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Clinically Significant Cross-Reactivities among Allergens

Key Words

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Abstract

Crossreactivity of IgE antibodies are occasionally unexpected and confusing. Moreover, the implications are not always the same. Some types of serologic crossreactivities usually produce clinical symptoms, whereas other do not. Even the latter type may be relevant, as it may contribute to the induction of immune responses to the crossreactive antigens ('crossreactive priming'). For the interpretation of IgE antibody assays it is important to appreciate that finding IgE antibodies to some allergen does not imply that the patient has ever been exposed to that allergen.

Introduction

Cross-reactivity among allergens may play a role both in the sensitization phase ('cross-reactive priming') as well as in the elicitation phase of the IgE-dependent allergic reaction. Furthermore, a combined effect is possible, since cytokines released from mast cells after triggering by a cross-reactive allergen may stimulate the production of (not necessarily cross-reactive) IgE antibodies to that allergen.

Cross-reactive priming is a stimulation of the immune system by a first antigen, which results in an enhanced immune response to a second cross-reactive antigen. This process is analogous to the effect of carrier preimmunization on the anti-hapten immune response due to the expansion of carrier-specific T or B cells. An additional possibility in the case of IgE-antibody responses is the IgE-facilitated antigen presentation via IgE receptors, e. g. on Langerhans cells.

In the case of *cross-reactive mast cell triggering* no stimulation of the immune system by the offending allergen is required. Allergic reactions to the ingestion of an apple, for example, are usually due to an immune response induced by inhaled cross-reactive birch pollen allergen *Bet v I*. A useful distinction between the primary allergen (i. e. the allergen that induced the immune response) and the cross-reactive allergen can usually be made by cross-absorption: in this example IgE binding to apple can be completely blocked by *Bet v I*, whereas the apple extract will usually give only a slight inhibition of the IgE binding to *Bet v I*. The explanation is that only a small fraction of the IgE antibodies to *Bet v I* are cross-reactive with the apple equivalent.

Mammalian Cross-Reactive Allergens

IgE antibodies to some mammalian serum proteins can be quite cross-reactive. Cat-allergic patients with IgE antibodies to cat serum often react not only with dog serum proteins, but also with serum proteins of other sources, e.g. swine and mouse [1, 2].

Bird-Derived Cross-Reactive Allergens

The cross-reactivity between chicken egg yolk and caged bird serum proteins [3–5] is perhaps not completely unexpected, but yet has clearcut practical implications: egg yolk sensitivity without egg white sensitivity in an adult strongly suggests an allergy towards caged birds. This might be an example where an inhalant allergen induces an allergy towards foods.

Invertebrate-Derived Cross-Reactive Allergens

One type of cross-reactivity is due to IgE antibodies to cross-reactive carbohydrate determinants (CCDs) [6–12] that often cross-react also with vegetable glycoproteins. Other cross-reactive structures exist as well. Of particular importance are at least two, as yet unidentified, allergens of *Dermatophagoides* which are cross-reactive with other invertebrate macromolecules, e.g. from prawns, snails or caddisflies [13, 14]. The role of tRNA [15, 16] in these cross-reactions remains to be established.

Pollen and Fruits and Vegetables

Several complicating features have troubled this field for a long time. First, to obtain a potent protein extract from vegetable material special precautions proved to be essential [17]. In contrast, CCD reactivity was very easily extracted. Second, the cross-reactive *Bet v* I-related proteins and, perhaps even more so, the cross-reactive protein profilin (see below), are poorly immunogenic in experimental animals and therefore are not easily demonstrated by CRIE techniques. In contrast, CCD structures are strongly immunogenic in experimental animals, but precipitate poorly and thus are also not easily identified by CRIE (but very easily in immunoblots).

As demonstrated by Calkhoven et al. [18], pollen cross-reactivity can be due to at least 3 distinct structures: (1) 18- to 20-kD *Bet V* I equivalents in apples, etc., but *not* in

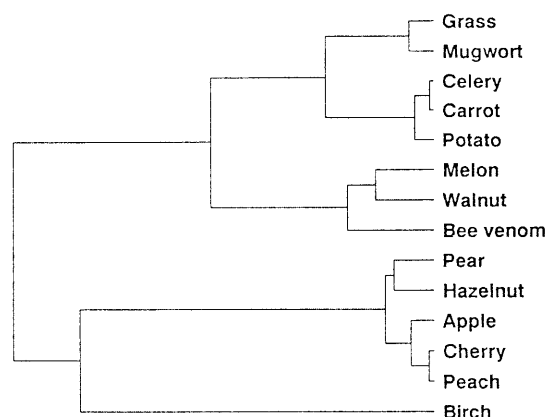


Fig. 1. Birch-apple cross-reactivity. Dendrogram obtained by agglomerative hierarchical clustering of the RAST results of 43 birch-apple-positive sera [18].

grass or weed pollen, celery, carrots, etc.; (2) a 14- to 18-kD protein [18–21] subsequently identified as profilin [22–24] in most vegetable source materials, particularly celery, potato, carrots and some spices, and (3) CCD in most vegetable and invertebrate source materials.

This list of cross-reactive IgE antibodies is by no means complete. The cross-reactivity between IgE antibodies to natural latex and some fruits, notably banana and avocado [25, 26], is important because of the widespread use of latex-based products. The relation with the 30-kD cross-reactive allergen found in fruits [27] needs to be established.

Mechanistic Questions and Implications

An intriguing question is whether IgE antibodies are more cross-reactive than other isotypes. If the answer were 'yes', the obvious question would be 'why'. It might indicate that there would be less affinity maturation in the IgE response and/or a preference for conserved epitopes by a lack of evolutionary pressure. Another possibility would be that the induction of IgE antibodies would be facilitated by cross-reactive priming (see below).

Another problem posed by cross-reactivity between allergens is whether mast cell triggering can be accomplished. I will take the birch-apple cross-reactivity as an example, assuming that this starts with a specific (i.e. non-cross-reactive) birch pollen allergy. Upon continuing pollen stimulation IgE antibodies against other epitopes

will develop, some of which will be cross-reactive with an epitope on an apple antigen. We now know that the *Bet v* I-related allergens are single-chain molecules. One would therefore expect at least two cross-reactive epitopes recognized by two different cross-reactive IgE antibodies in patients with apple sensitivity. Since some patients have no apple-specific IgE at all, one would predict that there are some patients with just one cross-reactive IgE antibody; these patients would be cross-reactive in a serologic test (RAST) but not in a bioassay (skin test, basophil test). We have not yet identified such a patient.

One example illustrating how a complex IgE response to grass pollen might develop is the case of potato/tomato sensitivity in children with grass pollinosis [28] and particularly in children that will subsequently develop grass pollinosis [2]. The first sensitization would be against foods. Cross-reactive IgE antibodies would develop. Upon contact between this cross-reactive IgE and a pollen grain in the airway mucosa, other antigen from the pollen grain would enter the site of the local allergic reaction and IgE antibodies against these other, non-cross-reactive components would develop.

Another example is that of the development of an IgE response to the cat allergen *Fel d* I (Cat1) in children with pork sensitivity [2]. The *Fel d* I molecule itself is not particularly cross-reactive: only reactivity with other feline

species has been found. However, a marked cross-reactivity was found between cat serum and pig serum, especially in young children. We identified 4 children with a transient IgE response to cat serum who subsequently developed IgE antibodies to *Fel d* I. A transient IgE response is typical for a food response. In these children we found a transient IgE response to pork and pig serum (but not beef or bovine serum). By RAST inhibition we found that pork serum inhibited the cat serum RAST. In this case the cross-reactive antibodies to pig serum proteins, by cross-reaction with cat serum proteins present on the cat skin flake, would have 'opened the gates' for *Fel d* I.

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