

Clinical importance of cross-reactivity in food allergy

Ronald van Ree

Purpose of review

Review of recent developments in the field of cross-reactivity in food allergy and the clinical relevance of these developments.

Recent findings

New foods have been added to the list of Bet v 1 and profilin-related food allergies. Clinical relevance of cross-reactions based on recognition of carbohydrate determinants and profilin is limited for the population of pollen-allergic patients as a whole. For selected food allergic patients, however, N-glycans and particularly profilin are potentially of clinical relevance. Lipid transfer proteins have further been established as clinically more severe allergens in several foods. This severity is attributed to their stability to proteolysis and processing. Storage proteins of several nuts and seeds have been identified as important allergens, but cross-reactivity between storage proteins of different foods appears to be limited. Using cross-reactivity as the basis for immunotherapy in food allergy seems promising but needs confirmation by double-blind, placebo-controlled trials.

Summary

The continued identification and characterization of cross-reactive allergens facilitates the study of factors determining clinical relevance of cross-reactivity and of possible efficacy of immunotherapy in food allergy.

Keywords

cross-reactivity, food allergy, clinical relevance, immunotherapy

Curr Opin Allergy Clin Immunol 4:235–240. © 2004 Lippincott Williams & Wilkins.

Department of Immunopathology, Sanquin Research, Amsterdam, The Netherlands

Correspondence to Dr Ronald van Ree, Department of Immunopathology, Sanquin Research, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands
Tel: +31 20 5123242; fax: +31 20 5123170; e-mail: r.vanree@sanquin.nl.

Current Opinion in Allergy and Clinical Immunology 2004, 4:235–240

Abbreviations

DBPCFC	double-blind, placebo-controlled food challenge
LTP	lipid transfer protein
SPT	skin prick test

© 2004 Lippincott Williams & Wilkins
1528-4050

Introduction

The first evidence for the existence of clinically relevant cross-reactive IgE antibodies came from clinical observations. In 1970 it was reported that ragweed pollinosis was frequently accompanied by allergy to melon and banana [1]. Soon after, two other pollen–food allergy syndromes were described: one for birch and apple [2,3] and one for mugwort and vegetables like celery and carrot [4]. At that time, the cross-reactive allergens responsible had not been identified. It took until the late 1980s to identify the most important pollen–food cross-reactive allergen – the major birch pollen allergen Bet v 1 – as a pathogenesis-related protein [5]. Valenta *et al.* [6] then discovered profilin as a cross-reactive allergen in virtually all pollen and plant foods. This ubiquity made them introduce the term ‘pan-allergen’. Cross-reactivity is not limited to pollen and plant foods. Shortly after the identification of tropomyosin as the major shrimp allergen [7], Witteman *et al.* [8] reported the cross-reactivity of IgE antibodies to tropomyosin of house dust mites. Sensitization to inhalant allergens is not always the basis for cross-reactivity. IgE antibodies to peanut allergens, for example, can cross-react with homologous proteins in other legumes like soybean and pea [9]. In such cases the food is inducing cross-reactive IgE antibodies.

When speaking of cross-reactivity we have to distinguish sensitization from symptom elicitation. It is quite obvious that only some cross-reactive IgE antibodies give rise to clinical food allergy [10,11]. Serological cross-reactivity is always broader than clinical cross-reactivity. Studying serological cross-reactivity by inhibition assays can reveal which allergen source causes sensitization, although it will not reveal which food will and which food will not give rise to clinical allergy. The answer to that question still heavily depends on carefully obtained clinical histories and the application of double-blind, placebo-controlled food challenges (DBPCFCs). We are only just beginning to understand why some IgE antibodies are linked to clinical food allergy and others are lacking significant biological activity [12]. Serologic tests for food allergy with improved clinical relevance will have to take into account IgE antibody affinity and the number of epitopes recognized. These factors determine whether mediator release from mast cells and basophils is induced efficiently enough to trigger clinical symptoms, that is to facilitate symptom elicitation [13].

Apart from its relevance to sensitization and symptom elicitation, cross-reactivity has been suggested as an avenue for the treatment of food allergy. It is a long-standing debate whether birch pollen immunotherapy is also beneficial as a treatment for apple allergy. Since it is well established that T cells play a central role in the mechanism of immunotherapy [14], cross-reactivity at the T-cell level certainly deserves attention. To date, data on T-cell cross-reactivity between, for example, birch and apple are very scarce [15]. Although never studied in double-blind, placebo-controlled clinical trials, most reports support a beneficial effect of birch pollen immunotherapy on related food allergy [16,17]. Conversely, there have been suggestions that immunotherapy for house dust mite allergy may induce allergy to snails by cross-reactivity [18]. Again these suggestions have not been substantiated by well controlled trials. Possibly the dose of a cross-reactive allergen is a decisive factor, making the difference between a beneficial or detrimental effect.

This review aims to give an overview of the most recent publications in the field of cross-reactivity in food allergy, thereby focusing on the following questions. What have we learned about the route of sensitization in food allergy? What does the recent literature tell us about the clinical relevance of cross-reactive IgE antibodies? How does immunotherapy for inhalant allergy affect cross-reactive food allergy?

Pollen-related food sensitization: the role of allergen exposure

Bet v 1 and profilin are the two main allergens involved in cross-reactivity between pollen and plant foods. Every now and then new foods are added to the list of potential pollen-related allergenic foods. A clear link to Bet v 1 or profilin is not demonstrated in all cases, however. Recently, allergy to chicory was added to the list of birch pollen induced food allergies [19]. The authors, however, demonstrated that neither Bet v 1 nor profilin was involved in cross-reactivity. Some years ago, Wüthrich *et al.* [20] published a case report of a patient from the Philippines with birch pollen allergy and typical oral allergy symptoms to apple, peach and celery. The patient also demonstrated these symptoms to jackfruit (*Artocarpus integrifolia*), a tropical fruit related to mulberry. Cross-reactivity to Bet v 1 and profilin could not be demonstrated.

Recently, two similar cases were identified among Dutch birch pollen allergic patients (S.T.H.P. Bolhaar, L. Zuidmeer, unpublished data). It was clearly demonstrated that IgE reactivity to jackfruit was completely inhibited with Bet v 1. The message from these observations is that a food well tolerated in a birch pollen free environment (e.g. The Philippines) becomes

a food allergen when a patient gets sensitized to birch pollen in a new habitat (e.g. Switzerland). By contrast, in birch pollen endemic areas (e.g. The Netherlands), introduction to new tropical fruits can result in the appearance of new food allergies.

Clinical relevance of pollen–food cross-reactivity: patient selection is an important factor

The clinical relevance of pollen–vegetable food cross-reactive IgE antibodies has been a matter of debate for a long time. This discussion was sparked off by the discovery of IgE antibodies directed to highly conserved N-glycans present in pollen and plant foods [21,22•]. The original claims for poor biological activity of these IgE antibodies were based on the observation that pollen-allergic patients with carbohydrate-specific IgE antibodies cross-react to virtually all plant foods without having any clinical food allergies. Poor biological activity was confirmed by skin prick test (SPT) and in-vitro basophil histamine release [23]. In a recent survey of 1831 patients selected on the basis of suspected respiratory allergies, Mari [24••] reported a high prevalence of anticarbohydrate IgE (23%), in particular in patients with multiple pollen sensitizations (71%). SPT analysis and clinical histories confirmed poor biological activity of anticarbohydrate IgE in these patients.

In contrast, several recent reports have demonstrated the capacity of carbohydrate-specific IgE antibodies to induce in-vitro basophil histamine release. Foetisch *et al.* [25••] purified a glycoprotein from tomato, β -fructofuranosidase, and showed that this allergen (Lyc e 2) can induce histamine release when basophils are sensitized with serum of tomato-allergic patients ($n=4$) that recognizes this protein selectively on the basis of its glycan structures. A recombinant Lyc e 2 expressed in *Escherichia coli* did not induce mediator release. In line with these observations, the plant glycoprotein horseradish peroxidase was biologically active but lost this activity upon deglycosylation. These experiments clearly demonstrate that sugar-specific IgE antibodies can induce mediator release. By contrast, six out of ten tomato-allergic patients with similar levels of anticarbohydrate-specific IgE did not show histamine release with these glycoproteins. Furthermore, the concentrations of Lyc e 2 needed to achieve mediator release were roughly between 1 and 10 $\mu\text{g/ml}$. Frequently, purified major (natural and recombinant) allergens have been shown to be biologically active at concentrations ranging from 0.001 to 10 ng/ml (R. van Ree, unpublished data) [26,27]. Whether the observed biological activity of Lyc e 2 plays a role in the reported clinical tomato allergy, therefore, remains to be established.

Bublin *et al.* [28**] studied the biological activity of IgE antibodies against carbohydrate epitopes using a glycoprotein isolated from celery tuber, Api g 5. To demonstrate the role of N-glycans in the induction of mediator release, the Api g 5 was chemically deglycosylated. This resulted in complete loss of biological activity. To prove that this was not simply caused by loss of structural integrity, the authors showed that reduction and alkylation had no effect on the IgE-binding potency of Api g 5. However, biological activity mediated by N-glycans was only shown for one out of eight celery-allergic patients, and again, required concentrations of the allergen were relatively high (0.1–1 µg/ml).

In summary, the overall impression is still that IgE antibodies against carbohydrate determinants are of limited clinical relevance, at least for the majority of pollen-allergic patients. This can clearly be concluded from those studies that analysed the biological activity of N-glycan-specific IgE antibodies among patients selected on pollen allergy, that is the whole carbohydrate-reactive population [23,24**]. However, this does not exclude the possibility that these IgE antibodies are clinically relevant in selected food-allergic patients. Clinical relevance cannot be concluded on the basis of in-vitro biological activity demonstrated assays with high concentrations of glycoallergens [25**,28**].

Not only has the clinical relevance of carbohydrate-specific IgE been disputed, but also the clinical importance of the pan-allergen profilin. Wensing *et al.* [29*] recently reported that pollen-plant food IgE cross-reactivity based on profilin is rarely accompanied by clinical food allergy. In that study, patients were selected on the basis of pollen allergy and one or more positive SPTs for plant foods. Several recent publications have demonstrated that profilin is an important allergen in selected food-allergic populations. Rodríguez-Pérez *et al.* [30*] reported that DBPCFC-confirmed peach-allergic patients in Spain can essentially be divided into two groups: those with IgE antibodies to profilin (Pru p 4) and those with IgE antibodies to lipid transfer protein (LTP or Pru p 3). Their assumption is that pollen sensitization is instrumental in causing peach allergy in the profilin-reactive group, whereas IgE antibodies to Pru p 3 are induced by exposure to peach. Although very plausible, there is not yet real proof that profilin actually causes peach allergy. Support for an important role of profilin in some clinical fruit allergies comes from a survey by Asero *et al.* [31*]. They selected 71 patients with fruit allergy but no sensitization to LTP or latex, and showed a strong correlation between clinical allergy to (water) melon, citrus fruits, tomato and banana with profilin sensitization. In yet another study [32*], virtually all patients selected on a history of allergy

to bell pepper and tomato were shown to have IgE antibodies against profilin from these fruits. A causal relation between IgE against bell pepper profilin or tomato profilin and clinical allergy to these plant foods was not claimed. Interestingly, the only two patients from the study by Wensing *et al.* [29*] for whom clinical importance of profilin-specific IgE was thought to be relevant had allergy to bell pepper (paprika) and tomato. Finally, profilin was shown to be a dominant allergen for patients selected with an allergy to melon [33*].

The overall impression from the studies into the clinical relevance of pollen-induced IgE antibodies against N-glycans and profilin is that they are of limited relevance to the whole population of pollen-allergic patients, but can have relevance for selected food-allergic patients.

Food lipid transfer proteins are responsible for food sensitization: or is there still some doubt?

LTP was identified by Pastorello *et al.* [34] and by Sanchez Monge *et al.* [35] as an important allergen in *Rosaceae* fruits. This protein has the characteristics needed to be able to reach the gut immune system in an immunogenic (sensitization) and allergenic (elicitation of systemic symptoms) conformation: it is extremely stable under the acidic and proteolytic conditions in the stomach and gut [36]. Sensitization to LTP has been reported in patients without pollen allergy, giving support to its role as a sensitizing food allergen [37,38*]. All studies on LTP demonstrate a higher frequency of systemic reactions than have been reported in patients with typical pollen-related food allergies [30*,36,37,38*,39*,40**,41*]. The degree of allergen stability is clearly the basis of this difference in clinical presentation [36]. Retained allergenicity of LTP was also reported after food processing steps like heating [39*,42] and fermentation [41*]. The spectrum of foods in which the role of LTP as an allergen is studied is rapidly increasing. Recently, grape, lettuce, hazelnut, sunflower and cereals were added to the list [40**,41*,43–45]. IgE antibodies against food LTPs have been shown to express variable degrees of cross-reactivity [36,44,46*]. Cross-reactivity between LTPs is not limited to foods. LTP has been identified as an allergen in latex [47*] and some pollen as well. Both major *Parietaria* allergens, Par j 1 and Par j 2, are LTPs [48*]. Also mugwort has been shown to express an allergenic LTP that is cross-reactive with food LTPs [49,50**,51**]. Finally, lettuce LTP was shown to have some degree of cross-reactivity with pollen from plane trees (*Platanus*) [40**]. The general consensus, however, is still that sensitization to food LTPs is primarily caused by food consumption and not by pollen exposure.

Seed storage proteins 2S, 7S and 11S: limited level of cross-reactivity between foods?

Seed storage proteins 2S albumin, 7S vicilin and 11S legumin have been identified as the major allergens in legumes like peanut, soy [52•,53,54] and lentils [55•], but also in tree nuts [56••,57•] and other seeds like sesame [58•] and sunflower [43,59•]. In their recent review of tree nut allergens, Roux *et al.* [56••] concluded that it is not yet established whether combined allergy to various tree nuts is caused by cross-reactivity or by independent sensitization to multiple tree nuts. Cross-reactivity at a clinical level between peanut and other legumes like soy and pea is certainly not common. Recently, Wensing *et al.* [60•] reported three cases of anaphylaxis to pea that translated into clinical cross-reactivity to peanut, but such cases are relatively rare. Nevertheless, it could be demonstrated that IgE antibodies to pea vicilin cross-reacted to the peanut vicilin, Ara h 1. In a study by de Leon *et al.* [61•], cross-reactivity between peanut and various tree nuts was convincingly demonstrated for patients with combined peanut and tree nut allergy.

Cross-reactivity and immunotherapy: beneficial or detrimental?

Most of the knowledge concerning the effect of birch pollen immunotherapy on cross-reactive fruit allergy is anecdotal by nature. Some clinical researchers have retrospectively analysed (groups of) birch pollen allergic patients and have concluded that immunotherapy is beneficial for the related food allergy [16,17]. Others have reported the absence of beneficial effects [62]. To assess the persistence of a beneficial effect, Asero [63•] recently performed open challenges with apple in a group of birch pollen allergic patients treated by immunotherapy. All 30 patients selected had reported complete disappearance of apple allergy upon completion of immunotherapy. It was demonstrated that over 50% of the treated patients were still able to tolerate apples up to 30 months after stopping treatment. Although supportive of a beneficial effect, these studies have not really provided conclusive proof. Double-blind, placebo-controlled trials as well as DBPCFCs are thus needed. Bolhaar *et al.* [64] recently completed a clinical trial using DBPCFC as a read-out for apple allergy. They compared two groups of patients with combined birch/apple allergy, one receiving immunotherapy and the other pharmacotherapy. Both SPT reactivity and DBPCFC with apple significantly decreased in the former group. The detrimental effects of immunotherapy have also been reported. Several years ago, it was first suggested that house dust mite immunotherapy could possibly induce allergy to snails [18]. Until now this issue has still not been resolved [65,66]. To that end, data obtained by double-blind, placebo-controlled trials are absolutely essential. Since it is well established that

T cells play an important role in the mechanism of immunotherapy, studies on the cross-reactivity between inhalant and food allergens at the T-cell level are needed. Evidence for T-cell cross-reactivity between Bet v 1 and Mal d 1 had been reported by Fritsch *et al.* [15]. Recently, similar results have been found for the Bet v 1 homologue in celery, Api g 1 [67•].

Conclusion

Cross-reactivity in food allergy is not limited to pollen-related food allergens: IgE antibodies against 'pure' food allergens have also demonstrated cross-reactivity. When studying the clinical relevance of cross-reactive IgE antibodies, the outcome is highly dependent on the criteria used to select patients, that is a broad serological or limited clinical selection. To establish whether cross-reactivity can be used to treat food allergy, well controlled clinical trials are required.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- 1 Anderson LB Jr, Dreyfuss EM, Logan J, *et al.* Melon and banana sensitivity coincident with ragweed pollinosis. *J Allergy* 1970; 45:310–319.
 - 2 Hannuksela M, Lahti A. Immediate reactions to fruits and vegetables. *Contact Dermatitis* 1977; 3:79–84.
 - 3 Andersen KE, Lowenstein H. An investigation of the possible immunological relationship between allergen extracts from birch pollen, hazelnut, potato and apple. *Contact Dermatitis* 1978; 4:73–79.
 - 4 Wüthrich B, Hofer T. [Food allergy: the celery–mugwort–spice syndrome. Association with mango allergy?]. *Dtsch Med Wochenschr* 1984; 109:981–986.
 - 5 Breiteneder H, Pettenburger K, Bito A, *et al.* The gene coding for the major birch pollen allergen Betv1, is highly homologous to a pea disease resistance response gene. *EMBO J* 1989; 8:1935–1938.
 - 6 Valenta R, Duchene M, Ebner C, *et al.* Profilins constitute a novel family of functional plant pan-allergens. *J Exp Med* 1992; 175:377–385.
 - 7 Shanti KN, Martin BM, Nagpal S, *et al.* Identification of tropomyosin as the major shrimp allergen and characterization of its IgE-binding epitopes. *J Immunol* 1993; 151:5354–5363.
 - 8 Witteman AM, Akkerdaas JH, Van Leeuwen J, *et al.* Identification of a cross-reactive allergen (presumably tropomyosin) in shrimp, mite and insects. *Int Arch Allergy Immunol* 1994; 105:56–61.
 - 9 Sicherer SH, Sampson HA, Burks AW. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy* 2000; 55:515–521.
 - 10 van Ree R, Aalberse RC. Pollen–vegetable food crossreactivity: serological and clinical relevance of crossreactive IgE. *J Clin Immunoassay* 1993; 16:124–130.
 - 11 van Ree R, Akkerdaas J, van Leeuwen A, *et al.* New perspectives for the diagnosis of food allergy. *Allergy Clin Immunol Int* 2000; 12:7–12.
 - 12 van Ree R, Aalberse RC. Specific IgE without clinical allergy. *J Allergy Clin Immunol* 1999; 103:1000–1001.
 - 13 van Ree R. Factors modulating allergen-induced histamine release. In: Bousquet J, Yssel H, editors. *Immunotherapy in asthma*. New York: Marcel Dekker; 1999. pp. 399–409.
 - 14 Akdis CA, Blaser K. Mechanisms of allergen-specific immunotherapy. *Allergy* 2000; 55:522–530.
 - 15 Fritsch R, Bohle B, Vollmann U, *et al.* Bet v 1, the major birch pollen allergen, and Mal d 1, the major apple allergen, cross-react at the level of allergen-specific T helper cells. *J Allergy Clin Immunol* 1998; 102:679–686.

- 16 Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998; 28:1368–1373.
- 17 Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. *Ann Allergy Asthma Immunol* 1995; 74:391–396.
- 18 van Ree R, Antonicelli L, Akkerdaas JH, et al. Possible induction of food allergy during mite immunotherapy. *Allergy* 1996; 51:108–113.
- 19 Cadot P, Kochuyt AM, van Ree R, Ceuppens JL. Oral allergy syndrome to chicory associated with birch pollen allergy. *Int Arch Allergy Immunol* 2003; 131:19–24.
- 20 Wüthrich B, Borga A, Yman L. Oral allergy syndrome to a jackfruit (*Artocarpus integrifolia*). *Allergy* 1997; 52:428–431.
- 21 Aalberse RC, Koshte V, Clemens JG. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. *J Allergy Clin Immunol* 1981; 68:356–364.
- 22 van Ree R. Carbohydrate epitopes and their relevance for the diagnosis and treatment of allergic diseases. *Int Arch Allergy Immunol* 2002; 129:189–197.
- A comprehensive review of IgE-binding plant N-glycans and their clinical relevance.
- 23 van der Veen MJ, van Ree R, Aalberse RC, et al. Poor biologic activity of cross-reactive IgE directed to carbohydrate determinants of glycoproteins. *J Allergy Clin Immunol* 1997; 100:327–334.
- 24 Mari A. IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the in vivo and in vitro reactivity. *Int Arch Allergy Immunol* 2002; 129:286–295.
- An excellent study into the biological activity and clinical relevance of carbohydrate-specific IgE antibodies. By including an impressive number of pollen-allergic patients, the study gives strong support to the view that these IgE antibodies are generally of limited clinical relevance.
- 25 Foetisch K, Westphal S, Lauer I, et al. Biological activity of IgE specific for cross-reactive carbohydrate determinants. *J Allergy Clin Immunol* 2003; 111:889–896.
- An elegant study that provides evidence to support that carbohydrate epitopes do have the capacity to induce IgE-mediated histamine release from human basophils. By using well defined and characterized purified proteins with and without glycans, the involvement of sugar moieties was firmly established.
- 26 van Oort E, de Heer PG, van Leeuwen WA, et al. Maturation of *Pichia pastoris*-derived recombinant pro-Der p 1 induced by deglycosylation and by the natural cysteine protease Der p 1 from house dust mite. *Eur J Biochem* 2002; 269:671–679.
- 27 van Oort E, de Heer PG, Lerouge P, et al. Immunochemical characterization of two *Pichia pastoris*-derived recombinant group 5 Dactylis glomerata isoallergens. *Int Arch Allergy Immunol* 2001; 126:196–205.
- 28 Bublin M, Radauer C, Wilson IB, et al. Cross-reactive N-glycans of Api g 5, a high molecular weight glycoprotein allergen from celery, are required for immunoglobulin E binding and activation of effector cells from allergic patients. *FASEB J* 2003; 17:1697–1699.
- A well designed study addressing the biological activity of anticarbohydrate IgE antibodies. By comparison of a physico-chemically well characterized purified glycoprotein from celery and a deglycosylated version thereof, biological activity of sugar-specific IgE is demonstrated.
- 29 Wensing M, Akkerdaas JH, van Leeuwen WA, et al. IgE to Bet v 1 and profilin: cross-reactivity patterns and clinical relevance. *J Allergy Clin Immunol* 2002; 110:435–442.
- An interesting clinical study among pollen-allergic patients, selected on the basis of a positive SPT to foods, that shows that profilin is generally of limited clinical relevance.
- 30 Rodriguez-Perez R, Fernandez-Rivas M, Gonzalez-Mancebo E, et al. Peach profilin: cloning, heterologous expression and cross-reactivity with Bet v 2. *Allergy* 2003; 58:635–640.
- This study illustrates the power of using individual food allergens from a single food to distinguish between patients with different routes of sensitization and clinical presentation.
- 31 Asero R, Mistrello G, Roncarolo D, et al. Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. *J Allergy Clin Immunol* 2003; 112:427–432.
- By correlating clinical histories and IgE titers against profilin, support is generated for a role of profilin in specific types of plant food allergies.
- 32 Willerroider M, Fuchs H, Ballmer-Weber BK, et al. Cloning and molecular and immunological characterisation of two new food allergens, Cap a 2 and Lyc e 1, profilins from bell pepper (*Capsicum annuum*) and Tomato (*Lycopersicon esculentum*). *Int Arch Allergy Immunol* 2003; 131:245–255.
- Convincing support for a dominant role of profilin in allergy for bell pepper and tomato, using well characterized recombinant profilins from both foods.
- 33 Rodriguez-Perez R, Crespo JF, Rodriguez J, Salcedo G. Profilin is a relevant melon allergen susceptible to pepsin digestion in patients with oral allergy syndrome. *J Allergy Clin Immunol* 2003; 111:634–639.
- A study that provides proof that profilin is a labile food allergen that is likely to be involved in allergy for melon.
- 34 Pastorello EA, Farioli L, Pravettoni V, et al. The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 1999; 103:520–526.
- 35 Sanchez-Monge R, Lombardero M, Garcia-Selles FJ, et al. Lipid-transfer proteins are relevant allergens in fruit allergy. *J Allergy Clin Immunol* 1999; 103:514–519.
- 36 Asero R, Mistrello G, Roncarolo D, et al. Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol* 2000; 122:20–32.
- 37 Fernandez-Rivas M, van Ree R, Cuevas M. Allergy to Rosaceae fruits without related pollinosis. *J Allergy Clin Immunol* 1997; 100:728–733.
- 38 Fernandez-Rivas M, Gonzalez-Mancebo E, Rodriguez-Perez R, et al. Clinically relevant peach allergy is related to peach lipid transfer protein, Pru p 3, in the Spanish population. *J Allergy Clin Immunol* 2003; 112:789–795.
- An elegant clinical study that establishes the dominant role of LTP for peach allergy among Spanish patients.
- 39 Pastorello EA, Pompei C, Pravettoni V, et al. Lipid-transfer protein is the major maize allergen maintaining IgE-binding activity after cooking at 100 degrees C, as demonstrated in anaphylactic patients and patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol* 2003; 112:775–783.
- This study illustrates the stability of LTP during heat processing.
- 40 San Miguel-Moncin M, Krail M, Scheurer S, et al. Lettuce anaphylaxis: identification of a lipid transfer protein as the major allergen. *Allergy* 2003; 58:511–517.
- Apart from the fact that these clinical researchers were able to recruit a sizeable cohort of patients with allergy to a rather unexpected food, the paper is food for thought for those interested in the route of sensitization. Whereas food LTPs are generally regarded as sensitizers, the high number of patients with accompanying respiratory allergy to plane pollen is too obvious to be ignored.
- 41 Pastorello EA, Farioli L, Pravettoni V, et al. Identification of grape and wine allergens as an endochitinase 4, a lipid-transfer protein, and a thaumatin. *J Allergy Clin Immunol* 2003; 111:350–359.
- This study demonstrates that stable allergens like LTP and thaumatin-like protein are present in grapes and are still allergenic in wine.
- 42 Asero R, Mistrello G, Roncarolo D, et al. Analysis of the heat stability of lipid transfer protein from apple. *J Allergy Clin Immunol* 2003; 112:1009–1011.
- 43 Papageorgiou PS, Shewry PR, Fido RJ, et al. Identification of lipid transfer protein (LTP) as a major sunflower seed food allergen in sunflower seed-induced systemic reactions. XXII Congress of the European Academy of Allergy and Clinical Immunology; Hannover: Pharma Service GmbH; 2003. p. 63.
- 44 Battais F, Douliet JP, Marion D, et al. Lipid transfer proteins of cereals in food allergy to wheat. XXII Congress of the European Academy of Allergy and Clinical Immunology; Hannover: Pharma Service GmbH; 2003. p. 206.
- 45 Schocker F, Luetkopf D, Scheurer S, et al. Recombinant lipid transfer protein Cor a 8 from hazelnut: a new tool for in vitro diagnosis of potentially severe hazelnut allergy. *J Allergy Clin Immunol* 2004; 113:141–147.
- 46 Asero R, Mistrello G, Roncarolo D, et al. Immunological cross-reactivity between lipid transfer proteins from botanically unrelated plant-derived foods: a clinical study. *Allergy* 2002; 57:900–906.
- An elegant clinical study illustrating the broad spectrum of allergenic food LTPs.
- 47 Beezhold DH, Hickey VL, Kostyal DA, et al. Lipid transfer protein from Hevea brasiliensis (Hev b 12), a cross-reactive latex protein. *Ann Allergy Asthma Immunol* 2003; 90:439–445.
- This study illustrates that LTPs are not only allergens in foods but also in latex.
- 48 Colombo P, Bonura A, Costa M, et al. The allergens of Parietaria. *Int Arch Allergy Immunol* 2003; 130:173–179.
- An excellent review on pollen LTPs that are structurally closely related to food LTPs but seem, nevertheless, not to be involved in pollen–food cross-reactivity.
- 49 Diaz-Perales A, Lombardero M, Sanchez-Monge R, et al. Lipid-transfer proteins as potential plant panallergens: cross-reactivity among proteins of Artemisia pollen, Castanea nut and Rosaceae fruits, with different IgE-binding capacities. *Clin Exp Allergy* 2000; 30:1403–1410.

- 50 Garcia-Selles FJ, Diaz-Perales A, Sanchez-Monge R, *et al.* Patterns of reactivity to lipid transfer proteins of plant foods and *Artemisia* pollen: an in vivo study. *Int Arch Allergy Immunol* 2002; 128:115–122.

A very interesting clinical study dealing with the role of pollen–food cross-reactivity in sensitization to LTPs. The data clearly show that generalizations with respect to route of sensitization cannot be made. Fruit LTPs seem to sensitize independently from pollen, whereas sensitization to chestnut LTP is probably induced by mugwort pollen.

- 51 Pastorello EA, Pravettoni V, Farioli L, *et al.* Hypersensitivity to mugwort (*Artemisia vulgaris*) in patients with peach allergy is due to a common lipid transfer protein allergen and is often without clinical expression. *J Allergy Clin Immunol* 2002; 110:310–317.

This well designed study illustrates that pollen–plant food cross-reactivity is not a one-way phenomenon. Traditionally the concept is that pollen is the sensitizer. Here convincing data are presented showing that a food can sensitize, resulting in clinically irrelevant cross-reactivity to pollen.

- 52 Mills EN, Jenkins J, Marigheto N, *et al.* Allergens of the cupin superfamily. *Biochem Soc Trans* 2002; 30:925–929.

A nice overview of the structural characteristics of allergens from the cupin superfamily to which most legume, seed and tree nut allergens belong.

- 53 Burks W, Helm R, Stanley S, Bannon GA. Food allergens. *Curr Opin Allergy Clin Immunol* 2001; 1:243–248.

- 54 Stanley JS, Bannon GA. Biochemistry of food allergens. *Clin Rev Allergy Immunol* 1999; 17:279–291.

- 55 Lopez-Torrejon G, Salcedo G, Martin-Esteban M, *et al.* Len c 1, a major allergen and vicilin from lentil seeds: protein isolation and cDNA cloning. *J Allergy Clin Immunol* 2003; 112:1208–1215.

The identification of vicilin from lentils as an important new allergen related to Ara h 1. This study also illustrates that the importance of food allergies is dependent on geographic and dietary differences.

- 56 Roux KH, Teuber SS, Sathe SK. Tree nut allergens. *Int Arch Allergy Immunol* 2003; 131:234–244.

An excellent overview of the current know-how on allergens from tree nuts. The review addresses a wide variety of tree nuts and deals with both pollen and non-pollen-related allergens.

- 57 Wang F, Robotham JM, Teuber SS, *et al.* Ana o 2, a major cashew (*Anacardium occidentale* L.) nut allergen of the legumin family. *Int Arch Allergy Immunol* 2003; 132:27–39.

A very extensive and detailed characterization of an allergenic storage protein from cashew nut.

- 58 Wolff N, Cogan U, Admon A, *et al.* Allergy to sesame in humans is associated primarily with IgE antibody to a 14 kDa 2S albumin precursor. *Food Chem Toxicol* 2003; 41:1165–1174.

Sesame allergy appears to be on the increase. Identification of major allergens is therefore of big importance.

- 59 Murtagh GJ, Archer DB, Dumoulin M, *et al.* In vitro stability and immunoreactivity of the native and recombinant plant food 2S albumins Ber e 1 and SFA-8. *Clin Exp Allergy* 2003; 33:1147–1152.

A well designed study illustrating the stability of 2S albumins from brazil nut and sunflower.

- 60 Wensing M, Knulst AC, Piersma S, *et al.* Patients with anaphylaxis to pea can have peanut allergy caused by cross-reactive IgE to vicilin (Ara h 1). *J Allergy Clin Immunol* 2003; 111:420–424.

A nice clinical study showing that pea sensitization can result in clinical peanut allergy.

- 61 de Leon MP, Glaspole IN, Drew AC, *et al.* Immunological analysis of allergenic cross-reactivity between peanut and tree nuts. *Clin Exp Allergy* 2003; 33:1273–1280.

This investigation clearly demonstrates that patients with combined peanut and tree nut allergies have cross-reactive IgE antibodies.

- 62 Moller C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. *Ann Allergy* 1989; 62:343–345.

- 63 Asero R. How long does the effect of birch pollen injection SIT on apple allergy last? *Allergy* 2003; 58:435–438.

A follow-up study after birch pollen immunotherapy suggests that a beneficial effect on apple allergy is long-lasting.

- 64 Bolhaar STHP, Tiemessen MM, Zuidmeer L, *et al.* Efficacy of birch pollen immunotherapy on cross reactive food allergy confirmed by skin tests and food challenges. *Clin Exp Allergy* 2004; (in press).

- 65 Meglio P, Plantamura M, Arabito E, *et al.* Does SIT to Der p protect from snail sensitization? *Allergy* 2002; 57:868–869.

- 66 Antonicelli L, Mariano M. Mite immunotherapy and food allergy to snail. *Allergy* 2003; 58:821–823.

- 67 Bohle B, Radakovics A, Jahn-Schmid B, *et al.* Bet v 1, the major birch pollen allergen, initiates sensitization to Api g 1, the major allergen in celery: evidence at the T cell level. *Eur J Immunol* 2003; 33:3303–3310.

An important contribution to the study of cross-reactivity between pollen and plant foods that shows that T-cell cross-reactivity is driven by birch pollen in parallel with B-cell cross-reactivity.