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Engineered Nanomaterial Exposure and the Risk of Allergic Disease

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Abstract

Purpose of review—Although the production and use of engineered nanomaterials (ENM) is rapidly increasing, we lack sufficient knowledge regarding their capacity to induce and/or promote allergic disease. As novel ENMs are being developed and used for biomedical applications, such as drug delivery, it will be critical to understand the relationship between physicochemical properties of ENMs and possible mechanisms of immunomodulation.

Recent findings—Cellular studies and a few animal studies have begun to examine the immunomodulatory effects of ENM exposure that may be predictive of developing allergic reactions. Specifically, the effects of direct ENM exposure on key immune cells recognized to facilitate allergic disease has been evaluated and will be discussed. However, few studies have reported specific physicochemical properties of ENMs that initiate allergic immune responses. Although limited, these descriptive studies point to the induction of cellular mechanisms that are well known to promote allergic disease.

Summary—The limited data currently available suggests that there is a potential risk for development of allergic responses following exposure to ENMs. As more ENMs are developed for consumer products and nanomedicines, further study on their potential for adverse immune interactions will be necessary for safe implementation of these novel materials.

Keywords

Nanoparticle; Mast Cell; Dendritic Cell; IgE; T cell

INTRODUCTION

Engineered nanomaterials (ENM) possess a high degree of functionality based on their unique physicochemical properties. These ENMs can be synthesized to have diverse chemical composition, shape, electrothermal conductance, solubility, and can be extensively modified by the addition of various surface groups. Based on these properties, ENMs have an extraordinary number of applications including their use as drug delivery systems,

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CONFLICTS OF INTEREST

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incorporation in many consumer products, and multiple uses in manufacturing processes. Types of ENMs currently being utilized can be broadly classified as carbon-based, metal, or metal oxides. As the usage of ENMs has increased so has concerns regarding their safety. Accidental exposure to ENMs may occur during manufacturing and processing in occupational settings while intentional exposure will occur during the use of nanomedicines or consumer products such as cosmetics. Considerable research in animal models has demonstrated negative cardiopulmonary health effects of ENMs, however, less consideration has been given to specific interactions with the immune system, while even less information exists on the potential of these materials to initiate or exacerbate allergic disease. Due to unique interactions with the immune system and the potential for these materials to act as adjuvants it is likely that ENMs may initiate or promote the development of allergic disease. Much of the concern regarding ENM safety has been based upon data demonstrating that an ENM may be more toxic than larger particles of the same chemical composition due to their increased reactivity, surface area, particle number on a mass basis, and altered deposition profile. The same unique properties that make ENMs useful for numerous applications also may specifically result in novel immune interactions resulting in the development or exacerbation of various allergic diseases such as asthma, dermatitis, rhinitis, and others. For example clinical trials evaluating Ferraheme, a polyglucose sorbitol carboxymethylether coated super-paramagnetic iron oxide nanoparticle, for the treatment of iron deficiency anemia in adult patients with chronic kidney disease demonstrated hypersensitivity reactions as a major safety concern (1). To evaluate the likelihood of an ENM contributing to allergic disease, we assessed publications from the last 3 years which focused on ENMs that are currently or proposed to be utilized as nanomedicines and/or where exposures may occur in occupational settings. Further, the literature search assessed cells well known to mediate allergic disease (e.g. basophils, mast cells, dendritic cells and T cells).

IS THERE A RELATIONSHIP BETWEEN ENM PHYSICOCHEMICAL PROPERTIES AND ALLERGIC DISEASE?

Nanomaterials have a vast array of physicochemical properties, which can be modified for specific applications. These properties include size, surface charge, shape, surface modifications, magnetism, and electrical and thermal conductivity. These diverse modifiable properties influence ENM interactions with the immune system. For example size is an easily altered property that has been shown to alter dendritic cell uptake and antigen presentation both *in vitro* and *in vivo* (2). Specifically, 40 nm nanoparticles were determined to migrate to lymph nodes and be taken up more efficiently by dendritic cells compared to larger size particles. Further, the 40 nm nanoparticles were found to activate dendritic cells suggesting that size is a modifiable characteristic of ENM that can be manipulated for variations in antigen delivery. Preliminary data from our laboratory has also demonstrated the importance of size, as 20 nm silver nanoparticles were found to induce mast cell degranulation *in vitro* whereas silver nanoparticles of 110 nm size did not elicit a mast cell response (unpublished data). Surface coatings also modulate immune cell responses as demonstrated by coating of superparamagnetic iron oxide nanoparticles with polylysine leading to enhanced uptake of these nanoparticles by dendritic cells *in vitro* (3). To date, few

studies have systematically evaluated physicochemical properties of ENMs that are responsible for immune cell activation and toxicity, which may lead to the development or exacerbation of allergic disease.

ENM-IMMUNE CELL INTERACTIONS

The immune system is comprised of a variety of effector cells and molecules whose interactions with ENM must be understood for risk assessment of these unique materials and their potential health effects. Due to their position at physiological-environmental interfaces and their role in eliminating pathogens and foreign substances it is likely that immune cells will interact with ENMs and that they will facilitate biological responses. Specifically, ENMs may facilitate allergic disease via an IgE-dependent response and/or interactions with mast cells, basophils, dendritic cells and T cells.

IgE is a key mediator of allergic disease by which mast cells and basophils are primed to respond to allergens. A few studies in animal models have begun to identify changes in IgE levels associated with ENM exposure. For example, utilizing a mouse model of atopic dermatitis, Hirai *et al* demonstrated that injections of amorphous silica nanoparticles significantly increased plasma levels of IgE, inflammatory cell infiltration, and ear thickness in a nanoparticle size dependent manner with the smallest nanoparticles initiating the greatest effect (4). Oral administration of silver nanoparticles to mice has also been shown to induce an increase in circulating inflammatory cytokines and IgE levels demonstrating that different routes of exposure may facilitate allergic responses (5). These findings demonstrate that sENMs may exacerbate an underlying allergic condition through increases in circulating IgE levels. These studies reported increases in non-specific IgE levels, however, there is currently a lack of understanding regarding the production of allergen specific IgE following ENM exposure. Lastly, these findings show that physicochemical properties such as size may play a role in the allergic response to ENMs therefore suggesting unique immune-interactions of materials at the nanoscale.

Mast cells populate tissues that are exposed to the external environment and coordinate immune responses through the synthesis and release of a variety of mediators. Mast cells are well recognized for their role in facilitating allergic responses in many disease conditions through allergen crosslinking of the high affinity IgE receptor (FcεRI) and subsequent release of histamine and a multitude of inflammatory mediators. Due to their location and immune regulatory role, mast cells may represent a key off-target cell type that could contribute significantly to allergic immune responses following ENM exposure. Despite their propensity to influence a number of physiological systems, there have been only a few reports of ENM activating mast cells. Titanium dioxide (TiO₂) nanoparticle exposure has been demonstrated to activate L-type Ca²⁺ channels on the membranes of mast cells *in vitro* which could exacerbate allergic inflammatory responses by enhancing degranulation with or without IgE sensitization (6). Cerium oxide (CeO₂) nanoparticles have also been shown to activate mast cells *in vitro* resulting in the release of a variety of inflammatory cytokines including TNF-α, IL-6, and osteopontin (7). Several studies have also described the direct activation of mast cells *in vitro* by various metal oxide nanoparticles (8–10). While not highly phagocytic, *in vitro* studies of mast cells have been shown internalization of SiO₂ and

TiO₂ resulting in a reduction in degranulation possibly through interference of intracellular signaling (11, 12). In contrast, the unique physicochemical properties of ENMs could be utilized for treatment of allergic disease. For example, C60 fullerene, a spherical ENM comprised of 60 carbon atoms, has been shown to inhibit mast cell mediated anaphylaxis in mice due to their antioxidant capabilities (13). Although the number of studies is somewhat limited, nanoparticles possess an ability to directly interact with mast cells thus supporting the need for further investigation on mast cell responses to ENMs.

Due to their relatively low abundance in circulation, basophils are an underappreciated immune cell that has a tremendous capacity for promoting the Th2 immune response (14). Despite this, there is a significant lack of studies investigating their possible response to ENM exposure. Since many nanomedicines are being developed for intravenous delivery, there exists a real possibility that basophil activation could lead to unwanted immune consequences. To date, the few studies that have examined basophil response have targeted basophils to inhibit allergic responses. For example, C60 fullerene *in vitro* and fullerene derivatives *in vitro* and *in vivo* have been shown to inhibit FcεRI mediated basophil degranulation and cytokine production (13, 15). Further, it has been proposed based on *in vitro* assessments that ENMs coated with antibodies for sialic acid immunoglobulin-like lectins, which are present on the surface of basophils, eosinophils, and mast cells could be utilized to inhibit their degranulation and allergic effects (16). While certain ENMs have shown potential for therapeutic benefit by inhibiting basophil activity it is likely that due to the vast number and diversity of ENMs being developed that some of these materials will adversely stimulate basophil responses. Stimulation of basophils would likely propagate Th2 responses resulting in an exacerbation of underlying allergic conditions.

Dendritic cells function by capturing and presenting antigen thus bridging the innate and adaptive immune system. Their ability to capture antigen makes them a likely target in the uptake of ENMs while their strong antigen presenting capability makes these cells a likely target for either immunosuppression or stimulation leading to immunomodulation. In fact, most studies of dendritic cells have focused on enhancing vaccine responses through the use of various nanoparticle formations (17–19). However, the same properties of nanomaterials that enhance vaccine responses may also pose a challenge to nanomedicines where the intended result is likely not immune stimulation. A number of studies have demonstrated the ability of dendritic cells to phagocytose ENMs. For example, a recent study of gold nanoparticles has shown that 18% of particles that reach the spleen in a mouse model are taken up by dendritic cells (20). In an *in vitro* assessment of quantum dot uptake it was shown that differentiation of monocytes to dendritic cells significantly increased cellular uptake six-fold (21). These findings demonstrate that the dendritic cell may be a site of nanoparticle accumulation, which could be used therapeutically, but also may pose some additional challenges to the safe use of nanotechnology.

Multi-walled carbon nanotubes have been shown to have immunomodulatory activity by decreasing the capacity of peripheral blood monocytes collected from human subjects to differentiate into functional dendritic cells (22). These findings suggest that exposure to ENMs may cause cytotoxicity to dendritic cells and it is likely that they may be immunosuppressive though inhibiting monocyte differentiation. These ENM-induced

changes in dendritic cell immune response and cytotoxicity are probably related to internalization of ENMs and intracellular alterations in cell signaling and induction of apoptotic pathways. Most importantly, a few studies have found that treatment of dendritic cells with ENMs is immunomodulatory. Schanen et al. 2013 demonstrated that exposure of dendritic cells to CeO₂ nanoparticles caused a Th2 type response from T cells following antigen presentation as demonstrated by increased cytokine production of IL-4, IL-5, and IL-10 (23), while exposure of dendritic cells to TiO₂ nanoparticles was found to elicit a Th1 type response as demonstrated by increased cytokine production of IL-2, IFN- γ , and TNF- α . Taken together, exposure to ENMs alters dendritic cell function, which may lead to downstream effects on the immune system such as impairment or stimulation of T cell proliferation and activation.

An *in vitro* evaluation of the toxicity induced by different porous silicon nanoparticles across multiple cell types including T cells, monocytes, macrophages, and B cells demonstrated that T cells were the most sensitive (24). Specifically, T cells demonstrated increased morphological changes, ATP depletion, and decreased proliferation compared to other cell types following exposure. An *in vitro* examination of T cell responses to cobalt nanoparticles demonstrated DNA damage, oxidative stress, and cytotoxicity following exposure. These findings suggest that direct interactions with ENMs can induce T cell toxicity (25). Recently, we compared the immune response of mice to intravenous exposure of multi-walled carbon nanotubes and graphene nanosheets, two carbon-based materials but of varying shapes and surface area (26). In these studies, we observed a Th2 immune response in the lungs and spleens of mice treated with graphene nanosheets once again suggesting physicochemical properties dictate immune outcomes. Additional *in vivo* studies have demonstrated that pulmonary exposure of C57BL/6 mice to single-walled carbon nanotubes and carbon nanofibers decreases the proliferation of T cells *ex vivo* 7 and 28 days following exposure respectively (27). These findings demonstrate *in vivo* responses to carbon-based nanoparticles, which have long lasting immunological effects that could impair immune function. Overall, the evaluation of T cell responses to ENM show an *in vivo* preference for initiating Th2-type immune responses, which can lead to increases in IgE and the progression towards an allergic state.

ADDITIONAL MECHANISMS BY WHICH ENM COULD PROMOTE ALLERGIC RESPONSES

An unexplored area of research that may evoke allergic immune responses is the interaction and structural alteration of macromolecules on the surface of ENMs. Upon introduction into a physiological environment, ENMs associate with a variety of macromolecules including proteins and lipids forming a 'corona'. This corona is a dynamic entity with macromolecules associating and dissociating constantly. The addition of these macromolecules creates a unique entity, which can modify the activity, distribution, clearance, and toxicity of an ENM. Studies have demonstrated that following association with an ENM these macromolecules undergo conformational changes, which could alter immune responses (28, 29). Conformationally altered proteins that are released from or remain bound to ENMs could alter antigen presentation by dendritic cells as an example. Further, presentation of

self or non-self peptides that have been altered due to biophysical interactions with an ENM may possess the potential to initiate autoimmune or allergic immune responses.

A major focus of biomedical nanotechnology research has been the utilization of nanoparticles as adjuvants for enhancing immune responses to vaccines. It has been well established that many larger sized particles can act as an adjuvant thereby exacerbating allergic responses. Due to the unique properties of ENMs such as size, surface area, and bioavailability, it is likely that materials of the same composition, but at the nanoscale may possess enhanced adjuvant-like activity. Many toxicity studies have demonstrated this principal by showing that materials of the same composition have increased toxicity at the nanoscale. Limited data currently exists regarding the adjuvant potential of ENMs; however, the current data available suggests that ENMs likely have adjuvant capacity. Examination of the adjuvant capacity of carbon nanofibers and nanotubes utilizing both an injection and intranasal model found both types of ENMs to have adjuvant capacity (30). Specifically, exposure to both carbon-based ENMs was found to increase serum ovalbumin-specific IgE, IgG1, and IgG2a levels compared to ovalbumin alone. Interestingly, in the intranasal model, carbon nanotubes produced an enhanced IgE response compared to carbon nanofibers, again suggesting that physicochemical properties of these materials has a large influence on immunogenicity. Another example using polyethylene glycol coated amorphous silica nanoparticles demonstrated concentration-dependent allergic airway adjuvant-like effects resulting from co-exposure with ovalbumin (31). Specifically, this consisted of increased ovalbumin-specific serum IgE levels, airway eosinophilia, Th2 and Th17 cytokines. Interestingly, these adjuvant-like effects were found at doses lower than was required to cause an innate immune response. Silver nanoparticles also have a capacity to function as an adjuvant resulting in exacerbation of Th2 immune responses compared to ovalbumin or bovine serum albumin alone (32). These findings suggest that co-exposures of ENMs and allergens will promote allergic responses and that this may occur at lower doses than required to stimulate an innate immune response.

CONCLUSIONS

Currently there is a significant lack of knowledge to understand the risk of allergic disease resulting from ENM exposures. The limited research to date regarding the direct interactions of ENMs with the immune system however suggests that this may be an area of concern. Due to the large number of ENMs being developed and produced; and the increased risk of human exposure, their ability to initiate or exacerbate allergic diseases requires assessment. Lastly, ENMs may induce allergic responses via multiple scenarios that are related to their unique physicochemical properties.

Acknowledgments

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KEY POINTS

- Humans are increasingly exposed to engineered nanomaterials (ENM) due to their incorporation into numerous consumer products and biomedical applications.
- ENMs directly interact with immune cells involved in allergic disease such as mast cells and dendritic cells.
- Physicochemical properties (e.g. size, charge, surface modifications) drive ENM immune cell interactions and IgE synthesis.
- ENMs may act as an adjuvant to promote allergic disease.
- To ensure the safe development of ENMs for biomedical applications it is critical we assess the potential of these novel materials to elicit allergic immune responses.