

HYPERSENSITIVITY AND NANOPARTICLES: UPDATE AND RESEARCH TRENDS

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Abstract

Nanotechnology holds a great promise for a wide range of medical-intent applications (diagnostic, treatment and prophylaxis of various diseases). Their advantages are due to their size, versatility and potential for multiple simultaneous applications. However, concerns have been formulated by scientific world due to insufficient data on toxicity of nanomaterials. One area of interest is represented by the interactions between nanoparticles and the components of the immune system. We review herein reported data on hypersensitivity reactions. The role exerted by nanoparticles in both immunostimulation and immunosuppression in allergen-driven mechanisms was studied, as well as future trends in worldwide research.

Keywords: nanoparticles, hypersensitivity, allergy

Introduction

Increasing evidence on possible interaction between nanoparticles and the immune system has been released lately, however, research data is still limited. Amongst the possible immune-related effects, sensitization as a result of nanoparticle exposure represents a current experimental goal for many research groups. It has been said that NPs may be responsible for inducing allergic sensitization (contact dermatitis). However, it has been said that NPs are unlikely to act as a hapten inducing a specific IgE production. Rather, it is considered that they are likely to act as adjuvant and induce a specific pattern of cytokines, antibody and cells that favor allergic sensitization to environmental allergens [1]. Importantly, stimulation of inflammatory cytokines has been demonstrated to be a keypoint in nanoparticle-induced immunostimulatory reactions. Different types of nanomaterials have been reported to

elicit this type of response [2-5]. However, several studies demonstrate the need for detailed characterization of nanomaterial, with detection of biological and chemical contaminants. Researchers have reported the observation that nanoparticles may not induce an allergic reaction by themselves, but rather joining the contribution brought by bacterial endotoxin and/or surfactants included into the formulation [2].

We here revise the most important updates on nanoparticle-related pro and anti-allergic data reported by various research groups.

Nanoparticles as allergy promoters

Carbon nanotubes

Intranasal or subcutaneous administration of carbon nanotubes (CNTs) has been demonstrated to enhance the allergen potential of egg albumin regardless of nanomaterial type (single or multi-walled). The mechanism promoting the response has been linked to be cytokinetic response [6].

Dendrimers

A case of epidermal dermatitis with necrolysis

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was reported following occupational exposure to final or intermediate products of dendrimer synthesis. The mechanisms, which may be also be interfered with reactive oxygen species used within the synthesis process, is to be further investigated [7,8].

Magnetite iron oxide nanoparticles

Ig E blood concentrations were significantly increased following iron oxide nanoparticles single-dose intra-tracheal installation. However, the concentration of IgE in the broncho-alveolar fluid did not reveal any change following treatment [9].

Titanium dioxide (TiO₂) and gold (Au) nanoparticles (NPs)

A recent study demonstrate the ability of TiO₂ and AuNPs to induce a two-fold (TiO₂) and three –fold (AuNPs) increase in airways hyperreactivity following inhalation, along with bronchoalveolar lavage cells, histology and total IgE alterations [10]. Also, other research groups have found that exposure to TiO₂ nanoparticles in the case of a pre-existent skin barrier dysfunction/defect can exacerbate AD symptoms through Th2-biased immune responses. Also, TiO₂ nanoparticles were demonstrated to exert a significant role in the initiation and/or evolution of skin pathologies following the barrier dysfunction/defect by histamine discharge even in the nonexistence of allergen [11].

Silver nanoparticles

In a recent experiment, repeated oral administration of AgNPs 1 mg/kg for 14 days in mice, induced significantly elevated TGF- in serum, and B cell distribution especially in small dimension AgNPs. Also, the repeated-dose toxicity of AgNPs (42 nm) was also investigated in mice by oral administration for 28 days. Cytokines including IL-1, IL-6, IL-4, IL-10, IL-12, and TGF- were also increased in a dose-dependent manner by repeated oral administration. In addition, B cell distribution in lymphocyte and IgE production were increased. Based on these results, it is suggested that repeated oral administration of nano-sized AgNPs may cause organ toxicity, inflammation and allergic responses in mice [7].

Polystyrene nanoparticles (PS)

A complex experiment has investigated the effects of different-size-PS nanoparticles on the atopic dermatitis (AD)-like skin lesions in NC/Nga mice assumed to show the skin barrier defect/dysfunction in the presence or absence of mite allergen. Male NC/Nga mice were administrated PS nanoparticles through intradermal injection. Different sizes of PS nanoparticles were used (25, 50, or 100 nm) and/or mite allergen administration into their right ears. PS nanoparticles aggravated AD-like skin lesions related to mite allergen, which was concordant to the local protein levels of interleukin-4, CCL2/monocyte chemotactic protein-1, CCL3/macrophage inflammatory protein-1 alpha, and CCL4/macrophage inflammatory protein-1 beta. Moreover, PS nanoparticles reduced interferon- γ expression. Also, treatment with PS nanoparticles

stimulated ear swelling and CC-chemokine expression in the absence of allergen. These effects were greater with the smaller PS nanoparticles than with the larger ones regarding overall trend. These results suggest that exposure to PS nanoparticles under skin barrier defect/dysfunction can exacerbate AD-like skin lesions related to mite allergen in a size-dependent manner. Suggested mechanisms involved T helper 2-biased immune responses. Furthermore, PS nanoparticles demonstrated the ability to stimulate skin inflammation via the overexpression of CC-chemokines even in the lack of allergen in atopic subjects [11].

Reducing the hypersensitivity induced by nanoparticles

Once detected, allergic reactions have become a point of interest in research. Efforts for avoiding and reducing hypersensitivity have been done and several strategies have been imagined.

Gene porter synthesis aimed for enhancement and improvement of the allergy protection has been one of the most recent strategies. A Den123-a nontoxic self-assembled dendritic spheroid nanoparticle composed of biodegradable monomers has been designed. Research showed higher and growing ratios of Ig2a/IgG1 were induced in mice receiving plasmids in combination with Den123. Also, increased gamma interferon release in splenocytes has been detected in the presence of both Den123 and DNA vaccine. IgE inhibition has been significant [12].

Designing and optimizing animal models for testing hypersensitivity has also been an intense line of research. Complement mediated hypersensitivity following liposomal nanoparticles has been studied by means of various models including pigs [13], rats [14], dogs [15]. Detected symptoms and laboratory abnormalities included: hypo/hypertension, arrhythmias, anaphylaxis, shock or even death. Dependence of symptoms on species, dosage and lipid composition has been demonstrated by various reports and is to be taken into account in animal model selection for a particular type of nanomaterial [16].

Nanoparticles as alleviating agents against hypersensitivity reactions/mechanisms.

Although many types of nanostructures have been demonstrating hypersensitivity-inducing properties, some structures have been demonstrating anti-allergic effects.

Recent studies reported a strong increase in NF- κ B p65 in the lung tissues nuclear protein extracts at 72 hours post OVA inhalation, compared with the level in controls. Administration of silver NPs revealed efficiency in decreasing NF- κ B p65 after OVA inhalation. Also, a detected decrease in cytosolic NF- κ B p65 was equally attenuated by silver NPs exposure [17].

Betamethasone disodium phosphate (BP) encapsulated in biocompatible, biodegradable blended nanoparticles (stealth nanosteroids) induced significant eosinophil number decrease in bronchoalveolar lavage fluid. A single dose injection containing 40 μ g BP in the

form of nanosteroids induced stable anti-allergic effect for 7 days [18].

Nanoparticle technology has also been involved to design an innovative nanoparticle P-selectin antagonist with potent anti-inflammatory roles in a murine model allergic asthma. Both in vitro and in vivo studies were conducted and a significant reduction of allergen-induced peribronchial inflammation airway and airway hyperreactivity was reported, demonstrating the efficiency of newly designed structure [19].

Chitosan combined with mixtures of hyaluronic acid and unfractionated or low-molecular-weight heparin was constructed to form nanoparticles using the ionotropic gelation technique. Ex vivo experiments testing the capacity of heparin to prevent histamine release in rat mast cells indicated that the free or encapsulated drug induced a significant response suitable for treatment of allergy-driven asthma [20].

Chitosan/IFN- γ pDNA nanoparticles (CIN) have been designed and their efficiency was tested. It has been demonstrated that prophylactic administration of CIN reduces sensitization to allergens, decreases allergen-induced AHR and inflammation, while therapeutic administration of CIN reverses established allergen-induced AHR [21].

General recognized as safe (GRAS)-based calcium carbonate or calcium phosphate nanoparticles that contain soft base ions have demonstrated efficiency in arresting soft acid metal ions such as nickel, being therefore useful in treatment of nickel allergy [22].

Another research group proposed a distinct design for treatment allergic inflammation in asthma. Chitosan nanoparticles were mixed with Imiquimod cream. The content of nanoparticles consisted in either siRNA green indicator (siGLO) or small interference natriuretic peptide receptor A (NPRA). After topic application of designed cred formulation, measuring of airway eosinophilia, hyperresponsiveness, pro-inflammatory cytokines and lung histopathology was performed. Results showed that transdermally applied siNPRA chitosan nanoparticles can represent a safe and efficient treatment choice for allergic asthma in humans [23].

A recent report demonstrates that Cyclosporin A-loaded solid nanoparticles in topic administration relieved symptoms of an in vivo murine model of atopic dermatitis. Involved mechanisms include the T helper (Th) 2 cell-related cytokines interleukin (IL)-4 and -5 alteration. These results suggest that the designed SNP may represent potent therapeutic agents to be applied in allergy-related skin disorders [24].

Research has shown that a nanogel containing surface modified nanoparticles (NPSO) improved skin permeation of ketoprofen and spantide II by transiting the nanostructures across the deeper skin layers. Also, by forming a thin layer on the skin surface (occlusive effect)

the designed formulation improved skin contact time and hydration of the skin. Therefore, the synthetic formulation improved response in ACD. Moreover, no interaction was detected between the spantide II and ketoprofen [25].

Reformulation of an already approved drug was another strategy for diminishing and eliminating hypersensitivity following administration of nanoparticles. A good example is the first generation formulation of paclitaxel in the nonionic surfactant Cremophor EL, a severely allergic product, which was successfully reformulated as Abraxane, namely paclitaxel-bound albumin nanoparticles. The later demonstrated hypoallergenic properties [26].

Conclusion

Nanoparticles represent a promising tool for an increasing number of diagnostic, therapy and prophylaxis. However, all evidences suggest a strong immunomodulating role of nanoparticulate structures. Further individual and intensive testing is needed for all physic-chemical properties of the particles. Controlling the pro and anti-allergic properties of nanoparticles represents one of the key elements towards their safe and efficient application.

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