



# Immune responses to engineered nanomaterials: Current understanding and challenges

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## Abstract

Engineered nanomaterials (ENM) are utilized in many applications due to their unique physicochemical properties. The increasing use of ENMs in consumer products raises concerns of potential adverse effects in humans and the environment. A common outcome of exposure (intentional, environmental or occupational) to ENMs is altered immune responses including inflammation, hypersensitivity, and immunosuppression. ENMs have been shown to interact with the immune system through key effector cells (*i.e.* mast cells and antigen presenting cells) or via complement activation leading to consequences to both innate and adaptive immunity. Further, upon introduction into a biological system, ENMs are rapidly coated with proteins, lipids and other macromolecules forming a biocorona which impacts immune cell and complement responses. In this current opinion, we highlight key studies and challenges in understanding cellular mechanisms of ENM-mediated immunomodulation and toxicity.

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## Keywords

Nanoparticles, Nanotoxicology, Immunomodulation, Immune activation, Immune suppression.

## 1. Introduction

Engineered nanomaterials (ENM) are materials with at least one dimension in the range of 1–100 nm. Due to their small size, large surface area, and in comparison to their bulk counterparts, ENMs possess unique physicochemical properties making them useful in a wide range of applications [1]. Advancements in physics, chemistry and material sciences has led to promotion of nanotechnology with a theoretically unlimited number of ENMs and applications ranging from electronics and catalysts to biosensors and drug delivery. There are diverse types of ENMs based on their composition

including carbon-based, metals, metal oxides, polymers, lipid-, and protein-based. For instance, carbon nanotubes are utilized for their mechanical strength and light weight while silver, gold and iron ENMs are widely utilized for their antimicrobial, optical, and magnetic properties, respectively. The number of consumer products that utilize ENMs is also exponentially increasing [2]. This raises concerns regarding potential human exposure and associated adverse effects of ENMs on human health and the environment. In general, various endpoints of toxicity have been demonstrated following exposure to a wide range of ENMs including formation of reactive oxygen species (ROS), disruption of mitochondrial respiration, induction of apoptosis, lipid peroxidation and DNA damage, however, specific molecular mechanisms are largely lacking [3]. Nonetheless, a common theme arising from many toxicological studies of ENM exposure is immunotoxicity including but not limited to inflammation and immunomodulation.

The immune system is one of the most important systems that can dictate toxicological and pathological consequences following exposure to ENMs (*e.g.* tissue accumulation *vs.* clearance). Importantly, the majority of immune responses to ENMs are largely due to their unique physicochemical properties such as size, surface coating/charge and shape. For instance, it has been demonstrated that ENM size influences uptake and activation of antigen presenting cells (APC), such as dendritic cells and macrophages, as well as nanoparticle trafficking to draining lymph nodes and subsequent T-cell responses [4–6]. Surface charge is another key factor which enhances cell membrane interaction, uptake and subsequent immune cell activation [7]. ENM shape has also been shown to influence internalization by cells with high aspect ratio ENMs being associated with higher toxicity due to frustrated phagocytosis in macrophages [7,8]. Understanding such physicochemical property-mediated changes in immunological responses remains a challenge and is of critical importance for future nanomedicine applications.

To date, the majority of studies examining ENM immunomodulation have demonstrated immune activation, however, an increasing number of studies are beginning to establish ENM mediated immunosuppression as an outcome. In both cases, exposure could be either intentional (*e.g.* medical application) or unintentional (*e.g.* consumer, environmental or occupational)

[9]. Further, activation of the immune system by ENMs could be beneficial and is being pursued in areas such as cancer therapy and vaccination or could be detrimental such as in autoimmune disorders and tissue remodeling. In this current opinion, we highlight key findings of cellular and molecular mechanisms of ENM-induced immunostimulatory and immunosuppressive properties (Fig. 1).

## 2. ENM-induced immune activation

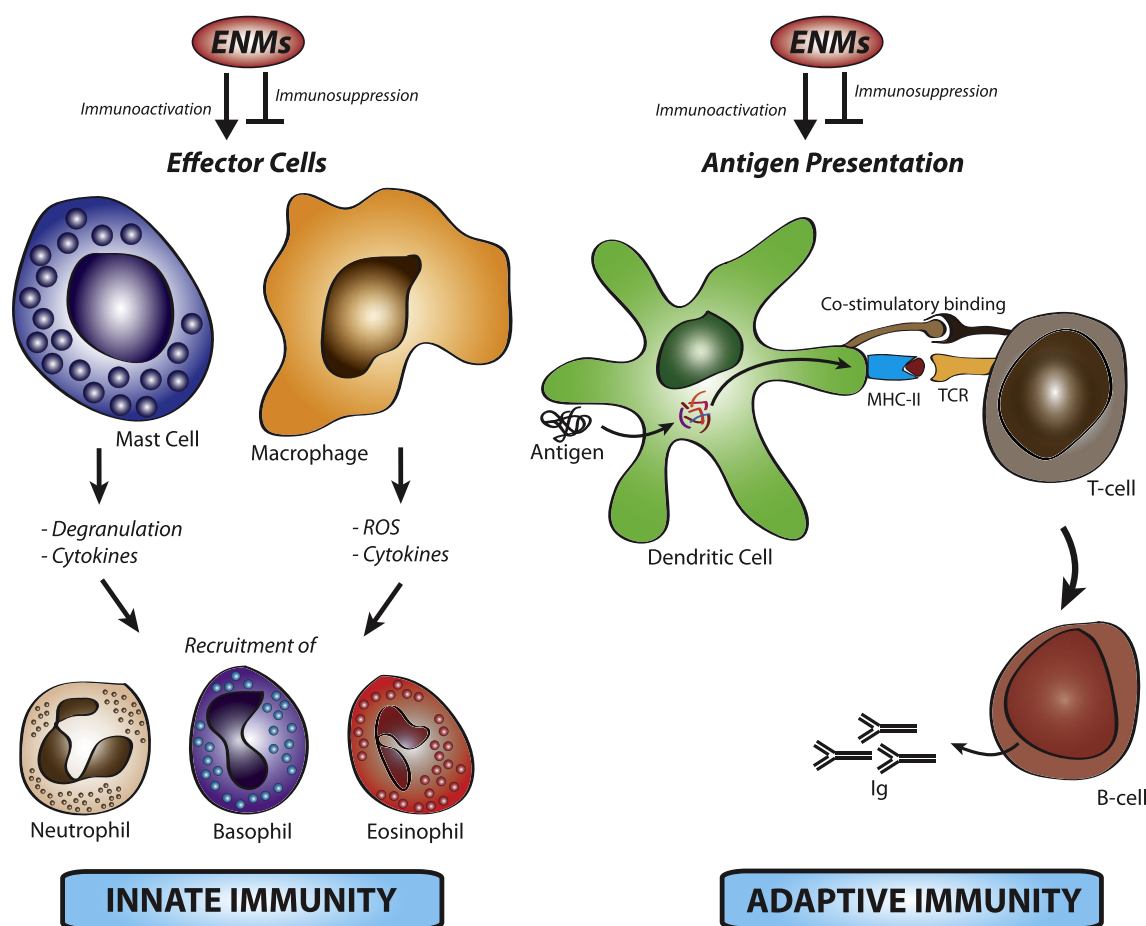
The majority of work regarding ENM-induced immunomodulation is focused on the activation of key immune cells such as macrophages, subsequent cellular inflammatory responses and toxicity. In this section, we discuss the role of complement activation, the inflammatory response in ENM-mediated immunomodulation and the impact of ENM immunomodulatory properties

on hypersensitivity immune reactions and adaptive immunity.

### 2.1. Complement activation

The complement system is an important part of the innate immune system in fighting pathogens. The complement system is composed of more than 30 plasma proteins that interact with each other in a cascade manner, leading to opsonization, lysis, release of chemotactic molecules and anaphylatoxins. ENMs have been shown to activate the complement system through the classical, alternative and lectin pathways with the prime consequence being surface opsonization, which subsequently leads to particle clearance by the reticuloendothelial system [10]. Importantly, several clinically approved ENM formulations (mostly liposomes and micelles) have been shown to activate complement

Fig. 1



**Potential direct mechanisms of engineered nanomaterial-induced immunomodulation.** Engineered nanomaterials (ENM) can activate or suppress immune responses through direct interaction with effector immune cells such as macrophages and mast cells leading to their activation and subsequent recruitment of other effector immune cells such as neutrophils. ENMs can also modulate immune responses through direct interaction with antigen presenting cells such as dendritic cells, which could affect their function toward an adaptive immune activation or suppression.

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