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Allergic Sensitization and the Environment: Latest Update

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Abstract

The prevalence of asthma and other allergic diseases is still increasing both in developed and developing countries. Allergic sensitization against common inhalant allergens is common and, although not a sufficient, a necessary step in the development of allergic diseases. Despite a small number of proteins from certain plants and animals being common allergens in humans, we still do not fully understand who will develop sensitization and to which allergens. Environmental exposure to these allergens is essential for the development of sensitization, but what has emerged clearly in the literature in the recent years is that the adjuvants to which an individual is exposed at the same time as the allergen are probably an equally important determinant of the immune response to the allergen. These adjuvants act on all steps in the development of sensitization from modifying epithelial barriers, to facilitating antigen presentation, to driving T-cell responses, to altering mast cell and basophil hyper-reactivity. The adjuvants come from biogenic sources, including microbes and the plants and animals that produce the allergens, and from man-made sources (anthropogenic), including unintended byproducts of combustion and chemicals now ubiquitous in modern life. As we better understand how individuals are exposed to these adjuvants and how the exposure influences the likelihood of an allergic response, we may be able to design individual and community-level interventions that will reverse the increase in allergic disease prevalence, but we are not there yet.

Keywords

Allergens; Diesel exhaust; Polycyclic aromatic hydrocarbons; Hygiene hypothesis; Pet protective effect

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Conflict of Interest

Young Yoo, and Matthew S. Perzanowski declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

The prevalence of asthma and other allergic diseases is high, with dramatic increases observed in Western countries in the latter half of the 20th century and in developing countries in this century.(1) In Australia, the increase in asthma and wheezing symptoms throughout the past decades has been well-documented with 14–16% of children having asthma symptoms in this century.(2) In Ghana, a population based study showed the prevalence of exercise-induced bronchoconstriction, suggestive of asthma, had doubled among Ghanaian school children over the ten-year of period between 1995 and 2005.(3) In China, where dramatic social and environmental changes have been taking place over the past 20 years, asthma prevalence also has increased, and in some cities, now approaches the prevalence seen in the US and Europe.(4, 5) Not only does the prevalence of allergic disease vary widely between countries, it varies widely within countries and even within cities. The NYC Department of Health reported that asthma prevalence among children entering primary school, varied by neighborhood from 3% to 19%.(6) While the causes of the increase in allergic diseases have not been fully elucidated, it is clear that they are multifactorial and in some way associated with ‘Westernization’, although that sweeping term is not especially useful given its lack of specificity. Part of the problem is that allergic diseases are complex and heterogeneous even within disease classifications. Therefore, a first step that may provide insight into the increase in allergic diseases in general, is improving our understanding of the causes for the increase in the population prevalence of allergic sensitization, which alone was probably not sufficient for the subsequent increase in allergic diseases, but certainly was necessary.

In this review we will focus on the role of environmental exposures in the foundational step in the development of allergic diseases, the development of allergic sensitization to inhalant allergens. In the past decade, our understanding of the complex interplay between anthropogenic and biogenic environmental exposures and the innate and adaptive immune responses to those exposures have taken us far beyond a model of a strict dose response relationship between allergen exposure and allergic sensitization. What has evolved is an understanding of the importance of what else is encountered when an allergenic protein is ‘seen’ by the immune system on the cellular, micro-environmental level and that these co-exposures come both from same source as the allergens and from other recent exposures. This insight may be starting to shed light on the underpinnings for the, now global, increase in allergic diseases.

Development of allergic sensitization

Allergens are proteins or chemicals bound to proteins against which individuals make IgE antibodies.(7) Allergic sensitization is the development of IgE antibodies to allergens that are ingested, absorbed or inhaled. This review will focus on allergic sensitization to inhalant allergens, but there also has been a dramatic increase in food allergy, and development of sensitization to foods has been suggested as a step that precedes the development of sensitization to inhalant allergens and allergic disease (reviewed in (8)) To better understand how environmental exposures can modulate the development of allergic sensitization, it is useful to examine where in the pathway they are acting. In the Figure for this review article,

we illustrate the important steps in the innate and adaptive immune response that lead to development of allergic sensitization and the exposures that could be modulating these steps. With the inhalant pathway to sensitization, animals or plants produce allergens that travel on particles that become suspended in the air, are inhaled and deposit in the airways. The first line of defense once the allergen containing particles have deposited in the airways is the epithelium, and alterations of this defense barrier by environmental exposures are discussed below. Before development of sensitization, the proteins that will become allergens are processed by antigen presenting cells (APC) and broken down into peptides that are presented on the APC.(7) The initiation of the immune response to allergens is mainly mediated via the pathogen recognition receptors (PRRs), which have crucial adjuvant roles in directing allergic sensitization. The PRRs are expressed not only in macrophage and dendritic cell (DC) but also in various nonprofessional immune cells such as epithelial cells, endothelial cells and fibroblasts.(7) Toll-like receptors (TLRs), a class of PRRs, are key components of the innate immune system that mediate recognition and response to microbial, fungal and viral products and their ligands, including endotoxin (recognized by TLR4), lipoproteins (TLR2 and TLR6), viral double- and single- stranded RNA (TLR 3 and TLR7/8) and bacterial CpG-containing DNA (TLR9).(9)

Once activated, the APCs traffic to the lymph nodes where the antigen is presented to the T-cell, which will orchestrate the adaptive immune response. This occurs through the selective expansion of helper-T lymphocytes (particularly of the Th2 type) that secrete a cluster of cytokines. Th2 cytokines orchestrate the allergic inflammatory cascade that occurs with allergic diseases including Th2 cell survival, B cell isotype switching to IgE synthesis, mast cell differentiation and maturation, eosinophil maturation and survival and basophil recruitment. Isotype switching of B cells to IgE synthesis is a prerequisite for allergic sensitization and provides the critical trigger mechanism for the immediate allergic response upon re-exposure to an allergen. IgE produced by the B cells is released into circulation and binds the α -chain of high-affinity Fc ϵ R1 on mast cells and basophils.(7) Cross-linking of receptor-bound IgE by allergen initiates cell activation and the release of preformed and newly generated mediators, cytokines, chemokines and growth factors.

There is substantial evidence that development and persistence of allergic diseases are determined by events occurring during pregnancy and the first few years of life.(10) Thus the timing of exposure to allergens and adjuvants is an important determinant of the long-term clinical outcomes of allergic diseases.

Allergen exposure and allergic sensitization

Allergen exposure was initially thought to be the primary factor in the development of both sensitization and asthma in a simple, linear dose-response manner. However, our understanding of the role of allergen exposure in the development of sensitization and asthma has evolved considerably over the last 25 years, proving that the relationship between allergen exposure and allergen-specific immune responses, sensitization, and asthma is complex. What biological characteristics of a protein make it allergenic has been the focus of several good review articles,(11, 12) and what seems to be important is the ability of the protein to be 'seen' by the immune system and to be encountered in the

presence of an adjuvant that directs a Th2 response. What has emerged in recent literature is the description of many potential adjuvants from biogenic and anthropogenic environmental sources, which is the focus of this review.

Biogenic roles of proteins from allergen sources

Proteins from common allergen sources (plants and animals) and some allergenic proteins, themselves, have been shown to act as adjuvants in several steps of the allergic sensitization pathway (Figure). Allergens that can disrupt the passive structural barrier of epithelial cells by intrinsic proteolytic activity may facilitate allergen penetration into local tissues and thus increase access of allergic proteins to the immune system.(13) Epithelial cells are considered not only a physical barrier but are increasingly recognized as playing a sentinel role in the interaction between environmental exposures and asthma.(14) Some studies have shown that airway epithelial barrier is defective in asthma with disrupted tight junctions, reduced antioxidant activity, and impaired innate immunity following environmental exposure.(15) Several studies have shown that peptidase allergens from dust mites compromise epithelial barrier function by degrading the extracellular domains of the tight junction proteins thus facilitating allergen delivery across epithelial layers.(15) Tight junction cleavage and increased permeability were accompanied by enhanced delivery of purified allergen across the epithelial layer and allowed allergen to access to immune system. In this context, it has been shown that the proteolytic activity of Der p 1 can drive allergic responses both to Der p 1 itself and to bystander allergens that lack intrinsic peptidase activity.(16) There is a great deal of evidence now showing how protease activity can damage tight junctions, activate complement and other signaling pathways.(17–19) The role of allergens influencing the epithelial barrier is reviewed in greater detail by Heijink et al.(20)

House dust mite allergens have been shown to signal through pathways related to TLR 4, thymic stromal lymphopoietin (TSLP) and granulocyte macrophage colony-stimulating factor (GM-CSF) to trigger a Th2 response.(21) House dust mite derived beta-glucan moieties were found to induce chemokine production from epithelial cells that lead to dendritic cell recruitment.(22) Structural homology of dust mite proteins to innate immune signaling molecules may be important in increasing the response to dust mite allergens. Der p 2 has structural homology to MD-2, a protein essential in the signaling of endotoxin through TLR 4, and Der p 7 has a similar structure to LPS-binding protein.(23, 24) In a mouse model, serine proteases in house dust mite extract were found to activate epithelial cells and lead to sensitization through the pattern recognition receptor, protease-activate receptor (PAR)-2.(25) However, in another study, house dust mite activated sensitization without the need of PAR.(26)

Proteins from allergenic sources have also been shown to act on antigen presenting cells (APC). A C-type lectin receptor, dectin-2, on dendritic cells (DCs) was shown to promote Th2 and Th17 cell differentiation in response to house dust mite.(27) In fact, C-type lectin receptors on DCs, including mannose receptor, have been found to be receptor for allergens from cockroach, dog and peanut and mannose receptor was shown to play a critical role in Th2 differentiation (reviewed in (28)).

Observations of inverse associations between domestic cat and dog ownership and allergic disease in epidemiology studies also have pushed forward our understanding of environmental exposures leading to allergic diseases. In fact, recent findings with pet exposure highlight interesting potential features of both biogenic proteins and microbial co-exposures (discussed in next section) acting as adjuvants of the immune system. Platts-Mills et al., described a 'modified Th2' response, whereby high doses of cat allergen were hypothesized to lead to a Th2 response that could have IgG4, but for which IgE was not a feature.(29) This protective effect of cat allergen exposure could be explained by the adjuvant effect of the peptides on chain 2 of the major allergen from cat, Fel d 1. These peptides have been shown to bind the major histocompatibility class 2 cell surface receptor, HLA-DR-7, and induce IL-10, a regulator cytokine of the Th2 response.(30, 31) In this way, a protein from an allergen source may be down-regulating the distal end of the allergic response.

Co-exposures from microbes

The adjuvant effects on the development of allergic sensitization that we have been discussing are based on the fundamental role of the innate immune system to sense molecular patterns from microbes, and based on that detection, direct and refine the development of an adaptive immune response. Therefore, microbial exposures can alter all of the steps in allergic sensitization described for the Figure and are possibly the most important mediator of allergic sensitization. Generally allergens are unable to drive the development of allergic sensitization and need adjuvants; therefore, microbial exposure must also be responsible for increasing allergic sensitization.

In many ways, the importance of microbial exposure as an adjuvant of the immune response to allergens is the underpinning the 'hygiene hypothesis', which asserts that, on a population level, decreased microbial exposure for humans, especially during early life, has led to an increase in allergic diseases. For more than a decade, the 'hygiene hypothesis' has been at the forefront of both epidemiological and experimental studies of allergic disease, beginning with studies to try and understand why older siblings and growing up on a farm were inversely associated with risk of allergic disease.(32) Initially, studies like the cross-sectional inverse association between domestic bacterial endotoxin and allergic sensitization among European farm children and the mouse model studies showing endotoxin acting in a pro-Th2 adjuvant at lower doses and anti-Th2 at higher doses were relatively straightforward and mutually supportive.(33, 34) However, as methods for measuring microbial exposure through polymerase chain reaction (PCR) have advanced dramatically in the past decade, (35) and the exogenous and endogenous microbes have been much better characterized, the role of microbial exposure in the development of allergic disease appears to be much more complicated. For example, in a large cross-sectional European study of children, gram-negative bacteria rods in house dust were inversely associated with atopy.(36) In a prospective birth cohort in the US, current gram-negative bacterial exposure, but not gram positive, was inversely associated with sensitization at a school age even after adjusting for early life exposure to endotoxin.(37) Many studies now indicate a relevance of the bacterial diversity of the gut to allergic disease (reviewed in (38)). For example, gut bacterial diversity in infancy was inversely associated with allergic sensitization at school age.(39) This

biodiversity of exposures has been expanded beyond the home, with a study finding that biodiversity around an individual's home and the bacteria on their skin were correlated and that both were lower among atopic individuals than among non-atopic individuals.(40)

Again examining the 'pet protective effect', but from a microbial adjuvant perspective, recent findings from a birth cohort in Detroit are intriguing. Instead of focusing on the proteins from the animal, Fujimura et al. investigated the microbes in the house dust from homes with a dog living in the home.(41) Exposing mice to microbes from homes with and without dogs, they found that these exposures altered the microbiome of the mice and that the dog home associated exposures were protective in the development of allergic sensitization (to cockroach allergen).

Co-exposures from combustion by-products

The ability of combustion byproducts to modulate the immune system has been demonstrated in animal and human models both in vitro and in vivo. Major components of inhaled pollution in industrialized cities are diesel exhaust particles (DEP) and their associated polycyclic aromatic hydrocarbons (PAH). DEP are probably the most well-established anthropogenic environmental adjuvant of allergic sensitization, which was demonstrated through a series of elegant human in-vivo experiments now going back more than 15 years.(42–44) With those experiments, co-exposure with DEP lead to the development of sensitization to a novel allergen, increased IgE response for established sensitization, increased Th2 cytokine production and increased activation of mast cells.(42–45) With one of the first of these studies, combined challenge with diesel exhaust particles and ragweed allergen lead to elevated expression of mRNA for Th2 cytokines in nasal lavage that was sixteen-times higher following ragweed plus DEP challenge compared with challenge with ragweed alone.(43) While the mechanism is not fully clear, there is evidence that DEP matter induces oxidative stress, influencing the uptake of antigen by dendritic cells and signaling to antigen specific T-cells in a pro-Th2 manner.(46–49) The recruitment of dendritic cells occurs by upregulation of CC chemokines, specifically in a CC receptor 2 dependent manner.(50 , 51) In addition, there is some recent evidence of epigenetic differences in regulatory T cells related to outdoor air pollution among asthmatics.(52)

PAH, both particulate and gaseous, are principal by-products of diesel and other hydrocarbon incomplete combustion. In a murine allergic sensitization model, ambient ultrafine particulate material collected from a highway acted as adjuvant in primary sensitization and augmented the secondary response to a novel allergen.(46, 53) In that experiment, the PAH content of the ultrafine particulate material correlated with its ability to act as an adjuvant.(46) In a prospective birth cohort study of children in low-income neighborhoods in NYC, we found that early life exposure to cockroach allergen was only associated with developing allergic sensitization to cockroach allergen later in childhood (age 5–7 years) among those children also exposed to higher levels of airborne PAH.(54) The effect we observed and those seen in the experimental human in vivo studies of DEP were modified by common polymorphisms in the glutathione - s transferase pathway, which is involved in detoxifying PAHs.(54, 55) The evidence for combustion byproducts acting as adjuvants has not been limited to particulate matter. In a murine model, ozone was found to

act as an adjuvant by promoting allergic sensitization through activation of pulmonary dendritic cells through the innate immune pattern recognition receptor, TLR 4.(56)

While there is considerable evidence that tobacco smoke could influence the pathways involved in allergic sensitization, including increased permeability of the epithelium to allergens, increased pro-allergic cytokine, TSLP and induction of Th2 in dendritic cells, the epidemiology is mixed, with studies showing increased, decreased and no risk for allergic sensitization with tobacco smoke exposure (reviewed in (57)). The reason for the divergent findings may be related to differing by other susceptibility factors like heredity.(58) The most recent NHANES population based study found an inverse association between serum cotinine and allergic sensitization, although it is important to point out that this was a cross-sectional study and reverse causation (smoking avoidance among those with allergic disease) is possible.(59)

Co-exposures from phthalates and BPA

Domestic exposure to two types of chemicals with endocrine disrupting abilities, phthalates and Bisphenol A (BPA), have become common in the past half century. There appear to be links to these chemicals and allergic disease, although whether the mechanism is through an allergic pathway is less clear.

Commonly used as plasticizers and in fragrances, phthalates are ubiquitous in the food and beverages we consume and domestic air we breathe. The 2000 NHANES study found detectible phthalate metabolites in greater than 75% of the US population.(60) Associations between phthalate exposure and allergic diseases in children, including eczema, asthma, and rhinitis, have been observed.(61–63) However, those studies were cross-sectional. Two studies, one cross-sectional, the other prospective, examined the association between phthalate exposure and allergic sensitization in young children, and neither found an association.(63, 64) However, in that prospective study we did find that prenatal phthalate exposure was associated with asthma development by school age.(65) Also, among those school-age children, we observed an association between current phthalate exposure and exhaled NO, a biomarker of airway inflammation.(66) However, we observed that the association was modified by asthma symptoms and not allergic sensitization, suggesting a non-allergic mechanism. In the larger 2005–6 NHANES study of adults, metabolites associated with high molecular-weight phthalates were positively associated with allergic sensitization, while one of the metabolites of the low molecular weight was inversely associated with allergic sensitization.(67) Results from animal studies also have not really clarified the associations, with di-(2-ethylhexyl)phthalate (DEHP) leading to a lack of an overall increase in inflammatory cells, but an increase nasal IL-13 in one study and increased IgG, but not IgE in another study.(68, 69) In a mouse model of mite allergic atopic-dermatitis, DEHP did increase atopic-dermatitis like skin lesions.(70)

Exposure to BPA, commonly used in beverage and canned food containers, also has become ubiquitous and there appear to be links with allergic diseases. Both prenatal and postnatal BPA have been associated with asthma outcomes in childhood, although prenatal associations have not been consistent.(71, 72) With our prospective birth cohort, in addition to associations with asthma, we did find associations with increased exhaled NO, suggestive

of an augment in the allergic pathway, but no association with allergic sensitization.(72) Among the NHANES study population, there was a borderline association between urinary BPA and a higher number of skin test positives to inhalant allergens.(73) Rogers et al., recently reviewed the evidence for BPA's influence on the immune response and describes effects on dendritic cells, CD4+T cells, regulatory T cells, B cells and macrophage.(74) In mouse studies, BPA was shown to increase IL-4 cytokine production in mesenteric lymph node cells, to increase allergic sensitization (IgE) and eosinophilic inflammation, and to increases histamine and cysteinyl leukotriene release in bone marrow derived mast cells.(75–77)

Biogenic and anthropogenic exposures and the increase in allergic diseases

Is there insight into the global increase in allergic disease prevalence to be gained by the recent advances in our understanding of how biogenic and anthropogenic exposures influence the likelihood that an individual will mount an allergic response to environmental allergens? Clearly the biological roles of microbial exposures have emerged as important and supportive of the 'hygiene hypothesis'. The decrease exposure in microbial quantity and diversity described mostly fit in ecologically with the timeline of the increase in allergic sensitization. Still, the relevance of domestic microbial exposure, especially from fungi, to allergic sensitization and disease is still neither fully understood nor consistently protective, and needs to be further elucidated. The emergences of separate, but equally compelling explanations of the 'pet protective effect' through adjuvants are also interesting. Bioactivity of the allergen and allergen associated proteins also offer some evidence as to why dust mite allergy in particular may dominate allergy where dust mites are common and potentially explains the dramatically high asthma prevalence seen in highly exposed communities like those in Australia.(2) Combustion byproducts also might offer an explanation for higher rates of urban asthma, although this is not the sole cause as some urban communities have low asthma prevalence despite higher combustion byproducts.(78) That is where the environment (adjuvant) by environment (allergen) interactions are compelling, as both exposures may be necessary.

Environmental interventions

Given our increasing understanding of the importance of co-exposure to adjuvants, what do we do? Allergen exposure has been the target of both primary and tertiary prevention strategies, with hope placed on the limited trials that have shown some success and skepticism driven (and legitimately supported) by the general lack of success of interventions limited to single intervention targets.(79, 80) Because allergic sensitization is common in many populations (i.e., ~50%), successful interventions would likely require community-based approaches for primary prevention. Certainly interventions with probiotics have been proposed in response to the 'hygiene hypothesis' as a way to compensate for the lost environmental microbial exposures, and some have had modest effects on reduced IgE and atopic dermatitis, but not asthma.(81, 82) However, a better understanding of which microbial products are essential to lead to allergen tolerance and how they might be delivered on the population level is needed. It is compelling to think that this type of intervention also could reduce the prevalence of auto-immune diseases that have increased in parallel with allergic diseases. Given the demonstrated adjuvancy of proteins from dust mite

and the clear importance of mite allergy to allergic disease, reduction of dust mite exposure still seems called for, but there is question as to whether sufficient reduction really can be obtained.(83) In NYC, recently enacted laws will eliminate the use of residual oil burning in residential boilers, which is expected to lead to a dramatic reduction in combustion byproduct particulate matter in NYC. It will be interesting to see if this decrease in allergic adjuvant exposure will have an effect on population level allergic disease prevalence and morbidity.

Conclusions

What clearly has emerged in our understanding of environmental exposures and allergic sensitization is that there is a complex interaction between exposures to allergens and biogenic and anthropogenic adjuvants. There is hope that understanding these complex interactions between these environmental exposure will lead to actionable intervention targets. Ultimately the goal is the implementation of population level interventions to decrease allergic sensitization in an attempt to reverse the allergic diseases epidemic.

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Figure 1. Biogenic and anthropogenic adjuvants in the pathway to allergic sensitization
Checks indicate studies demonstrating or suggesting adjuvant effects.