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EDITORIAL

Mite allergens

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1. Introduction

Sensitization to house dust mite allergens (HDM) is a major risk factor for asthma worldwide, particularly in the Tropics where they grow abundantly all year [1]. They are also risk factors for rhinitis [2] and food-induced anaphylaxis [3]. Some other potential activities have been suggested for HDM or their components, for example, oxidative damage to proteins, lipids, and DNA in lung cells [4] or induction of gastrointestinal inflammation by the enzymatic properties of Der p 1 [5]. Molecular studies have been improved by the production of HDM allergens as recombinant molecules, now available for component resolved diagnosis (CDR) and the designing of potential allergy vaccines. Here I analyze how these developments have been useful and what remains to be done to get closer to personalized medicine.

2. The allergic response against mite allergens

There are more than 30 clinically relevant mite species; two of them *Dermatophagoides pteronyssinus* (Pyroglyphidae family) and *Blomia tropicalis* (Echimyopodidae family) are widely distributed [2,6]. Since each of them has at least 20 IgE-binding components (Der p 1 to Der p 30 and Blo t 1 to Blo t 21, isoforms not included), in tropical places it is possible to be exposed to a variable number of epitopes from at least 40 potential allergenic components from mites. However, although little information is available, it is likely that the level of expression, the stability, and the possibility of remaining airborne of these proteins are not the same. In addition, the individual genotype and the exposure to other environmental conditions are known to influence the final immune response. Therefore, it is expected that heterogeneity of the allergic responses against HDM is the rule, being the specific IgE responsiveness the best known phenotype resulting from this process. Since the same conditions for both sensitization and triggering are usually present in a particular environment, it has been assumed that specific IgE is a proxy that represents almost all the properties and circumstances that make a component allergenic. However, recognition by specific IgE antibodies (IgE-binding) is necessary but not sufficient to be an allergen.

3. The allergenicity of mite extracts and their IgE-binding components

An allergen does not only induce specific IgE but also allergy reactivity and symptoms; in this regard, the clinical impact of HDM has been consistently documented by epidemiologic studies and provocation experiments in both human and animal models. These studies, with few important exceptions, have been performed with mite extracts and are supported by the successful results obtained with HDM-specific immunotherapy [7] and the discovery of new pathways in asthma pathophysiology. For example, some HDM allergens, in addition to be highly allergenic, may have a direct effect on bronchial epithelia, inducing inflammation through IgE-independent mechanisms [8], which possible makes them more pro-inflammatory. Besides, the identification of innate-immunity mechanisms in the early phases of immune response has revealed important clues about the mechanisms of sensitization [9].

In addition, genetic studies have identified variants of several genes such as *HLA-DRB1*, *IL4*, *IL13*, etc., associated with the IgE response to mite allergens [10], which is important for understanding the atopic component of asthma predisposition and improving the accuracy of diagnosis. In connection with this, an interesting information comes from studies that evaluate early patterns of IgG responses and IgE sensitization (ratio IgG/IgE) to mite and other allergens, which suggest the existence of protection from allergy symptoms in individuals with the highest IgG/IgE ratios [11–13]. These findings are similar to those found during chronic helminth infections, where IgG response is stronger than that of IgE and allergy symptoms are almost absent; in fact, we have discovered parasite components that bind IgE with high frequency but are not allergenic [14] and this could occur to mite IgE-binding components whose allergenic properties have not yet been fully tested.

4. Mite allergens and precision medicine

Mite allergy diagnosis is also going through an interesting time, and decision algorithms (combining extracts and components) for diagnosing mite allergy in temperate and tropical countries have been recommended [15]. There are a number of mite IgE-binding components available for CDR, including

species-specific and cross-reacting molecules, most of them with well-defined structural and epitope data, although not all with empirically demonstrated allergenicity. A necessary step, the determination of the IgE reactivity against mite components in different populations and environments, has partially accomplished [16–18]. However, the analyses of these data have been based on the frequency of IgE reactivity, not including other aspects of allergenicity. As a result, components have been classified as ‘major’ and ‘minor’ allergens, which could be erroneously interpreted as if only the former were clinically important. Therefore, there are still important aspects to solve if we want to make allergy diagnosis accurate and personalized.

First, a full characterization of the allergenic potential of each component, beyond IgE reactivity, is essential. Other recognized criteria for allergenicity should be considered, among them the strength of the IgE response, the capability to activate basophils or histamine-releasing and the induction of symptoms under appropriate *in vivo* provocation tests. It is important to mention that frequently similar structural and functional properties between recombinants and their natural counterparts are assumed, but this should be confirmed, especially when allergenicity is not detected. Information about a detailed allergenicity evaluation is currently available for only 10% of all IgE binding proteins in the databases. Completing this task will allow a better assessment of the pathogenic role of each mite allergen as has been recently suggested for Der p 23 [17,18] and could be great independently of its IgE-binding frequency [19–21]. Recognizing that regional combinations of mite allergens are more appropriate and less expensive than large panels of just IgE-binding components will also help. No doubt that having truly and pertinent allergenic components in an array will avoid the use of ‘indiscriminate battery of IgE tests’ (<http://www.choosingwisely.org/societies/american-academy-of-allergy-asthma-immunology/>). Also important for personalized medicine, in regions where helminthiasis are still prevalent, arrays containing relevant allergens will have to add particular components such as *Ascaris lumbricoides* tropomyosin that is highly cross reactive with the mite’s counterpart [22] but at the same time could be a risk factor for asthma [23].

Determining the complete allergenicity of IgE-binding components will help to find more disease-associated allergens, in addition to Der p 1 and Der p 2 [24], but also could show that not all mite IgE-binding components are allergenic. Furthermore, it will provide clinically relevant targets for searching genomic markers useful in precision diagnosis and improve the mapping of potentially diagnostic epitopes. Of course, all these advances will make easier the selection of reagents for personalized immunotherapy and the design of mite allergy vaccines. Needless to say that it will help to select appropriate batteries of allergenic components for skin prick test, an *in vivo* safe and predictive provocation test that has stood the test of time.

Second, evaluating the IgG/IgE ratio could provide relevant information about the clinical significance of mite components. More studies are necessary in this field because those published so far suggest that IgE reactivity information is not enough to complete the actual picture of the immune

response to allergens. In terms of precision medicine, the differential diagnosis between ‘protective’ and ‘pathologic’ responses is important because at the end what is most representative of the complex process of induction and expression of the immune responses to mite allergens is the presence of symptoms, which also seem to depend on the relative weight of specific IgG and IgE antibody responses.

Third, the concept of ‘major’ and ‘minor’ allergens is contrary to that of personalized medicine, where the important point is the capability of the molecule to induce allergic symptoms, even in few patients. Although in the past it helped to focus on those components afflicting the majority of the patients, its current usefulness is debatable if we want to improve the sensitivity and specificity of allergy diagnosis.

Fourth, the traditional way of allergy diagnosis in doctor’s office, based in clinical history and skin tests for deciding the pertinence and specificity of immunotherapy, is an approximation to the current concept of personalized medicine. If a complete set of clinical relevant mite allergenic components become available, it can and should be made available for skin testing, in addition to mite extracts. The best combinations for defining genuine sensitization can be arranged, although *in vitro* diagnosis will be necessary in some cases. However, potential obstacles to this *in vivo* diagnostic option are legislation and the increasing costs in production, quality and licensing [25].

5. Conclusions

The allergenicity and clinical impact of extracts from *B. tropicalis* and *D. pteronyssinus* have been unequivocally demonstrated, but this has been done only for some of their IgE-binding components. Filling this gap is crucial for diagnosing allergy on the basis of the full allergenic potential and clinical impact of molecules, an approach that will permit a better selection of reagents for immunotherapy. Nowadays, *in vitro* microarrays that include mite components are available for molecular diagnosis of IgE sensitization; however, the easiest and convenient way to make this diagnosis is by skin prick test in doctor’s office, using the appropriate combinations of standardized mite extracts and recombinant allergens.

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Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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