

A structural basis for food allergy: the role of cross-reactivity

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Purpose of review

Immunologic cross-reactivity, which is important in many aspects of host defense and immune-mediated diseases, is a prominent feature of allergic disorders. The goal of this article is to define allergenic cross-reactivity and its role in food allergy, review current understanding of mechanisms of cross-reactivity, and consider how advances in our ability to predict cross-reactivity can impact diagnosis and treatment of food allergy.

Recent findings

Recent evidence suggests that specific T cells, in addition to IgE, developed in response to inhaled allergens can cross-react with related food allergens, leading to distinct clinical reactions. Several new cross-reactivities have been identified, including food–food, pollen–food, and latex–venom associations. Debate continues regarding prediction of allergenicity based on protein structure, and clinical relevance of in-vitro testing. Cross-reactivity is also being used to develop specific immunotherapy for treatment of food allergy.

Summary

A thorough understanding of immunologic cross-reactivity is essential to advancing our knowledge about food allergy. This knowledge will help elucidate the pathogenesis of the disorder and prevent exposures to allergenic, genetically engineered foods. New insight will allow for better utilization of current diagnostic tools and the development of more accurate tests and therapies for food allergy.

Keywords

allergen cross-reactivity, food allergy, oral allergy syndrome

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Introduction

The phenomenon of immunologic cross-reactivity occurs when an adaptive immune response to one antigen results in reactivity to structurally related antigens. Such cross-reactivities are important in many aspects of host protection and immune mediated diseases, including allergic diseases, where they can impact both diagnostic and therapeutic approaches. For instance, cross-reactivity must be considered when deciding whether to skin test to single or multiple related aeroallergens and which extracts to include in immunotherapy. Cross-reactivities, however, are particularly important in food allergy, where they often are responsible for the disorder, affect the scope of disease and reliability of diagnostic testing and also have implications for current and potential therapies.

A role of cross-reactivity in food allergy was reported as early as 1942 with the recognition that individuals sensitized to pollen allergens were more likely to exhibit allergic symptoms upon eating certain fruits [1]. Since then many studies have confirmed that the immunologic mechanism underlying this observation is IgE antibodies developed in response to inhaled proteins that cross-react

with proteins in the food. Tuft *et al.* [1] also recognized that the reactions were limited to fresh food. The symptoms of the reactions they described were limited to the oral cavity (palatal pruritus, tongue and lip edema, etc.), so they were termed oral allergy syndrome (OAS). It later became clear, however, that in some patients the symptoms progress to involve organ systems beyond the oropharynx. Therefore, the terms ‘pollen–food syndrome’ and ‘class 2 food allergy’ were proposed. Other associations have been described, however, which are thought to have the same type of underlying molecular mechanisms, but in which the initial sensitizer is not pollen (e.g. latex–fruit syndrome, dust mite–shrimp tropomyosin allergy). Cross-reaction between IgE antibodies to drug and food antigens has even been proposed [2], making the term pollen–food syndrome too restrictive to completely cover the manifestations of these mechanistically related reactions. A more inclusive name for these syndromes might include the terms ‘cross-reactivity,’ ‘inhaled’ and ‘ingested.’

The scope of the problems caused by cross-reactivity of IgE antibodies is indicated by the large number of these syndromes described and the high prevalence of the

association between sensitivity to aero allergens and reactivity to certain foods [3]. These associations range from the classically and structurally defined birch-apple syndrome to newly described associations between cypress and peach, mesquite and lima bean, and molds and spinach [4–6]. Here we discuss the molecular mechanisms which can lead to cross-reactivity, newer strategies for predicting these reactivities, and some practical implications of cross-reactivity for the diagnosis and treatment of food allergy.

Mechanisms of cross-reactivity

The definition and methods that have been used to identify cross-reactivity allergic syndromes strongly imply that this phenomenon is based on IgE recognition of structural similarities between the sensitizing aeroallergens and one or more food proteins, which otherwise might not induce sensitization via gastrointestinal exposure. This type of cross-reactivity is most easily understood when the sensitizing and cross-reacting proteins belong to the same family of proteins and are easily recognizable by the similarity in their amino acid sequences (e.g. tropomyosins). When the specific cross-reacting aeroallergen and food proteins have not been identified or structurally characterized the molecular basis of cross-reactivity are more difficult to establish. While most cross-reactivity syndromes are thought to be due to IgE antibodies, there is also support for a role of T cells in cross-reactive food allergy as well [7,8]. This T cell mediated cross-reactivity may be independent of IgE-mediated mechanisms, occurring even in the context of denatured proteins and may have downstream effects on other allergic manifestations such as atopic dermatitis [9,10].

Still it appears that IgE antibody is the major player, especially in clinical expression of the phenomenon and most efforts have focused on identifying characteristics of molecules that make them targets for IgE binding. Although the particular characteristics of a molecule which make it likely to induce an IgE response have not been fully delineated, it has become clear that most of the currently defined allergens can be grouped into a limited number of protein families, whose members share some structural commonalities. For some groups, the IgE cross-reactivity is based on highly similar amino acid sequences (e.g. tropomyosin). Members of other cross reacting groups may have much less sequence identity, but share a discrete three-dimensional structure, or have similar overall conformation which accounts for their cross-reactivity (e.g. Profilins and PR-10 family). Yet others induce IgE cross-reactivity because of sharing epitopes based on linear sequence homology as well as others which lack sequence identity but have conformational similarity (e.g. PR-5 and seed storage proteins)

[11,12]. Examples of highly cross-reacting allergen groups are described below.

Lipid transfer proteins

LTPs (LTP, PR-14) are of great interest because they are associated with severe symptoms of food allergy [13] and are resistant to digestion and heating [14,15]. A number of new associations involving cross-reactive LTPs have been described including rice, plane tree pollen, strawberry, cabbage and others [13,16–19]. The ubiquitous nature of LTPs among plant species means that they have been considered panallergens.

Profilins

Classically, profilins have also been considered panallergens that sensitize primarily via a pollen source. The clinical relevance of IgE binding to profilins is not clear however. Additionally, there is evidence of incomplete cross allergenicity of some profilins [20,21]. In contrast to LTPs, they tend to produce much milder symptoms of food allergy, which may be due to their sensitivity to proteolysis by chymase, leading to decreased IgE reactivity [22].

Cross-reactive carbohydrate determinants

The role of cross-reactive carbohydrate determinants (CCDs) in food allergy continues to be debated. CCDs are widely distributed and structurally conserved in many plants and insects and may even play a role in animal allergy [23]. Plant proteins with glycans that contain xylose and fucose have been shown to induce IgE responses. The diffuse presence of these glycans means that anticarbohydrate IgEs have been thought to be a candidate for inducing clinical cross-reactivity. CCDs have been repeatedly found to cause IgE binding *in vitro*. It has been postulated, though, that they are unable to cross link IgE and lead to cellular degranulation and therefore clinical symptoms. Recent focus on the role of Cit s 1 in orange allergy revealed dissociation between *in vitro* (specific IgE) and *in vivo* (skin prick testing) evidence of allergenicity, raising the question of false positive *in vitro* studies due to N-linked glycans [24]. Further investigation revealed a structure containing a single site of glycosylation, which is the IgE-binding epitope. This monovalent nature of the structure was proposed as a reason for the lack of *in vivo* response. Despite several studies minimizing the clinical importance of CCDs, there continue to be reports in the literature asserting their importance [25]. Additionally, there is evidence that carbohydrates on IgE can be a target for binding by food components. Pramod *et al.* [26] investigated the ability of potato lectin to activate basophils and mast cells. They found that binding of the lectin to the glycans on IgE induces degranulation and histamine release. Since lectins are ubiquitous in plants, this may have important implications especially

in individuals with an atopic predisposition and thus high total IgE.

Predicting cross-reactivity

The primary structures of 75% of known food allergens have been defined. This has allowed for grouping of allergens into families (e.g. Pfams) based on structural similarities that may be reflected in common domains and protein folding, as well as amino acid sequence. Using bioinformatics databases to explore sequence and three-dimensional structures, Jenkins *et al.* [27] found that about 65% of plant-derived food allergens belong to four families. This type of clustering of allergens should allow for development of techniques to predict the potential for cross-reactivity.

Multiple strategies have been used to group food allergens and to try to develop a method for predicting the allergenicity of new proteins introduced into the food supply based on their similarity to known allergens. These include searching for identical short stretches of amino acids (6–8 amino acids). Allermatch (<http://allermatch.org>) is a web-based tool that identifies short peptide sequence matches. Another set of algorithms evaluates sequence similarity over longer stretches. These include BLAST (Basic Local Alignment Search Tool) and FASTA. The current consensus is that proteins with >35% identity over 80 amino acids or with identity of six consecutive amino acids have the possibility of inducing cross-reactivity [28]. Using this criterion, however, is likely to give a significant number of false positives [29,30]. Some argue that true clinically relevant cross-reactivity is better indicated by 50–75% identity between proteins [30]. Some authors have used sequence data to identify shared allergen motifs in order to determine potential allergenicity and cross-reactivity [31]. A third way of evaluating proteins for possible cross-reactivity is via comparison of three-dimensional structure. These approaches can take into account not only linear, but also conformational epitopes. Since a significant portion of IgE binding to allergens is due to conformational epitopes, these approaches have broad potential for identifying cross-reactivities missed by simple alignments of contiguous sequences. Certain folds and elements of structure may be shared between proteins whose amino acid sequence similarity would not have predicted cross-reactivity. This is because these shared structures frequently involve interactions between amino acids distant from one another in primary sequence. The Structural Database of Allergenic Proteins (SDAP) website (<http://fermi.utmb.edu/SDAP/>) has tools which can evaluate protein pairs for short and long stretches of similarities and take into account similarities in the physicochemical properties different amino acids in evaluating allergenicity [32].

The importance of conformational epitopes in OAS is suggested by the recognition that the patients react to fresh, but not cooked forms of the same, food. In addition, these reactions might be limited to the oropharyngeal regions because the offending proteins are rapidly denatured by gastric acidity and enzymes, thereby destroying conformational epitopes before the proteins or their fragments are absorbed in the gastrointestinal track. Another limitation in our ability to identify allergenic cross-reactivity is the limited number of allergens for which IgE epitopes have been identified. Random phage display is a common tool used to this end. Once epitopes have been identified, computer programs under development can assist in mapping them to the known structure of the allergen. In this way, conclusions about structural motifs responsible for IgE binding can be made and extrapolated to other foods including novel food proteins [33]. This approach is often limited, however, by the relatively small number of allergens for which the three-dimensional structure has been defined. The role for homology modeling of food protein in these approaches remains to be elucidated.

In addition to the molecular methods above, some groups have examined the pattern of food proteins to which an individual reacts to predict the risk for other cross-reactivities. Sanchez-Monge *et al.* [34] found that patients who were allergic to chestnut without latex allergy had reactivity to Cas s 8 and other LTPs from different foods as opposed to proteins typically implicated in latex–fruit syndrome (e.g. class I chitinase). In contrast, patients with latex–chestnut allergy demonstrated reactivity to avocado chitinase, Pers a 1. Radauer *et al.* [20^{••}] showed that profilins from certain species are capable of inducing IgE antibodies that tend to be cross-reactive (e.g. timothy, birch, celery and latex), while others induce species specific IgE. Others have demonstrated the tendency of certain allergens from a food to induce a clinical phenotype of OAS due to cross-reactivity, whereas other allergens from that same food have the tendency to produce systemic symptoms and reaction to that food only [35].

Implications of cross-reactivity in the diagnosis of food allergy

Currently, both false positives and false negatives limit our ability to accurately diagnose food allergy.

False positives

The mainstay of treatment of all types of food allergy is avoidance. One of the dilemmas we face in counseling patients concerns the scope of foods to be avoided. This is a concern especially in young children in whom overly restrictive diets can have detrimental effects on growth and development. Many studies have demonstrated that

positive skin prick testing (SPT) and in-vitro evidence of IgE antibodies to foods do not always correlate with presence of clinical symptoms [11,36]. For instance, when patients known to have a food allergy were tested for cross-reactive foods via SPT and ImmunoCap, < 15% of positive results were clinically relevant [36]. Therefore, instructing patients to avoid all foods known to induce cross-reactivity is very likely to lead to unnecessarily restricted diets. Likewise, avoidance based on SPT and/or ImmunoCap will eliminate foods that are likely to cause no clinical symptoms. Asero *et al.* [37] found that a group of 49 patients who were monosensitized to LTP could tolerate carrot, potato, banana and melon.

False negatives

Another aspect of this problem is false negative results. Crespo *et al.* [36] found several clinically relevant food allergies on double blind placebo controlled food challenge (DBPCFC) that were not demonstrated with SPT. This finding demonstrates the potential for missing important allergens on in-vivo testing. The same is true of in-vitro testing for food specific IgE. Processing of commercial antigen extracts, lack of standardization and other issues contribute to false negatives, which continue to make food challenge necessary for accurate diagnosis.

Implications of cross-reactivity in the treatment of food allergy

Although the current therapy for food allergy is heavily dependent on avoidance, there is movement toward the use of immunotherapy. An additional implication of recognizing cross-reactivity in food allergy is the possibility that this can be used in immunotherapy. Some prior studies suggested that specific pollen immunotherapy would ameliorate symptoms resulting from the associated food in some OAS [38]. There continues to be mixed evidence, however, with regard to the effect of immunotherapy with pollen allergens on related food allergy [39,40]. Kinaciyan *et al.* [41] found that one year of SLIT with birch pollen extract did not improve OAS to apple despite measurable decrease in birch related symptoms with therapy. Niederberger *et al.*, [42] however, concluded that there is evidence supporting the efficacy of subcutaneous immunotherapy using modified birch allergens for treatment of OAS. Their study demonstrated the formation of anti-Api g 1 IgG₁ which decreased histamine release by Api g 1 and decreased symptoms in seven of 25 treated patients. Likewise, Alonso *et al.* [43] demonstrated increased tolerance for offending foods and decrease in food specific IgE after subcutaneous immunotherapy for plane tree pollinosis. With such conflicting evidence, there is no absolute consensus, but pollen immunotherapy continues to be part of the armamentarium for treatment of OAS.

Another possibility for immunotherapy in food allergy involves the use of altered proteins which retain their ability to stimulate production of IgG, but do not bind IgE. Reese *et al.* [44^{••}] studied the effect of oligomerization and mutation of the major carrot allergen, Dau c 1, on antigenicity. They concluded that the mutated, misfolded antigen caused less IgE binding than native protein monomers or oligomers and was able to induce IgG with capacity to block IgE binding to allergen. Thus, the mutant Dau c 1 could serve as an immunotherapeutic agent for treatment of carrot allergy unresponsive to birch pollen immunotherapy. This technique has also been investigated in other types of food allergy where cross-reactivity plays a role, such as multiple fish allergy due to antiparvalbumin IgE. Swoboda *et al.* [45[•]] developed a recombinant parvalbumin mutant using the major carp allergen, Cyp c 1. They demonstrated its suitability as a vaccine by showing less IgE reactivity, less histamine release and less skin reactivity compared to the wild type protein. Additionally, the mutant Cyp c 1 induced IgG antibodies that cross reacted with parvalbumins from multiple fish species and inhibited IgE binding to wild type Cyp c 1. This technique for causing conformational changes to allergens via induction of point mutations has been shown repeatedly to yield proteins which have immunotherapeutic potential [46,47].

Conclusion

The increasing prevalence of food allergy makes development of better diagnostic and treatment modalities increasingly important. A thorough understanding of immunologic cross-reactivity is essential for advancing our knowledge about food allergy because of the key role it plays in the disease. The ultimate goal could be to understand the phenomenon of cross-reactivity at the level of the sharing of individual IgE epitopes and the constellation of epitope recognition that leads to the cross pathogenicity. Further investigations will help elucidate the pathogenesis of the disorder and prevent the introduction of allergenic genetically engineered foods. In addition, insight into cross-reactivity will enhance the value of current diagnostic tools as well as development of new, more accurate modalities. Finally, the phenomenon can be used in the development of new therapies for food allergy.

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