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Invited review article

# Allergens, sources, particles, and molecules: Why do we make IgE responses?

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*Abbreviations:*
USA, United States of America; UK, United Kingdom; kDa, kilodalton; OLIN, Obstructive Lung Disease in Northern Sweden Studies; NC, North Carolina; TN, Tennessee; AK, Arkansas; MI, Missouri; VA, Virginia; GOS, galacto-oligosaccharide; IU/mL, international units per milliliter; APC, antigen presenting cell; DCs, dendritic cells; IL, interleukin; GC, germinal center; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin; MD2, lymphocyte antigen 96; Th2, Type 2 (helper T cells); TSLP, thymic stromal lymphopoietin; DNCB, dinitrochlorobenzene; TGF, transforming growth factor; TLR, Toll-like receptors; IFN, interferon; CCD, carbohydrate cross-reactive determinants; $MMXF^3$, horseradish peroxidase; $MUXF^3$, Bromelain; $MMF^3F^6$, Insect core 3-fucosylated N-glycan; GalNAc, N-Acetylgalactosamine; GlcNAc, N-Acetylglucosamine

ABSTRACT

Allergens are foreign proteins or glycoproteins that are the target of IgE antibody responses in humans. The relationship between subsequent exposure and the allergic symptoms is often or usually obvious; however, there is increasing evidence that in asthma, atopic dermatitis and some forms of food allergy the induction of symptoms is delayed or chronic. The primary exposure to inhaled allergens is to the particles, which are capable of carrying allergens in the air. Thus, the response reflects not only the properties of the proteins, but also the biological properties of the other constituents of the particle. This is best understood in relation to the mite fecal particles in which the contents include many different immunologically active substances. Allergic disease first became a major problem over 100 years ago, and for many years sensitization to pollens was the dominant form of these diseases. The rise in pediatric asthma correlates best with the move of children indoors, which started in 1960 and was primarily driven by indoor entertainment for children. While the causes of the increase are not simple they include both a major increase in sensitization to indoor allergens and the complex consequences of inactivity. Most recently, there has also been an increase in food allergy. Understanding this has required a reappraisal of the importance of the skin as a route for sensitization. Overall, understanding allergic diseases requires knowing about the sources, the particles and the routes of exposure as well as the properties of the individual allergens.



## Introduction

In public usage an allergy is a reaction that follows exposure to a foreign agent with a predictable time relationship. In many cases, this implies a rapid or immediate relationship but patients can be “allergic” to poison ivy, which takes 6–24 h, or to red meat in the alpha-gal syndrome which takes 3–6 h.[1,2]

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Allergic diseases can be characterized by the nature of the immune response that gives rise to the unwanted symptoms or by the form of the clinical presentation (Table 1). Many of these diseases have rapid onset after exposure, which greatly simplifies identifying the cause. Thus, exposure to a cat can cause sneezing, eye itching and wheezing within a few minutes; similarly the sting of a wasp or yellow jacket can cause generalized hives within 10–15 min, and eating peanuts can cause full-blown anaphylaxis within 20 min. On the other hand, there are many allergic diseases for which the symptoms take longer to develop, and the symptoms may be much less obviously related to the relevant exposure. In addition, there are now several situations in which the route of exposure that gives rise to sensitization is not the same as the route that precipitates symptoms (Table 2)

The three diseases included in Table 2 illustrate the fact that the skin is an excellent route for inducing IgE antibodies. The first example was actually schistosomiasis. In this case, Taliafero and Taliafero demonstrated in 1931 that the serum of patients with the disease could transfer skin sensitivity into the skin of non-infected individuals.[3] The importance of the skin as a route of sensitization has now been established for three diseases: i) peanut allergy[4]; ii) delayed anaphylaxis to red meat in patients with IgE to galactose alpha-1, 3-galactose[5]; and iii) wheat sensitization related to wheat dependent exercise induced anaphylaxis[6,7] (Table 2). It should also be noted that many of the patients with diseases shown in Table 1 do not describe an immediate response to exposure. In some cases, this may be because the inflammation in the tissues is induced by a T cell mechanism, but the apparent delay may also represent either a delayed inflammatory response following mast cell mediator release or the effects of chronic low dose exposure. There is also another allergic disease characterized by IgE to milk for which a diet avoiding cow's milk can be an effective treatment; however, the relevance of the IgE antibodies to the disease is not clear.[8–10] This disease is eosinophilic esophagitis, which presents a special challenge because the disease includes a progressive eosinophil-rich inflammation without any obvious immediate phase.

## Size of particles and proteins: relevance to sensitization

### *Particles and the delivery of inhalant allergens*

The purification of allergens started in the 1960's with ragweed and grass pollen, which were the major causes of hay fever in the USA and UK respectively.[11–13] At that time it was already recognized that exposure depended on both the nature of the proteins and the properties of the particles carrying them. It cannot be stressed too strongly that there is no such thing as airborne protein molecules—the saturated vapor pressure of molecules that are ≥5 kDa is close to zero. Thus the only relevant source of airborne allergens is on particles that are capable of becoming airborne (Fig. 1). For the outdoor exposures, it is possible both to count and identify pollen grains or fungal spores. However, this counting depends on the fact that these particles stay airborne. By contrast, the indoor environment is characterized by very low rates of air movement and particles as big as mite fecal particles or pollen grains fall rapidly. There are major differences between the particles on which dust mite and cat allergens become airborne.[14–16] The way in which small particles or flakes of dander remain airborne leads to very different calculations about the quantity of allergen that can be inhaled. However, it is worth remembering that a large proportion of the particles inhaled through the mouth will impact on the back of the throat, and are subsequently swallowed.

The best studied of the allergen particles are the fecal particles of dust mites. After the purification of the group I and group II proteins it rapidly became clear that the major form in which they become airborne was on these particles.[17,18] In addition, it was already suggested that Der p 1 was a digestive enzyme. With the cloning of Der p 1, it became clear that it had major homology with cysteine proteases.[1,19] A whole series of studies were carried out on the relevance of the enzymatic activity, and this was followed by the increasing realization that the fecal particles were a veritable treasure trove of toll-like receptor ligands, as well as foreign proteins (Table 3). The message is clearly that these particles have great potential to induce an IgE response, and also that it is very unlikely that the response can be attributed to one of these constituents alone.

**Table 1**
Allergic diseases.

| | Source | Mechanism/Exposure |
|---|---|---|
| *Immediate reactions:* | | |
| Venom anaphylaxis | Bee, wasp or fire ant stings | IgE + injected |
| Penicillin anaphylaxis | Penicillins (oral or injected) | IgE + injected or swallowed |
| Peanut anaphylaxis (Other foods) | Peanut products (oral or skin) | IgE + swallowed |
| *Immediate + Delayed or chronic reactions:* | | |
| Seasonal allergic rhinitis | Pollen grains | IgE + inhaled |
| Allergic asthma | Dust mite, cockroach, cat, dog, *Alternaria* | IgE + inhaled |
| *Non-immediate reactions:* | | |
| Atopic dermatitis | Many allergens (both food and inhalant) + Infection of the skin | IgE and T cells + multiple routes of exposure |
| Poison ivy | Chemicals in the plant | T cells + contact |
| Delayed anaphylaxis to red meat | Tick bites give sensitization to alpha-gal | IgE + oral mammalian meat |

**Table 2**
Alternate routes of exposure.

| Source | Route | IgE response | Syndrome |
|---|---|---|---|
| Tick bites | Skin | IgE to alpha-gal | Delayed anaphylaxis to red meat |
| Peanuts (e.g., peanut butter) | Skin | IgE to Ara h 1 and Ara h 2 | Immediate reactions to oral peanut |
| Wheat in soap | Skin of face | IgE to wheat | Wheat dependent exercise induced anaphylaxis |