

Allergens from mites: implications of cross-reactivity between invertebrate antigens

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Group 1 and 2 allergens are probably the most important mite allergens. Some mite allergens, such as tropomyosin, are widely cross-reactive. The prevalence of sensitization to invertebrates cannot be based solely on skin test or serologic data with the allergen extracts currently available. Purified (recombinant) allergens, selected for low cross-reactivity, are urgently needed.

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House dust as a cause of allergic disease was discovered in the early 1920s by Kern (1921), Cooke (1922), and Storm van Leeuwen (1922). Mites were mentioned as a possible source of allergen in asthma by, among others, Storm van Leeuwen (1924) and Varekamp (1925), but at first these mite reactions were linked to occupational exposure to storage mites. In 1928, Dekker postulated that asthma in Germany was in 60 out of 100 cases due (at least in part) to allergens produced by mites in the house, particularly *Tyrophagus*, *Glycyphagus* (*Lepidoglyphus*), and *Acarus* (*Aleurobius*). It was not until 1964 that it became clear that mites of the genus *Dermatophagoides* were the main source of indoor allergen (see Ref. 1 for an early history of the house-dust mite with relevant references).

This conclusion was primarily based upon two sets of observations:

- 1) the correlation between the allergenic potency of dust extracts and the number of mites in the dust samples
- 2) the correlation between the skin reactivity to a dust extract and the skin reactivity to a mite-culture extract.

When RAST technology became available, neutralization experiments showed that in most sera (The Netherlands) IgE-binding to dust extract was more than 80% inhibitable by mite (*D. pteronyssinus*) extract. The remaining activity was largely due to cat and dog allergens (2, 3). In some,

more exceptional cases, the IgE-binding activity of house-dust extract was due to bird allergens (4), rodent allergens, or food allergens (5). In rare cases, the source of IgE-binding activity in house dust proved to be elusive.

Up to now, 10 *Dermatophagoides* proteins have been identified as allergens of *D. pteronyssinus*:

Der p 1: 25-kDa cysteine protease; predominant in mite-culture extracts, often the major protein component; cross-reactivity between *D. pteronyssinus* and *D. farinae*/*D. microceras* lower than expected

Der p 2: 14 kDa, epididymal protein? less extensively excreted; more cross-reactive

Der p 3: 30 kDa, serine protease

Der p 4: 60 kDa, amylase

Der p 5: 14 kDa, unknown function

Der p 6: 25 kDa, chymotryptic serine protease

Der p 7: 22-28 kDa (on SDS-PAGE; ≥60 kDa by size-exclusion chromatography; unknown function

Der p 8: 26 kDa, glutathione-S-transferase (6)

Der p 9: 24 kDa, collagenolytic serine protease

Der p 10: 37 kDa (on SDS-PAGE; 74 kDa by size-exclusion chromatography); tropomyosin.

Cross-reactivity

It is unusual for human sera to be exclusively reactive to *D. pteronyssinus*, but virtually all sera

react to *D. farinae*. In a patient population selected for skin reactivity to *D. farinae*, a correlation coefficient $r=0.954$ ($n=79$) was found for Group 1, $r=0.984$ ($n=82$) for Group 2, $r=0.405$ ($n=52$) for Group 3, and $r=0.796$ ($n=36$) for Group 5 (7).

Most sera that react to *D. pteronyssinus* will also react to extracts of storage mites (8–10). This is largely due to cross-reactivity. The major cross-reactive component is rarely Group 1; occasionally, it is Group 2; and, in some cases, it is tropomyosin (11).

Cross-reactivity with nonmite invertebrates (e.g., cockroach) complicates diagnostic, as well as epidemiologic, studies (11–13).

IgE to Der p 8 (GST: glutathione-S-transferase) was also found to be highly cross-reactive with distantly related GSTs. For example, this was found in experiments in which recombinant fusion proteins were tested for IgE binding. The pGEX-vector codes for GST from *Schistosoma mansoni* as fusion protein. The vector control was found to be occasionally positive with mite-positive sera, and this binding was inhibitable with *D. pteronyssinus* extract.

We found IgE reactivity to extracts of a wide variety of invertebrate organisms (including shrimp, cockroach, and chironomids) to be strongly associated with IgE reactivity to *D. pteronyssinus* extract (12). By means of RAST inhibition, we could demonstrate that, in most instances, *D. pteronyssinus* extract was the most efficient inhibitor and thus the most probable IgE-inducing stimulus. A notable exception was the group of mite-positive patients with shrimp allergy: in these sera, shrimp extract was the most efficient inhibitor.

A formal proof that IgE antibodies reactive to one or several mite components were actually induced by exposure to mite allergen is not easy to obtain. Similarly, the finding that a patient has IgE antibodies reactive to cockroach or silverfish is no proof that cockroach or silverfish is of any relevance to that patient. A high level of exposure of that patient may be used as supportive argument, but still does not prove the point, because, for example, houses that contain increased levels of silverfish antigen are also likely to contain increased levels of mite allergen.

Conclusions

- 1) Group 1 and 2 allergens are probably the most important mite allergens.
- 2) Some allergens are widely cross-reactive.
- 3) The prevalence of sensitization to invertebrates cannot be based solely on skin test or serologic

data with the allergen extracts currently available. Purified (recombinant) allergens, selected for low cross-reactivity, are urgently needed.

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