

# PLANT-DERIVED FOOD ALLERGENS: AN OVERVIEW

R. Asero, MD (1)

**P**lant-derived foods represent the most frequent cause of food allergy in adults. Although a systematic study of this type of food allergy started only few years ago, the use of molecular biology techniques has rapidly brought to the identification, characterization and sequencing of a large number of allergenic proteins (1-4). These recent advances tell us clearly that as clinicians we can no longer look at vegetable food allergens merely from a botanical point of view, and that we have to change our mind to a molecular classification. One has to admit that the impact of such approach on clinical practice is still limited by the lack of both natural and recombinant allergenic molecules for diagnostic use. Nonetheless, while we wait for such new, specific diagnostic tools, the skilful use of some indirect "markers" that are already available for routine use will be of help in the detection of the causative allergen(s) in a large number of cases. The importance of diagnosing vegetable food allergy at a molecular levels is evident if one considers that:

- each plant-derived food may contain a number of different allergens;
- different allergenic proteins in the same food may show different physical/chemical characteristics (heat-stability/labability; pepsin-stability/labability, etc.) that strongly influence the clinical expression of allergy;
- a large number of allergens show immunologic cross-reactivity with homologue proteins present in botanically unrelated sources.

## CLASSIFICATION OF THE MAIN VEGETABLE FOOD ALLERGENS

### Proteins homologous to Bet v 1

About 98% of birch pollen allergic patients are sensitized to the major allergen Bet v 1, a pathogenesis-related protein class 10. Proteins homologue to Bet v

1 are present in a large spectrum of plant-derived foods, although those most frequently involved in clinically relevant cross-reactions include Rosaceae (5), tree nuts (6), Apiaceae (including celery, carrot, fennel, and parsley) (7), peanut (8) and kiwi (9). Most vegetable food proteins homologue to Bet v 1 are extremely labile and easily destroyed by heat, oxidation, extraction procedures, and pepsin-digestion (10). From a clinical point of view this translates into a good tolerance of heat-processed foods as well as of commercial fruit juices, and in clinical symptoms that very rarely differ from oral allergy syndrome; from a diagnostic point of view such lability is the main reason why most commercial food extracts for SPT (particularly of Rosaceae) are completely insensitive (11). Although in these patients in-vitro tests work frequently much better than SPT with commercial food extracts (11), SPT with fresh fruits and vegetables remain the best way to diagnose the food allergy (11). The detection of IgE to rBet v 1 can be adopted as a marker of this clinical condition (12).

### Profilin

Profilin is a largely cross-reacting 12-15 kDa protein present in all eucaryotic cells. Typically, patients sensitized to profilin show skin reactivity as well as specific IgE to virtually all pollens and to a large number of plant-derived foods. Although the clinical relevance of profilin as a food allergen has been questioned, it has been involved in adverse reactions to *Apiaceae* (13), hazelnut (6), *Rosaceae* (14), tomato (14), pumpkin seed (15), zucchini (16), litchee (17), pineapple (18) and banana (19), and persimmon (20). Profilins seem more heat-stable than proteins homologue to Bet v 1 but are equally pepsin-sensitive; as a consequence sensitized patients generally experience only oral allergy syndrome following the ingestion of the offending foods, and systemic reactions are exceptional. Allergy to melon, watermelon, citrus fruits, banana and tomato are markers of profilin hypersensitivity once latex allergy has been ruled out (21). IgE specific for rBet v 2 (birch profilin) can be detected by a com-

(1) Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI) (Italy).

mercial kit (ImmunoCAP, Pharmacia, Uppsala) although its sensitivity has been questioned (12).

### **Food allergies associated with mugwort pollen allergy**

Some patients with mugwort pollen allergy experience food allergy to celery and other spices (22). In several cases these reactions are systemic because cross-reacting allergens are both heat- and pepsin-stable (23). Other relevant food allergies observed in mugwort pollen-allergic patients include honey, chamomile, and sunflower seed (24).

### **Lipid transfer proteins (LTPs)**

LTPs are pathogenesis related proteins group 14 (1). During the last 10 years several studies have shown the immunologic cross-reactivity of LTPs from Rosaceae LTPs (25), and between LTPs from Rosaceae and from botanically unrelated plant-derived foods (26). Peach seems to cause the primary sensitization to this allergen, and cross-reactivity to LTPs of botanically unrelated vegetable foods depends on the level of peach LTP-specific IgE (27). Due to their pepsin-resistance (26) and heat-stability (28) LTP are potentially harmful allergens; systemic reactions following the ingestion of Rosaceae, walnut, hazelnut, maize, beer, grapes, mulberry, peanut, and mustard have been reported in LTP-allergic patients. Due to the superficial distribution of LTP allergic patients frequently report good tolerance of peeled fruits. Commercial extracts of *Prunoideae* (plum and peach) contain virtually only LTP; a positive SPT with these extracts is therefore a marker of sensitization to this protein (26).

### **Thaumatococcus-like proteins (TLPs)**

TLPs are 30 kDa pathogenesis-related proteins group 5. They have been recently identified as allergens in apple (29), cherry (30), bell pepper (31), kiwi (32) and grapes (33). Their real clinical significance remains ill-defined due to the extreme rarity of monosensitized patients. Although TLP seems resistant to proteases and pH- or heat-induced denaturation (34) all patients described so far had oral allergy syndrome.

### **Seed storage proteins**

■ **2S Albumins:** 2S albumins are small heterodimeric proteins consisting of 2 subunits bound by disulphide bridges. They are extremely stable and are the major

allergens in mustard (Sin a 1; Bra j 1) (35, 36), Brazil nut (Ber e 1) (37), walnut (Jug r 1) (38), castor seed (Ric c 1; Ric c 3) (39), sesame seed (Ses i 1; Ses i 2)(40), cashew (Ana o 3), and sunflower seed (41), and a minor allergen in peanuts (Ara h 2, 6, 7) (42) and hazelnut (43). Interestingly, sensitization to 2S albumins may occur both via the gastrointestinal and the respiratory tract (44). The 2S albumin of Brazil nut has been responsible for allergic reactions to transgenic soybean (45). 2S albumins from different sources show a certain sequence identity (46% between 2S albumins from walnut and Brazil nut) but comparatively little is known about clinical cross-reactivity reactions. Cross-reactivity between 10 kDa allergens in sesame seed and poppy seed (46), sunflower seed and mustard (47), and walnut and hazelnut (48) has been described.

### ■ **Vicilin-like proteins and legumin-like proteins:**

Vicilin-like proteins include major allergens from peanut (Ara h 1)(49), lentil (Len c 1)(50), hazelnut (Cor a 11) (51), walnut (Jug r 2) (51), cashew (Ana o 1)(52), sesame (Ses i 3) (40).

Legumin-like proteins include allergens from peanut (Ara h 3)(53), hazelnut (Cor a 9) (51), cashew (Ana o 2) (54), and walnut (Jug r 4)(51). Despite the presence of homologous proteins in peanuts and tree nuts, those allergic to one are unlikely to be allergic to the other although high rates of in-vitro and skin test cross-sensitization have been shown in peanut allergic patients (51). In some cases cross-reactions within legumes occurs (55). In contrast, clinical cross-reactivity between tree nuts in patients sensitized to vicilins and legumins is rather frequent (51) although it is not the rule; a 37 % risk in this sense has been calculated (56). Several combinations of cross-reactions are reported in the literature: walnut/hazelnut/Brazil nut (48), coconut/walnut (57), coconut/hazelnut (58), peanut/almond (59), pistachio/cashew (60).

Patients hypersensitive to these allergens frequently experience severe systemic allergic reactions due to their extreme heat- and pepsin-resistance. The stability of these allergens translates also into an excellent sensitivity of commercial food extracts for SPT (46-48).

### **Proteases**

Primary kiwi allergy is associated with sensitization to a 30 kDa protease called actinidin (61). Other, potentially cross-reacting, proteases are present in fig (ficin), papaya (Papain), pineapple (bromelain), and latex of the ornamental plant *Ficus benjamina* (62).

## Alliin lyase

Some patients are allergic to members of the botanical family of *Amarillidaceae* (garlic, onion, leek, and shallot). When cross-reactivity between these foods occurs Alliin lyase is probably the sensitizing allergen (63). In other cases hypersensitivity to a single member of the family is observed (64,65).

**Key-words:** Allergy, allergen, sequence, cross-reactivity, co-recognition, IgE.

## References

- Breiteneder H., Ebner C. - Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000;106:27-36.
- Hoffmann-Sommergruber K. - Plant allergens and pathogenesis-related proteins. *Int Arch Allergy Immunol* 2000;122:155-166.
- Breiteneder H., Radauer C. - A classification of plant food allergens. *J Allergy Clin Immunol* 2004;113:821-30.
- Ferreira F., Hawranek T., Gruber P., Wopfner N., Mari A. - Allergenic cross-reactivity: from gene to the clinic. *Allergy* 2004;59: 243-67.
- Ebner C., Birkner T., Valenta R. *et al.* - Common epitopes of birch pollen and apples. Studies by Western and Northern blot. *J Allergy Clin Immunol* 1991;88:588-94.
- Hirschwehr R., Valenta R., Ebner C. *et al.* - Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen. *J Allergy Clin Immunol* 1992;90:927-36.
- Helbling A., Lopez M., Schwartz H.-J., Lehrer S.-B. - Reactivity of carrot-specific IgE antibodies with celery, apiaceous spices and birch pollen. *Ann Allergy* 1993;70:495-99.
- Mittag D., Akkerdaas J., Ballmer-Weber B.-K. *et al.* - Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol* 2004;114:1410-7.
- Voitenko V., Poulsen L.-K., Nielsen L. *et al.* - Allergenic properties of kiwi fruit extract: cross-reactivity between kiwi fruit and birch pollen allergens. *Allergy* 1997;52:136-43.
- Bjorksten F., Halmepuro L., Hannuksela M. - Extraction and properties of apple allergens. *Allergy* 1980;35:671-7.
- Ortolani C., Ispano M., Pastorello E.-A. *et al.* - Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683-90.
- Van Ree R., van Leeuwen W.-A., Akkerdaas J.-H., Aalberse R.-C. - How far can we simplify in vitro diagnostics for Fagales tree pollen allergy? A study with three whole pollen extracts and purified natural and recombinant allergens. *Clin Exp Allergy* 1999;29:848-55.
- Vallier P., Dechamp C., Valenta R. *et al.* - Purification and characterization of an allergen from celery immunochemically related to an allergen present in several other plant species. Identification as a profilin. *Clin Exp Allergy* 1992;22:774-82.
- Van Ree R., Fernandez-Rivas M., Cuevas M. *et al.* - Pollen-related allergy to peach and apple: an important role for profilin. *J Allergy Clin Immunol* 1995;95:726-34.
- Petersen A., Vieths S., Aulepp H. *et al.* - Ubiquitous structures responsible for cross-reactivity between tomato fruit and grass pollen allergens. *J Allergy Clin Immunol* 1996;98:805-15.
- Fritsch R., Ebner H., Kraft D., Ebner C. - Food allergy to pumpkin seed: characterization of the allergens. *Allergy* 1997;52:335-7.
- Reindl J., Anliker M.-D., Karamloo F. *et al.* - Allergy caused by ingestion of zucchini (*Cucurbita pepo*): characterization of allergens and cross-reactivity to pollen and other foods. *J Allergy Clin Immunol* 2000;106:379-85.
- Fah J., Wuthrich B., Vieths S. - Anaphylactic reaction to lychee fruit: evidence for sensitization to profilin. *Clin Exp Allergy* 1995;25:1018-23.
- Reindl J., Rihs H.-P., Scheurer S. *et al.* - Profilin, an important cross-reacting allergen in pollen-sensitized subjects with banana and pineapple allergy. XX EAACI Congr.; May 9-13, 2001, Berlin, Germany.
- Anliker M.-D., Reindl J., Vieths S., Wuthrich B. - Allergy caused by the ingestion of persimmon (*Diospyros kaki*): detection of specific IgE and cross-reactivity to profilin and carbohydrate determinants. *J Allergy Clin Immunol* 2001;107:718-23.
- 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;112:427-32.
- Pauli G., Bessot J.-C., Dietemann-Molard A. *et al.* - Celery sensitivity: clinical and immunological correlations with pollen allergy. *Clin Allergy* 1985;15:273-9.
- Heiss S., Fischer S., Muller W.-D. *et al.* - Identification of a 60 kd cross-reactive allergen in pollen and plant-derived food. *J Allergy Clin Immunol* 1996;98:938-47.
- Garcia-Ortiz J.-C., Cosmes Marin P., Lopez-Asunsolo A. - Allergy to foods in patients monosensitized to *Artemisia* pollen. *Allergy* 1996;51:927-31.
- Pastorello E.-A., Ortolani C., Farioli L. - Allergenic cross-reactivity among peach, apricot, plum, cherry in patients with oral allergy syndrome. An in vivo and in vitro study. *J Allergy Clin Immunol* 1994;94:699-707.
- 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.
- Asero R., Mistrello G., Roncarolo D., Amato S. - Relationship between peach lipid transfer protein IgE levels and hypersensitivity to non-Rosaceae vegetable foods in patients allergic to lipid transfer protein. *Ann Allergy Asthma Immunol* 2004;92:268-72.
- Asero R., Mistrello G., Roncarolo D. *et al.* - Analysis of the heat stability of lipid transfer protein from apple. *J Allergy Clin Immunol* 2003;112:1009-11.
- Hsieh L.-S., Moos M., Lin Y. - Characterization of apple 18 and 31 kd allergens by microsequencing and evaluation of their content during storage and ripening. *J Allergy Clin Immunol* 1995;96:960-70.
- Inschlag C., Hoffmann-Sommergruber K., O'Riordain G. *et al.* - Biochemical characterization of Pru a 2, a 23 kDa thaumatin-like protein representing a potential major allergen in cherry (*Prunus avium*). *Int Arch Allergy Immunol* 1998;116:22-8.
- Jensen-Jarolim E., Santner B., Leitner A. *et al.* - Bell peppers (*Capsicum Annuum*) express allergens (profilin, pathogenesis-related protein P23 and Bet v 1) depending on the horticultural strain. *Int Arch Allergy Immunol* 1998;116:103-9.
- Gavrovic-Jankulovic M., Cirkovic T., Vuckovic O. *et al.* - Isolation and biochemical characterization of a thaumatin-like kiwi allergen. *J Allergy Clin Immunol* 2002;110:805-10.
- Pastorello E.-A., 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;111:350-9.
- Breiteneder H. - Thaumatin-like proteins - a new family of pollen and fruit allergens. *Allergy* 2004;59:479-81.
- Menendez-Arias L., Moneo I., Dominguez J., Rodriguez R. - Primary structure of the major allergen from yellow mustard seeds, Sin a 1. *Eur J Biochem* 1988;177:159-66.
- Monsalve R.-I., Gonzalez de la Pena M.-A., Menendez-Aria L. *et al.* - Characterization of a new oriental mustard (*Brassica juncea*) allergen Bra j 1: detection of an allergenic epitope. *Biochem* 1993;293:625-32.
- Pastorello E.-A., Farioli L., Pravettoni V. *et al.* - Sensitization to the major allergen of Brazil nut is correlated

- with the clinical expression of allergy. *J Allergy Clin Immunol* 1998;102:1021-7.
38. Teuber S.-S., Dandekar A.-M., Peterson W.-R., Sellers C.-L. - Cloning and sequencing of a gene encoding a 2S albumin seed storage protein precursor from English walnut (*Juglans regia*), a major food allergen. *J Allergy Clin Immunol* 1998;101:807-14.
  39. Bashir M.-E., Hubatsch I., Leinenbach H.-P. *et al.* - Ricin 1 and Ricin 3, the allergenic 2S albumin storage proteins of *Ricinus communis*: complete primary structure and phylogenetic relationships. *Int Arch Allergy Immunol* 1998;115:73-82.
  40. Beyer K., Bardina L., Grishina G., Sampson H.-A. - Identification of sesame seed allergens by 2-dimensional proteomics and Edman sequencing: seed storage proteins as common food allergens. *J Allergy Clin Immunol* 2002;110:154-59.
  41. Kelly J.-D., Hlywka J.-J., Hefle S. - Identification of sunflower seed IgE-binding proteins. *Int Arch Allergy Immunol* 2000;121:19-24.
  42. Kleber-Janke T., Cramer R., Appenzeller U. *et al.* - Selective cloning of peanut allergens, including profilin and 2S albumins, by phage display technology. *Int Arch Allergy Immunol* 1999;119:265-74.
  43. Beyer K., Grishina G., Bardina L. *et al.* - Identification of an 11S globulin as a major food allergen in hazelnut-induced systemic reactions. *J Allergy Clin Immunol* 2002;110:517-23.
  44. Axelsson I.-G., Ihre E., Zetterstrom O. - Anaphylactic reactions to sunflower seed. *Allergy* 1994;49:517-20.
  45. Nordlee J.-A., Taylor S.-L., Townsend J.-A. *et al.* - Identification of a Brazil nut allergen in transgenic soybeans. *N Eng J Med* 1996;334:688-92.
  46. Asero R., Mistrello G., Roncarolo D. *et al.* - A case of sesame seed-induced anaphylaxis. *Allergy* 1999;54:526-33.
  47. Asero R., Mistrello G., Roncarolo D., Amato S. - Allergenic similarities of 2S albumins. *Allergy* 2002;57:62-3.
  48. Asero R., Mistrello G., Roncarolo D., Amato S. - Walnut-induced anaphylaxis with cross-reactivity to hazelnut and Brazil nut. *J Allergy Clin Immunol* 2004;113:358-60.
  49. Sicherer S., Sampson H.-A., Burks A.-W. - Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy* 2000;55:515-21.
  50. Lopez-Torres G., Salcedo G., Martin-Esteban M. *et al.* - Len 1, a major allergen and vicilin from lentil seeds: protein isolation and cDNA cloning. *J Allergy Clin Immunol* 2003;112:1208-15.
  51. Teuber S.-S., Comstock S.-S., Sathe S.-K., Roux K.-H. - Tree nut allergy. *Curr Allergy Asthma Rep* 2003;3:54-61.
  52. Wang R., Robotham J.-M., Teuber S.-S. *et al.* - Ana o 1, a cashew (*Anacardium occidentale*) allergen of the vicilin seed storage protein family. *J Allergy Clin Immunol* 2002;110:160-6.
  53. Koppelman S.-J., Knol E.-F., Vlooswijk R.-A. *et al.* - Peanut allergen Ara h 3: isolation from peanuts and biochemical characterization. *Allergy* 2003;58:1144-51.
  54. Wang F., Robotham J.-M., Teuber S.-S. *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.
  55. Wensing M., Knulst A.-C., 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;111:420-4.
  56. Sicherer S. - Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;108: 881-90.
  57. Teuber S.-S., Peterson W.-R. - Systemic reaction to coconut (*Cocos nucifera* L.) in two subjects with tree nut hypersensitivity and demonstration of cross-reactivity to legumin-like seed storage proteins: new coconut and walnut food allergens. *J Allergy Clin Immunol* 1999;103:1180-5.
  58. Nguyen S.-A., More D.-R., Whisman B.-A., Hagan L.-L. - Cross-reactivity between coconut and hazelnut proteins in a patient with coconut anaphylaxis. *Ann Allergy Asthma Immunol* 2004;92:281-4.
  59. De Leon M.-P., Glaspole J.-N., Drew A.-C. *et al.* - Immunological analysis of the allergenic cross-reactivity between peanut and tree nuts. *Clin Exp Allergy* 2003;33:1273-80.
  60. Fernandez C., Fiandor A., Martinez Garate A., Martinez-Quesada Y. - Allergy to pistachio: cross-reactivity between pistachio and other Anacardiaceae. *Clin Exp Allergy* 1995;25:1254-9.
  61. Pastorello E.-A., Pravettoni V., Ispano M. *et al.* - Identification of the allergenic components of kiwi fruit and evaluation of their cross-reactivity with timothy and birch pollens. *J Allergy Clin Immunol* 1996;98:601-10.
  62. Diez-Gomez M.-L., Quirce S., Aragonese E., Cuevas M. - Asthma caused by *Ficus benjamina* latex: evidence of cross-reactivity with bug fruit and papain. *Ann Allergy Asthma Immunol* 1998;80:24-30.
  63. Kao S.-H., Hsu C.-H., Su S.-N. *et al.* - Identification and immunologic characterization of an allergen, alliin lyase, from garlic (*Allium sativum*). *J Allergy Clin Immunol* 2004;113:161-8.
  64. Asero R., Mistrello G., Roncarolo D., Amato S. - A case of onion allergy. *J Allergy Clin Immunol* 2001;108:309-10.
  65. Asero R., Mistrello G., Roncarolo D. *et al.* - A case of garlic allergy. *J Allergy Clin Immunol* 1998;101:427-8.

