their mode of action and the underlying cellular pathways. As we know that our immune system protects us from entry of pathogenic microbes or substances. Sometimes, immune cells recognize nanomaterials as foreign and thus multi-level immune responses might be generated against them causing toxic reactions (Nel et al., 2006) . For example, localized toxicity in the form of granuloma formation was observed in various organs of animals exposed to nanotubes (Poland et al., 2008). Therefore, materials that are recognized as self are important for the delivery of drug/antigen/genetic elements. It has been well established that chemical nature, size and charge of the nanomaterials could determine the compatibility with the immune system (Dobrovolskaia et al., 2008; Aggarwal et al., 2009). For example, coating of polyethylene glycol (PEG) over nanoparticles could potentially reduce the immune system recognition due to hydrophilic nature of PEG (Moghimi, 2002). However, anti-PEG antibodies were detected after the administration of PEG coated liposomes (Ishida et al., 2007) that could potentially increase the clearance of PEG coated nanoparticles from circulation (Ishida et al., 2006). Therefore, generation of particle-specific immune responses could reduce the therapeutic potential of the delivered biomolecules. On the other hand, nanomaterials could be engineered specifically either for the stimulation of antigen presenting cells (APCs) or for direct delivery of antigens to specific cells/tissues.

Nanomaterials are delivered inside the body through various routes viz., nasal, oral, subcutaneous or by circulatory route (a common method of delivery of nanomaterials). Interestingly, based on the charge and route of delivery, nanoparticles have differential effect on the elicited immune responses (Keijzer et al., 2011). These materials are generally cleared from the body by different mechanisms including endocytosis, cell membrane penetration and direct transportation through cell membrane channels (Garnett & Kallinteri, 2006). Changing the surface properties of nanomaterials alters their interactions with blood proteins and cells (Stevens & George, 2005). Therefore, interactions of nanomaterials with blood proteins is an important parameter for determining their distribution inside the body and their half-life (Dobrovolskaia & McNeil, 2007; Smith et al., 2013). Nanomaterials whose surfaces are compatible for binding of plasma proteins such as opsonins are phagocytosed by macrophages and thereby rapidly cleared from the blood. Albumin, apolipoproteins, immunoglobulins, complement and fibrinogen are the common plasma proteins, which can bind with nanomaterials like metal particles, liposomes and carbon nanotubes. Moreover, binding of plasma proteins depends on the particle composition, surface morphology and the method of synthesis (Dobrovolskaia & McNeil, 2007). Among them, surface characteristics mainly decide the binding of plasma proteins to nanomaterials (Gessner et al., 2002; Xu & Du, 2003; Smith et al., 2013). For example, PEG nanoparticles showed less binding of plasma proteins that decreased due to the difference in surface charge (Aggarwal et al., 2009). Therefore, more studies are required to sort out these important characteristic features. Other potential interactions of nanomaterials could be with blood cells such as RBCs and platelets, main players in the cascade of blood coagulation. For example *in vitro* polyvinyl chloride (PVC) nanoparticles were shown to enhance human

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