

The antigenicity of house dust mites

C. SCHOU & P. LIND

INTRODUCTION

Fragments and faeces of house dust mite occur as airborne particles, and will therefore be inhaled and reach the human immune system primarily through the mucosal membrane of the airways. Investigation of the mites' antigens has therefore been concentrated on molecules eluted from the fragments under conditions that resemble those found on the respiratory tract mucosal membranes, i.e. molecules that dissolve at physiological pH and ionic strength.

The following identification of the allergenic molecules is based on the assumption that the caused allergy is IgE-mediated, and the allergens therefore have the ability to bind that class of immunoglobulin.

In the investigation using crossed immunoelectrophoresis (CIE) it has been shown that extracts of house dust mites contain more than 50 different antigenic molecules that can be eluted under specific conditions (16). Using crossed radio immunoelectrophoresis (CRIE) approx. 13 of these antigens can be identified as binding IgE; i.e., molecules with allergenic properties (15).

Using serum from a large panel of people allergic to house dust mites, it has been shown that especially two allergens are important, i.e. that IgE from the majority of patients bind to these molecules. Several other allergens are also significant, but as yet only superficially studied.

The major part of the work with defining the allergenicity of house dust mites has been focused on three *Dermatophagoides* species: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Dermatophagoides microceras*. The most impor-

tant allergens from these species are Group I (respectively Der p I, Der f I and Der m I) and Group II (Der p II, Der f II and Der m II).

The allergen nomenclature follows the guidelines laid down by the International Union of Immunological Societies (IUIS) (24) and is formed by a name composed of the genus name's three first letters, a space, the first letter of the species' name, a space, followed by a Roman numeral.

Groups I and II, depending on the patient selection criteria, will react with IgE from 60-100% of the people studied who are allergic to mites.

The purified allergens have been investigated for ability to trigger basophile histamine release in children with allergic asthma caused by house dust mites. By comparing the median threshold concentration for release of histamine, Der p I was shown to be 10 times as potent as Der p II on a molar basis. The basophilic sensitivity for the two allergens for each patient correlated with the IgE binding to these allergens in CRIE (21).

Group I allergens. These are heat labile, very easily soluble proteins (1) that are possibly glycosylated. After storage for 1 h at 56°C they lose 50% of their antigenicity. The molecules are pH stable in the area of pH 4 to pH 10 and are also trypsin resistant (17). Group I allergens have been purified by physicochemical methods and have a molecular weight of 24-27 kDa, depending on the analysis used. The molecules show several bands in isoelectric focusing (pI 4.7-7.4) (2, 11, 12) and it is therefore assumed that posttranslational modifications take place.

It is known that the Group I allergens that are synthesized by the mites leave the animals via the intestinal system and are found in the faecal particles in large quantities (19). Amino acid sequencing from the amino terminal of the purified Group I allergens shows a large degree of identity between the three species and indicates that the molecules are structural homologues in the three mite species (13). The gene for Der p I has recently been sequenced and the allergen's total amino acid sequence deduced (5). The molecule's length is 222 amino acids and its molecular weight is 25,371 Da. The Group I allergens possess a large sequence homology with cystein proteases (e.g. cathepsins and papain) and it is therefore assumed that the allergens are intestinal enzymes of consequence for the mites' digestion. The Group I allergens' antigenic structure has been investigated in both human and murine systems. It has been shown that human IgE reacts with both the Group I determinants that are common for the three mite species and the species-specific determinants (3, 13, 14). More detailed studies of the immunological cross-reactivity at the antibody level have been made with monoclonal mouse antibodies. At least three topographically distinct antigen determinants of the allergen Der p I have been found, and for each determinant there is the possibility of developing antibodies with different spectrums of species-specificity to the homologous molecules. Human IgE reacts with the same determinants (13).

Immunological cross-reactivity is more often seen between Der f I and Der m I than between either of these and Der p I. The larger sequence homology between Der f I and Der m I than between either of these and Der p I supports the apparent close taxonomic relationship between *D. farinae* and *D. microceras*. Anatomical data indicate the two as sibling species (9).

The Group I allergens' interaction with the immune system at the T-cell level is as yet only sporadically investigated, and the few studies made have been performed with peripheral blood lymphocytes, i.e. without a possibility for judging the single T-cell clone's reaction pattern. By using the gene sequence currently available for Der p I and probably soon for Der

f I and Der m I, it will be easier to demonstrate the structural basis for differences and similarities between the three species' Group I allergens and thereby allow a more detailed study of the allergic immune response to these molecules.

Group II allergens. These allergens are easily soluble proteins with a molecular weight of 14–15 kDa, depending on the method of analysis used. Group II allergens are more pH stable than those in Group I, i.e. they tolerate pH values of between 2 and 12. Group II molecules are stable at 56°C and tolerate 100°C for 10 min. A heterogeneous pattern in isoelectric focusing (pI 5.0–8.3) also applies for this group of allergens (11). It is known from comparison of extracts manufactured on the basis of whole mite cultures and those from pure mite bodies that Group II allergens are primarily associated with the somatic parts of the mites (8). Der p II from *D. pteronyssinus* and Der f II from *D. farinae* show a large degree of identity in the amino terminal amino acid sequence (8). The gene for Der p II has recently been cloned and the allergen's complete amino acid sequence been deduced. The protein consists of 149 amino acids with an MW of 14,131 Da (4). The two molecules also resemble each other concerning allergenicity, since quantitative intradermal testing of patients with the purified allergens gives a high correlation between IgE responses against the two antigens. Der m II from *D. microceras* has been purified, but not yet as thoroughly investigated as the other Group II allergens. The amino acid sequence data and the strong immunological cross-reactivity supports the suggestion that Group II allergens are structurally homologous proteins in the three mite species. As yet the Group II allergens' antigenic structure has not been studied in such detail as that for Group I, but access to larger amounts of pure allergen will allow analysis to define the interaction between the allergen and antibodies/regulatory T-cells. A study with cloned humane CD4-positive T-cells has shown that a T-cell reactive determinant is found on Der f II which is not shared with Der p II (18).

Group I versus Group II allergens. Nothing indicates that the two groups of allergens share structural similarities or immunological cross-reactivity.

Other allergens. A varying occurrence of sensitivity towards other mite allergens is found according to the selected patient population; e.g. a structurally distinct allergen, Der f III from *D. farinae*, reacts with IgE from 16% of 65 people allergic to mites in an American study (8). Another important, but as yet little studied allergen is antigen 23 from *D. pteronyssinus* and *D. farinae*, which is known to bind IgE in up to 60% of the analysed people allergic to mites (2). It has been shown that extracts based on whole mite cultures or pure mite bodies have similar measurable influence on the immune system during immunotherapy (22). This accords with the observation that both types of extract, in spite of different relative concentrations of Groups I and II, represent the whole spectrum of significant allergen molecules.

Cross-reactivity with other mites. It is not yet clear to what degree immunological cross-reactivity occurs between house dust mites and storage mites. Several studies with RAST inhibition of sera from storage mite allergics showed no significant allergenic cross-reactivity between *D. pteronyssinus* and the four storage mites *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Glycyphagus domesticus* and *Acarus siro* (20). One study indicates, however, a weak cross-reactivity between *D. pteronyssinus* and the above-mentioned storage mites (7). The phylogenetic relationship between house dust mites and the mentioned storage mites is more remote than between the house dust mite species themselves, so from the taxonomic viewpoint alone only a weak immunological cross-reactivity between the two groups of mites could be expected. Some cross-reactivity between *D. farinae* and scabies mites (*Sarcoptes scabiei*), at least with rabbit sera, has been found (6). As yet the clinical significance of these observations is unknown. It is not yet clear what importance the house dust mites of the genus *Euroglyphus* have as sources of allergen, but as more specific reagents are developed

it will become possible to evaluate these species' contribution to the development of house dust mite allergy.

The future. Continued study with detailed analysis of the antigenic structure of Group I and II allergens using peptide synthesis and recombinant DNA technique will hopefully give a clearer picture of how the allergic immune response is regulated. It is possible that both B-cell and T-cell specificity becomes altered in the course of an allergic disease, and such changes can be investigated with these techniques. The acquired knowledge will be useful in the development of therapeutic methods which will be more specific and predictable in their effect on the human immune system than those available at present.

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