CHAPTER

10

Respiratory System, Part Two: Allergy and Asthma

Harri Alenius[*,**], *Michael R. Shurin*[†], *Galina V. Shurin*[†], *Don Beezhold*[‡], *Anna A. Shvedova*[‡]

*University of Helsinki, Helsinki, Finland; **Systems Toxicology Unit, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; †University of Pittsburgh Medical Center, Pittsburgh, PA, United States; ‡National Institute for Occupational and Safety Health, Morgantown, WV, United States

OUTLINE

ALLERGIC REACTIONS AND ASTHMA

Allergy is defined as disease resulting from an exaggerated response by the immune system to specific but otherwise innocuous antigens, called allergens. Allergic reactions are commonly divided into four classes of hypersensitivity reactions according to the specific immunologic mechanisms mediating the response. The term hypersensitivity describes

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objective and reproducible symptoms initiated by exposure to a defined allergen at a dose tolerated by normal persons. Hypersensitivity can be antibody-mediated or cell-mediated. Antibody-mediated hypersensitivity involves IgE-induced release of inflammatory mediators from mast cells (Type I), IgG or IgM mediated cytotoxic reactions (Type II), and immune complex mediated reactions (Type III) (Murphy et al., 2012). Cell-mediated or delayed type reactions (Type IV) are mediated primarily by T cells but monocytes/macrophages, NK, and granulocytes can also participate. The allergic response can be divided into early events, called early phase reactions, which are mediated by short-lived agents, such as histamine. Late phase reactions involve leukotrienes, cytokines, chemokines, and the recruitment and activation of eosinophils, basophils, and antigen specific T cells. Typically, proteins and other high molecular weight allergens elicit the immediate type I allergic reactions while low molecular weight chemicals induce the delayed type IV hypersensitivity reactions.

Asthma is a term that describes a group of clinical symptoms of generally reversible acute obstructive airway disease. Asthma is often characterized by expiratory airflow limitation due to bronchial hyperresponsiveness. The pathogenesis of asthma is not completely understood, but asthma is defined as "a heterogeneous disease, usually characterized by chronic airway inflammation" (Fanta, 2009). The most common form of asthma, allergic asthma, is triggered by allergen-induced activation of submucosal mast cells in the lower airways leading to immediate bronchial constriction and amplified secretion of mucus by the airway epithelium. Allergic asthma is typically characterized by chronic airway inflammation in the presence of Th2 lymphocytes, eosinophils, neutrophils, and other leukocytes. These cells work together to cause remodeling of the airways, accompanied by augmented mucus production. Th2 cytokines, such as IL-4, IL-5, and IL-13, may directly affect airway epithelial cells and cause the induction of goblet-cell metaplasia and secretion of mucus (Lloyd and Hessel, 2010). Persistent inflammation can also lead to irreversible fibrotic airway remodeling induced by improper activation of smooth muscle cells and lung fibroblasts. In addition to Th2 lymphocytes, mast cells are important contributors in the development, maintenance, and augmentation of asthma with release of acute-phase mediators and also producing variety of inflammatory cytokines (Galli et al., 2008).

There is strong evidence showing an imbalance of reducing and oxidizing equivalents in the lungs, produces an environment conducive to acceleration of oxidative stress in asthma. Endogenous and exogenous reactive oxygen species, such as superoxide anion, hydroxyl radical, hypohalite radical, and hydrogen peroxide, and reactive nitrogen species, such as nitric oxide, peroxynitrite, and nitrite, play a major role in the airway inflammation that is a key element of asthma severity outcomes (Sahiner et al., 2011).

ENGINEERED NANOPARTICLES AND ALLERGY

Engineered nanoparticles (ENP) are well known to interact with immune cells, including the alteration of phagocytosis and activation or inhibition of immune cells (Dobrovolskaia et al., 2015) (and see Chapter 13). Studies on inhalation of nanoparticles consistently demonstrates them to be potent inducers of sterile inflammation, a response to noxious nonviable stimuli orchestrated by damage-associated molecular patterns (DAMPS) and cytokines

of the IL-1 family. Nanoparticles can also "trigger" hypersensitivity reactions since patients with bronchial asthma are highly sensitive to inhaled substances including particulate matter. Unfortunately, the mechanism of allergy to nanostructures as well as a possible modulation of allergen effects by binding to nanomaterials is generally unknown. In this regard, the concept of pseudoallergy, a response that resembles a true allergic reaction, but lacks a specific allergen, should be introduced. The mechanisms of pseudoallergy are not known, but may involve nonspecific complement activation, inflammatory responses, or alterations in histamine metabolism.

Acute exposure to different types of silica nanoparticles (SNP) alone or in conjunction with ovalbumin, a high molecular weight protein allergen, were shown to induce strong airway inflammation and airway hyperresponsiveness. In ovalbumin-SNP asthma models, ovalbumin (OVA) with SNP-treated mice displayed substantial airway inflammation, which was significantly higher than in mice treated with OVA without SNP (Park et al., 2015). Furthermore, three types of metal oxide nanoparticles, TiO_2, ZnO, and SiO_2, were shown to increase serum concentrations of total IgE, OVA-specific IgG1, and OVA-specific IgE (ZnO only) following pharyngeal aspiration 24 h prior to sensitization with inhaled ovalbumin (Horie et al., 2015), suggesting that they have the potential to aggravate allergic reactions. Interestingly, the rapid onset of serious nickel allergy in a nanonickel occupationally exposed worker was recently reported (Journeay and Goldman, 2014).

Accumulating data suggests that when allergen is bound to ENP, IgE can still recognize the allergen. Comparative analysis of basophil activation from allergic patients in response to free allergen or gold nanoparticles conjugated with the major allergens of birch pollen, timothy grass pollen, and house dust mite revealed that depending on the allergen, different effects were observed after binding to ENP, including enhanced allergic recognition of some of the tested allergens (Radauer-Preiml et al., 2016). These observations may help in the development of more sensitive allergen testing or cell specific delivery of pharmaceuticals for prevention of allergic responses. Several studies reported different effects of another ENP, C_{60} fullerenes, a potent free radical scavenger, on mast cells and basophils. Using human skin and lung mast cells and peripheral blood basophils, Ryan et al. (2007) demonstrated a marked inhibition of IgE-dependent mediator release when cells were preincubated with C_{60} fullerenes. Furthermore, in the mouse model of mast cell-dependent anaphylaxis, fullerenes prevented the in vivo release of histamine. In addition to possible stabilization of FcεRI-mediated mast cell and basophil responses, fullerenes and specifically engineered fullerene derivatives may stabilize these responses through non-IgE-mediated mechanisms related to the potent free radical scavenging activity of fullerenes, including the absorption of induced cellular reactive oxygen species, calcium and prostaglandin D2 resulting in reduced activation of ERK1/ERK2 signaling (Dellinger et al., 2013).

In spite of the potential for sensitization to certain airborne ENPs (nickel), can still be used in the development of better immunotherapy for patients with allergy. Polyethylene glycol modified nanoparticles can envelop an allergen and deliver it to specific cells serving as nanocarrier that degrades when it encounters the acidic part of these cells, simultaneously releasing the allergen and removing the packaging (Pohlit et al., 2015). Another interesting study focusing on the development of oral dispersible tablets containing prednisolone-loaded chitosan nanoparticles opens a new avenue for the better management of asthma in pediatric patients (Chen et al., 2015). Interestingly, the use of magnetic core-shell nanoparticles as a

microchip for allergy diagnosis has increased capture kinetics by a 1000-fold by quantifying IgE (Teste et al., 2011).

Although the pulmonary delivery of locally-acting drugs encapsulated in nanocarriers provides several advantages for the treatment of respiratory diseases, including asthma, potential health effects of ENP are of great importance and should be carefully evaluated with the growing number of their commercial applications and demonstrated potential for pulmonary exposure in the workplace. Further studies using well-characterized ENP, well controlled protocols and appropriate routes of exposure are required in order to clarify differential allergic effects and provide information suitable for risk assessments of ENP. Moreover, it seems impossible to assess the risks associated with the use of ENP without considering alterations and transformation with life cycle of the particles, both in the environment and inside of the human body or experimental model systems.

CARBON NANOTUBES AND ALLERGIC PULMONARY INFLAMMATION

Among ENPs, single and multiwalled carbon nanotubes (SWCNT and MWCNT), are some of the most promising nanomaterials that have been manufactured broadly during the last decade. Because of their fiber-like morphology, much attention is paid to the health outcomes of pulmonary exposure to these nanoparticles, and in several animal studies, carbon nanotubes (CNTs) have been reported to cause asthma-like responses.

Park et al. (2009) found pulmonary inflammation and enhanced humoral immune responses after intratracheal instillation of MWCNT in mice. Proinflammatory, Th1-type and Th2-type cytokines were increased by the immune cells in both BAL fluid and in the blood. The elevated numbers of B cells, IL-10, and total IgE were observed after a single intratracheal instillation. The authors concluded that this combination of responses was an allergic reaction in the mice treated with MWCNTs (Park et al., 2009). However, the reported pulmonary response was not typical of allergic inflammation since many characteristic features of allergic airway inflammation, such as eosinophilia and goblet cell hyperplasia were not observed (Fanta, 2009). In a study by Hsieh et al. (2012) , a single intratracheal instillation of SWCNT induced airway hyperreactivity and chronic airway obstruction in mice and also lead to persistent lung parenchymal injury. Global gene expression analysis revealed that exposure to SWCNT upregulated proteinases and metalloproteinases, chemokines and macrophage receptors. Results suggest that exposure to SWCNT may cause irreversible obstructive airway disease via sterile inflammation although classical features of allergic airway inflammation were not found (Hsieh et al., 2012).

Inhalation exposure is the best method to mimic real-life scenarios, however, the number of such studies is still limited. In the study by Rydman et al. (2014), healthy mice were exposed by inhalation to two types of MWCNT, rigid rod-like and flexible tangled CNT. Short-term inhalation (4 days) of rigid rod-shaped CNT (rCNT), but not of tangled CNT, induced all the signs of allergic airway inflammation (Fig.10.1A). Exploration of the early events by transcriptomics analysis revealed that a 4 h exposure to rCNT causes dramatic up-regulation of genes involved in innate immunity and cytokine/chemokine pathways. Early proinflammatory cytokines as well as proallergic cytokines and chemokines were synthetized by rCNT-activated

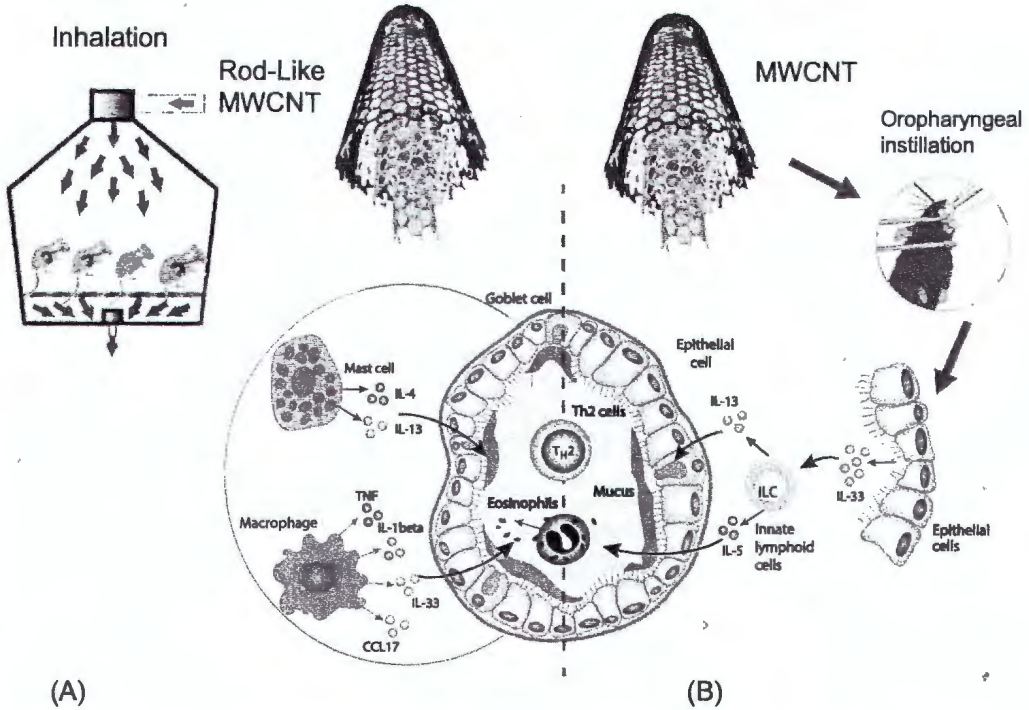

FIGURE 10.1 **Effects of carbon nanotubes on allergic airway inflammation.** (A) Rydman et al. (2014) reported that inhalation exposure to rod-like MWCNT induces fast and early production of Th2 cytokines (IL-4 and IL-13) from lung mast cells and proinflammatory (TNF and IL-1β) and proallergic cytokines (IL-33 and CCL17) from alveolar macrophages. Repeated exposure to rod-like MWCNT finally leads to establishment of allergic airway inflammation with recruitment of eosinophils and Th2 lymphocytes, mucus hypersecretion, and airway hyperreactivity. (B) In contrast, Beamer et al. (2013) concluded that oropharyngeal instillation with MWCNT induces airway epithelial damage and secretion of IL-33. This, in turn, results in activation of so-called innate lymphoid cells to produce Th2 cytokines (IL-5 and IL-13) which induces mucus secretion, pulmonary eosinophilia, and airway hyperreactivity.

alveolar macrophages, while mast cells were likely an early source of rCNT induced Il-4 and Il-13 (Fig. 10.1A). These observations emphasize the diverse abilities of different type of CNTs to impact the immune system, and they also suggest that inhalation exposure to rCNT may cause asthma-like allergic airway inflammation without the conventional specific protein allergen or treatment with artificial adjuvant substances (Rydman et al., 2014).

Rydman et al. (2015) investigated the airway effects of two different type CNT (long tangled, and long rod-like CNT) and crocidolite asbestos in mice after a single pharyngeal aspiration exposure. Results demonstrated that pulmonary inflammation progresses over time; starting from neutrophilic infiltration at 4–16 h and then changing to eosinophilia, peaking at 7 days after the rod-like CNT exposure. In line with pulmonary eosinophilia, Charcot-Leyden-like crystals were seen in acidophilic macrophages 28 days after the exposure to rod-like CNT. To explore the functional role of IL-1β in CNT induced pulmonary inflammation, they utilized pharmacological TNF and IL-1 receptor antagonists as well as IL1R knock-out mice. The lack of IL-1β was able to prevent acute neutrophilic infiltration but it has no effect on Th2 type

inflammation, see 1 month after the exposure to rod-like CNT (Rydman et al., 2015). These results demonstrate that IL-1R interaction mainly regulates neutrophilic inflammation in the acute inflammatory response, but this interaction is not critical for Th2 dominated chronic type response. In line with this, Køobler et al. (2015) reported that the longer and thicker CNT resulted in more severe pulmonary eosinophilia and induction of crystalline bodies in alveolar macrophages compared to shorter and thinner CNT. Moreover, it has been shown that eosinophil peroxidase (EPO) derived from in vitro and ex vivo activated eosinophils is able to promote SWCNTs biodegradation (Andón et al., 2013) and that pulmonary exposure to MWCNTs mediates Th2 type inflammation with EPO release into the pulmonary inflammation foci (Girtsman et al., 2014).

MODULATION OF ALLERGEN-INDUCED AIRWAY INFLAMMATION BY CNTs

Ovalbumin (OVA) induced experimental asthma is one of the most widely studied allergic asthma model worldwide. There are several variations of the model in which sensitization is done by repeated intranasal or intratracheal administration with OVA, but without adjuvant, or repeated intraperitoneal injection with adjuvant. Additionally, house dust mite extract (HDM) and other purified allergens have been used to induce Th2 type allergic immune responses in mice.

Several studies have examined the risk of exposure to a combination of CNTs with allergen. For instance, Inoue et al. (2009, 2010) examined the effects of MWCNT and SWCNT by repeated intranasal exposure with and without OVA allergen. Exposure to both SWCNT and MWCNT augmented OVA-induced pulmonary inflammation. Exposure to MWCNT also exhibited adjuvant activity for allergen-specific IgG1 and IgE, augmented lung T helper cytokines and chemokines (Inoue et al., 2009). Similarly, exposure to a combination of MWCNT and ovalbumin allergen induced an increase in airway resistance, airway inflammation, goblet cell hyperplasia, and the production of antigen-specific antibodies (Inoue et al., 2010).

Interestingly, exacerbations of allergen-induced airway inflammation and mucus-cell metaplasia by MWCNT could be enhanced by deficiencies in COX-2, and was associated with the activation of a mixed Th1/Th2/Th17 immune response (Sayers et al., 2013). A similar protective role for STAT1 in chronic allergen-induced airway inflammation and exacerbation of lung remodeling caused by aspiration of MWCNT has been recently suggested when MWCNT were reported to further increase ovalbumin-induced goblet cell hyperplasia, airway fibrosis and subepithelial apoptosis in Stat1−/− mice compared with WT mice (Thompson et al., 2015).

Nygaard et al. (2009) reported that both SWCNT and MWCNT together with OVA strongly augmented serum levels of OVA-specific IgE, the number of eosinophils in BAL, and the secretion of Th2-associated cytokines in the draining lymph nodes in mice. In line with this, Li et al. (2014), showed in Wistar rats that exposure to SWCNT exacerbated OVA-induced allergic asthma. Interestingly, SWCNT induced allergic asthma exacerbation was prevented by concurrent administration of vitamin E suggesting that the relief of several asthma related symptoms was explained by antagonistic effects of vitamin E (Li et al., 2014). In the study by Ryman-Rasmussen et al. (2009), significant airway fibrosis

was observed at 14 days in mice that received a combination of ovalbumin and MWCNT, when compared to mice that received OVA or MWCNT only. Further analysis suggested that airway fibrosis resulting from combined OVA sensitization and MWCNT inhalation requires platelet-derived growth factor (PDGF), a potent fibroblast mitogen, and TGF-β1, which stimulates collagen production (Ryman-Rasmussen et al., 2009). These findings propose that individuals with preexisting allergic inflammation may be susceptible to airway fibrosis from inhaled MWCNT.

Individuals can also be sensitized to various chemicals especially in the occupational setting. Staal et al. (2014) studied MWCNT responses by using high IgE-responding Brown Norway rats with trimellitic anhydride (TMA)-induced respiratory allergy. Large MWCNT agglomerates were found in granulomas especially in the allergic rats, suggesting decreased macrophage clearance. Moreover, exposure to MWCNT decreased serum IgE levels and the number of lymphocytes in bronchoalveolar lavage suggesting that some allergy-associated immune responses were modulated by MWCNT exposure (Staal et al., 2014).

MECHANISMS OF CNT-INDUCED/MEDIATED ALLERGIC RESPONSES

IL-33 (IL-1F11) is a cytokine that belongs to the IL-1 family and is linked to Th2-type immune responses (Liew et al., 2010). Beamer et al. (2013) showed that MWCNT exposure results in elevated levels of IL-33 in the lavage fluid, enhanced AHR, eosinophil recruitment, and production of Th2-associated cytokines and chemokines. Exposure to MWCNTs elicited also infiltration of innate lymphoid cells into the airways which in turn provoked IL-33-dependent airway inflammation (Fig. 10.1B). They also demonstrated these MWCNT regulated events were dependent on IL-13 signaling and the IL-33/ST2 axis, but independent of T and B cells (Beamer et al., 2013).

Ronzani et al. (2014) investigated the effect of MWCNT using HDM allergen induced asthma model. HDM extract induced levels of HDM-specific IgG1, pulmonary eosinophilia and neutrophilia, production of collagen and mucus, as well as expression of Th2 cytokines and chemokines, were dose-dependently increased in mice exposed to HDM and MWCNT compared to HDM alone. These effects were associated with an increased production of allergy promoting cytokines TSLP, IL-25, IL-33, and GM-CSF in the airways. Data also suggest a role for airway epithelium and innate cytokines in these effects (Ronzani et al., 2014). Under conditions of increased reactive oxygen species (ROS) production both from the ENPs and by immune system components (e.g., neutrophils), the antioxidant system is rapidly depleted. Several studies have shown that ROS overproduction is in direct correlation with airway tract hyperresponsiveness upon methacholine challenge (Sahiner et al., 2011). It was also found that individuals lacking antioxidant defense are more susceptible to asthma (McCunney, 2005) and accumulation of oxidatively modified proteins, discovered in a variety of airway cells, such as chitinase-like Ym1/Ym2, FIZZ1 and SP-D, could play an important role in the pathogenesis of asthma (Zhang et al., 2009).

The study by Kapralov et al. (2012) provided the evidence of the surfactant-derived lipid-protein coating on SWCNTs in mice upon pulmonary exposure, including SP-D. In another study, two different types of MWCNT (Mitsui-7 and NM-401) induced eosinophil influx with

significant increases in *Chi3L3* (encoding for Ym1) mRNA levels (Køble et al., 2015). These studies suggest that a weakened antioxidant defense is associated with an elevated inflammatory response.

Several systemic immune effects of CNT-induced inflammation have been recognized in recent studies. Mice that inhaled MWCNT had suppressed systemic immune function, as inhaled MWNTs can activate the release of TGF-β in the lung. TGF-β has a direct effect on prostaglandin production by spleen cells, leading to potent immune suppression (Mitchell et al., 2009). Analysis of SWCNTs on allergic airway inflammation also suggests that SWCNT can exacerbate murine allergic airway inflammation via enhanced activation of T helper immunity and increased oxidative stress (Inoue et al., 2010). Some effects of SWCNT can be explained by the direct effect of SWCNT on DC and altered ability of DC to activate proliferation of T cells (Tkach et al., 2011).

Upregulation of myeloid-derived suppressor cells (MDSC), reported by Shvedova et al. (2013) in SWCNT-exposed mice may also trigger the activation of allergic response in lungs, as MDSC are phenotypically similar myeloid derived regulatory cells, that play major role in both pulmonary inflammatory response and hyperresponsiveness (Deshane et al., 2011).

The ability to alter the allergen-induced airway inflammation was confirmed for graphene oxide (GO). Hence, exposure to GO has been shown to modulate the allergic pulmonary response in a murine model of ovalbumin-induced asthma: GO amplified airway hyper-responsiveness, airway remodeling (goblet cell hyperplasia and smooth muscle hypertrophy), production of OVA-specific IgG2a, macrophages recruitment in broncho-alveolar lavage (BAL) fluid and macrophage production of the mammalian chitinases, CHI3L1 and AMCase, whose expression is associated with asthma. However, at the same time, exposure to GO reduced BAL IL-4, IL-5, and IL-13 and decreased the level of eosinophils in BAL fluid (Shurin et al., 2014).

CONCLUSIONS

It is evident that inhalation of ENM can elicit asthma and allergy-like pulmonary inflammation in murine models. Although mechanisms are not completely known, it is likely that the ENMs induce sterile inflammation through damage-associated molecular patterns (DAMPS) and secretion of the IL-1 family members (including IL-33) and thereby play an important role in allergic inflammation. Evidence exits that rod-like multiwalled carbon nanotubes are especially adept at inducing innate immune-mediated asthma-like reactions. Not unexpectedly, airway exposure to ENPs also exacerbates Th2 inflammation in mouse models suggesting that subjects with underlying allergies may be more susceptible to inhalation of ENP compared to healthy subjects. Importantly, new evidence demonstrates that airborne ENMs may also alter the functional activity of antigen-presenting cells, such as dendritic cells, in the lungs and systemically. In line with this, strong evidence exits that patients with bronchial asthma are highly sensitive to inhaled substances including particulate matter. Despite the growing evidence of the involvement of ENPs in inflammatory reactions, the mechanism by which nanostructures possibly modulate allergic responses are still poorly known. The evidence suggests that both innate and adaptive immune responses may be involved in the modulation of asthmatic reactions after exposure to ENMs. Understanding the interplay

between sterile and allergen induced airway inflammation will be important in discerning the influence of nanoparticles on allergic disease.

TAKE-HOME MESSAGES

- Inhalation of ENPs has been shown to influence both innate and adaptive immunity mediated asthma-like reactions in mouse models.
- Airway exposure to ENPs can exacerbate preexisting allergic pulmonary inflammation in mice.
- Although the influence of ENP on allergic diseases is still poorly known, the evidence derived from mouse studies suggest that ENPs may also have an important impact on allergic diseases in humans.

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Disclaimer

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