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Food allergens

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Abstract

A food allergen may be defined as a substance that reacts with IgE antibodies, induces allergic sensitisation or induces allergic reactions. Some allergens only induce allergic sensitisation but do not provoke symptoms, while others bind IgE but do not induce mast cell degranulation. There is no common structure that can predict whether a given antigen may be a strong food allergen. A complete food allergen, e.g. fish parvalbumin, is capable of stimulating the immune system to produce IgE antibodies, and degranulate mast cells upon subsequent contact. The reason(s) for why some patients with IgE to ovalbumin tolerate eggs, and why some react on one occasion but not on another, are mostly unclear, but may be related to changes in gut permeability induced by other food substances or by gastro-intestinal inflammation prior to the allergen contact. IgE antibodies to fruit or vegetables often show cross-reactivity, due to carbohydrate structures. These cross-reactive glycans have been designated cross-reactive carbohydrate determinants (CCD). Anti-CCD antibodies are highly cross-reactive. The antibodies do not have clinical significance because CCD-containing foods are usually well-tolerated by patients with IgE antibodies to CCD. These IgE antibodies may cause confusion in relation to allergy diagnosis. © 1997 Elsevier Science B.V.

Keywords: Food allergen; IgE; Cross-reactivity

1. Introduction

The terminology ‘food allergen’ is ambiguous, because it has at least three interpretations:

1. a food substance that reacts with IgE antibodies;
2. a food substance that induces allergic reactions;
3. a food substance that induces allergic sensitization.

Some food substances do all three of the above, (complete allergens). However, some will do 1, but not 2 or 3 (‘non-elicitors’), whereas others will do 1 and 2, but not 3 (‘non-sensitizing elicitors’).

Before turning to the main topic of this study, the first category of ‘true’ food allergens, I will first briefly comment on ‘incomplete’ food allergens, i.e. the two other categories (which is more fully discussed elsewhere in this issue Vieths, 1997).

2. The two types of incomplete food allergens

2.1. Non-sensitizing elicitor

A food substance that induces allergic reactions, or: non-sensitizing elicitor (e.g. the apple allergen that crossreacts with the major birch pollen allergen Bet v1 (Vieths et al., 1994; Ebner et al., 1996; Schoening et al., 1996) is usually not responsible for the induction of IgE antibodies: the lymphoid cells of the immune system never ‘see’ the apple allergen. The IgE antibodies are induced by a crossreacting allergen. In the example mentioned birch pollen grains in the nose release Bet v1 molecules, which results in an immune response, including IgE antibodies, to many epitopes on this molecule. Most of these antibodies are specific for the birch protein, but some are crossreactive, e.g. with the homologous protein from the apple. These IgE antibodies circulate through the body and will fix a.o. to mast cells in the oral area. Upon subsequent oral contact with apple proteins the local mast cells will react and this will induce peri-oral symptoms.

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Another well-known vegetable protein in this category is profilin (Calkhoven et al., 1987; Valenta et al., 1991, 1992a,b; Van Ree et al., 1992, 1995) for which pollen from grasses and trees as well as weeds are relatively common sensitizers, and raw vegetables are good elicitors (e.g. carrots).

2.2. *Non-elicitor*

A non-elicitor (e.g. some vegetable or invertebrate glycoproteins (Aalberse et al., 1981a,b; 1983; Aalberse, 1989; Koshte et al., 1989; Aalberse, 1992, 1995; Aalberse and Van Ree, 1996; Petersen et al., 1996; Vieths and Schöning, 1996) are usually, but not necessarily, non-sensitizing) reacts with IgE on the mast cell, but this interaction does not trigger the mast cell to degranulate. The reasons for this lack of mast cell stimulation are unclear, but might possibly be related to monovalency of the allergen. One of the dogmas of allergy is, that an allergen has to bind via at least two epitopes in order to crosslink two IgE antibodies on the mast cell surface. A monovalent allergen will bind only a single IgE antibody and this interaction will therefore not result in IgE receptor crosslinking or mast cell stimulation. The reason why particularly vegetable glycoproteins are prone to this monovalent-like behaviour will now be discussed (even if I do not as yet have a good understanding of all the mechanisms involved).

3. What is special about vegetable glycoproteins

From the immunological point of view, glycoproteins may be considered as hapten–carrier complexes, with the glycan as hapten: a substance that is unable on its own to induce antibodies, but will do so when presented to the immune system on a suitable carrier protein molecule. The inability of the hapten on its own to induce antibodies is not due to lack of suitable B cells, but to the lack of recognition of the hapten by the helper T cells that are required for efficient B cell activation and differentiation. The carrier part of the hapten–carrier complex is therefore required to activate these T cells. Carrier-specific T cells will stimulate not only carrier-specific B cells, but also hapten-specific B cells. Similarly, pure glycans are usually poor immunogens, but the same glycan may elicit anti-glycan antibodies when coupled to a protein backbone. The glycan part of mammalian glycoproteins is usually not immunogenic, because most glycans are common to all mammals and the immune system develops tolerance to its own structures. However, glycans from non-mammalian sources, e.g. vegetable glycoproteins, are distinct from mammalian glycans and strong anti-glycan antibody responses are often found. Antibodies to vegetable glycans are often, but not always, crossreactive,

i.e. these antibodies do not clearly distinguish different vegetable glycans. The consequence is that these anti-glycan antibodies often react with very different glycoproteins from non-related plants.

Crossreactivity may even be found with invertebrate glycoproteins or glycans. These crossreactive glycans were designated 'Crossreactive Carbohydrate determinants' or CCDs (Aalberse et al., 1981a,b). The structure of some strongly immunogenic crossreactive non-mammalian glycans has been elucidated (Ishihara et al., 1979; Kaladas et al., 1983; Van Kuik et al., 1986; D'Andrea et al., 1988; Faye and Chrispeels, 1988; Hayashi et al., 1990; Prenner et al., 1992; Staudacher et al., 1992; Driouich et al., 1993; Faye et al., 1993) and for selected antibodies differences in immune reactivity have been found to depend on a fucose and a xylose.

4. Relevance of anti-CCD antibodies for food allergy

Three aspects make the CCD structure require special attention.

4.1. *Stability*

The carbohydrate structure is more stable than most protein structures, both in relation to heat as well as to gastrointestinal enzymes. In standard laboratory tests such as immunoblotting, the CCD structure stands out prominently and may mask more relevant structures.

4.2. *Cross-reactivity*

As mentioned earlier, anti-CCD antibodies tend to be highly cross-reactive, so a serum that, due to whatever type of immunizing contact, has IgE antibodies to CCD will be positive in IgE antibody assays for a very wide range of vegetable sources.

4.3. *Tolerance*

CCD containing foods are usually well tolerated by patients with IgE antibodies to CCD.

These three points indicate the confusion that CCD-reactive antibodies may cause in relation to allergy diagnosis.

5. CCD reactivity in specific allergy serology

To avoid the above mentioned diagnostic confusion it is desirable to have two artificial types of reagents.

5.1. CCDs without a (relevant, potentially IgE-binding) protein backbone

Using exhaustive protease digestion, CCD (with only a few amino acids attached) may be obtained with less than 0.1% of the peptidic immune reactivity, but this procedure also destroys part of the CCD immune reactivity, possibly by traces of glycosidase activity in the protease used (proteinase K).

5.2. Protein backbones without CCDs

The second type of reagent can be obtained using recombinant proteins expressed in a microbial or mammalian host (see below). Alternatively, the CCD structure may in principle be removed and/or degraded by enzymatic or chemical means. However, none of the commercially available glycosidases we tested so far is very efficient in cleaving off CCD from native glycoprotein, presumably because of shielding by the peptidic part. Periodate is usually efficient in destroying CCD immune reactivity, but some loss of peptidic immune reactivity may occasionally be found.

6. CCD in relation to recombinant allergens

The glycosylation pattern of a recombinant protein is determined largely by the host used for its expression. This means that these IgE-binding epitopes will not be found when vegetable glycoproteins are expressed in microbial expression systems, but also the reverse: expression of microbial or mammalian glycoproteins in plant or invertebrate expression systems will induce CCD-type epitopes on these proteins.

If the lack of symptom elicitation via CCD-anti-CCD can be substantiated, the above-mentioned differences in glycosylation pattern will have to be interpreted in a way very different from the more familiar situation, where IgE binding is associated with clinical allergy. The use of recombinant vegetable glycoproteins lacking the CCD structure due to the expression in a microbial host may be a distinct advantage from the diagnostic point of view, because the test system becomes more specific and more relevant. From the nutritional point of view, the use of a vegetable or insect expression system would not be a counter indication, even if the recombinant glycoprotein would be shown to have acquired IgE-binding properties due to the attachment of host derived CCD-type glycans.

7. Major true food allergens

Now I would like to return to my main designated topic: the true food allergens. For this I will focus on

‘major’ allergens, but there is some discussion on the definition of this concept. In my view a major allergen is:

1. an allergen that makes a difference
2. an allergen that on its own (quantitatively as well as qualitatively) mimics the activity of the source material.

7.1. Complete food allergen

A complete food allergen, e.g. fish parvalbumin, is capable of stimulating the immune system to produce IgE antibodies, and upon subsequent contact it is capable of stimulating sensitized mast cells. Not everyone with IgE to ovalbumin will have symptoms upon ingestion and some patients may react on one occasion, but not on another. The reason(s) for these discrepancies are mostly unclear, but may be related to changes in gut permeability induced by other food substances or by gastro-intestinal inflammation prior to the allergen contact. Some patients may have IgE reactive to different species of fish, but react only to a single species (Bernhisel-Broadbent et al., 1992a). This might indicate that only some (in this case: species-specific) of the many antigens the patient has IgE to is causing the symptoms.

These true food allergens tend to be relatively heat- and/or protease-resistant (Astwood and Fuchs, 1996), but it is not clear whether this is a requirement for both the induction phase as well as for the elucidation phase. Looking at lists of characterized true food allergens (Table 1, see also Yunginger, 1991) does not give any obvious clue to the nature of allergenicity. It is clear from the different model systems that the IgE response is strongly T cell dependent. Therefore, both the T-cell branch as well as the B-cell branch of the immune system has to be stimulated. This means that the material has not only physically to reach the immune system (i.e. has to cross the mucosal barrier), but it also has to be in a ‘good shape’ to be immunogenic (obviously, a non-immunogenic substance will not induce allergy). The ‘shape’ of the molecule is important for recognition by B cells and by antibodies. Fully denatured proteins usually do not have a sufficiently fixed shape and therefore do not induce antibodies easily (even if the denatured proteins are fit to stimulate T cells: T cells interact only with small peptides, with no secondary structure).

7.2. Antigen or allergen

Then, however, comes the next part of the problem: the relation between antigenicity and allergenicity, or: what makes an antigen an allergen. Perhaps the reciprocal question should also be asked: what makes a good antigen a poor allergen? Do such ‘poor’ allergens

really exist, or is every good antigen a good allergen? An interesting observation is, that patients are usually 'sensitized' (i.e. have IgE binding) to distinct proteins in the offending food, monospecific sensitization is the exception. This is clear from the immunoblot patterns e.g. with fish, egg or milk. This finding supports the view that allergen-induced mast cell triggering may induce subsequent sensitization to antigens that happen to be near (Mudde et al., 1990; Aalberse, 1991; Santamaria et al., 1993; Mudde et al., 1995).

Table 1
Some major, well-characterised food allergens

Fish parvalbumins

Cod (*Gadus Callarias*) allergen M = Gad d1 (Aas, 1987)
Salmon (*Salmo salar*): Sal s1 (Lindström et al., 1996)
Calcium-binding proteins predominantly in white muscle of lower vertebrates
12 kDa; pI 4.75; single glucose to Cys 18
See also Bernhisel-Broadbent et al., 1992a,b; Pascual et al., 1996

Milk β lactoglobulin

Member of the ligand-binding calycons (or lipocalins) (Flower et al., 1993), related to retinol-binding protein and some important mammalian allergens (e.g. rodent urinary protein, dog allergens Can f1 and Can f2)
Dimer (2 $\times$ 21 kDa); pI 5.2

Egg (Djurtoft et al., 1991)

Ovalbumin: 43 kDa, 1% glycosylation
Ovomucoid: 28 kDa, 25% glycosylation
Ovotransferrin: 78 kDa, 3% glycosylation

Shrimp tropomyosin (Pen a 1 and Met e 1) (Beach Daul et al., 1983; Morgan et al., 1989; Daul et al., 1990; Lehrer et al., 1990; Morgan et al., 1990; Daul et al., 1994; Leung et al., 1994)

Penaeus setiferus (white; New Orleans)
P. aztecus (brown; New Orleans)
P. indicus (white; Bethesda or Bangalore?)
Pandalus borealis (Atlantic Ocean; Pink Maine shrimp)
Metapenaeus ensis (South China Sea)
Crangon crangon (small North Sea shrimp)
Dimer (2 $\times$ 35 kDa), pI 5.2
2.9–4% glycosylation
Recovered in high yield from cooking fluid
Relation to mite, cockroach, snail (Aalberse et al., 1993; Wittman et al., 1994)

Peanut (*Arachis hypogaea*) Ara h1 and Ara h2 (Burks et al., 1995a,b; Buschmann et al., 1996)

Ara h1: 65 kDa, pI 4.6, Con-A reactive, vicilin-like seed storage glycoprotein
Ara h2: 17kDa, pI 5.2

Mustard seed 14 kDa allergen (González de la Peña et al., 1996)
Yellow mustard *Sinapis alba*: Sin a1

Brassica juncea Bra j1
2S seed storage protein; 2 chains (39/88 aminoacids)

7.3. T cell help

One important factor is the type of T cell help that an antigen induces. T cells provide in various ways help to B cells; without this help no B cell will develop into an IgE secreting plasma cell. T cell help comes in two flavours: type 1 and type 2. Type 1 help is induced mostly by microbial antigens. A characteristic feature is the production by the T cell of the cytokine interferon- γ . This type of immune response leads to the production of, for example, IgG1 antibodies (in the human), but it does not lead to the production of IgE. Also, little or no IgG4 is induced. Type 2 help, in contrast, is induced by multicellular parasites, e.g. gut parasites. A characteristic feature is the production by T cells of the cytokines IL-4 and IL-13, which are essential for the production of IgE antibodies. These cytokines, in addition, favour the production of IgG4 antibodies over IgG1 antibodies.

7.4. Immunoglobulins

The classical food allergen ovalbumin is distinctive by inducing a marked IgG4 response, even in normal subjects. In contrast, a distinctly atypical food antigen, gliadin from wheat, induces IgG responses in a subpopulation of normal subjects (in addition to a marked IgG as well as IgA response in patients with coeliac disease), but this response is, characteristically, predominantly of the IgG1 type, with very little IgG4 (or IgE). This might be taken as an example of a fairly potent food antigen, which is a very poor IgE-inducing allergen, possibly because of the stimulation by wheat components of type 1 helper T cells.

However, the situation is not as simple as this. A banana protein, a lectin called BanLec-1 (Koshte et al., 1990), is a potent IgG4 inducing antigen, with little induction of IgG1 antibody (Koshte et al., 1992). It is therefore presumably an antigen that induces a strong type 2 T helper response. Yet, it is not a very potent IgE inducing allergen.

7.5. Location of sensitization

The possibility should be kept in mind that the allergic sensitization might occur not in the gastro-intestinal tract, but in the naso-pharynx, following trapping of a food particle in the epiglottal/nasal mucosal area. Such a sterile foreign body reaction, that may result in a type 2 helper T cell stimulation, might explain why some particulate foods (peanuts, true nuts, mustard and kiwi seeds, celery stick fibres, fish bones, egg shell fragments) are more prone to act as true food allergen sources.

I have argued elsewhere (Aalberse, 1996) that IgE responses may occur either as part of a normal immune

response (eutopic IgE production), but also as part of a low-grade, inefficient 'ectopic' immune response, elicited by trivial, non-inflammatory antigens. These trivial (as opposed to microbial) antigens are incapable of triggering the regulatory mechanisms that organize the normal immune response.

8. Recommendations for future research

The nature of allergenicity of food proteins is still largely obscure. The three aspects of 'allergenicity' should be clearly distinguished: IgE binding potential, mast cell triggering potential and IgE inducing potential. The relation between 'normal' immune responses to foods and allergic immune responses could provide useful information on the etiologic aspects, including the relation between atopic ('neonatal') versus non-atopic ('late-onset') sensitization.

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