

Allergenic cross-reactivity, food allergy and pollen

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Abstract

Pollen-allergic patients frequently present oral allergy-like symptoms after ingestion of several kinds of plant foods. The majority of these reactions are due to three distinct cross-reactive structures that are present in birch pollen. Proteins that share common epitopes with Bet v 1, the major birch pollen allergen, occur in other kinds of tree pollen, apples, stone fruits, celery, carrots and nuts. Approximately 70% of patients who are allergic to birch pollen may experience symptoms after consumption of foods from these groups. In contrast to Bet v 1, two minor allergenic structures which sensitise ≈ 10 –20% of all pollen-allergic patients are also present in grass and weed pollen, namely profilin and cross-reactive carbohydrate determinants. Profilins can induce symptoms to almost all kinds of plant foods, whereas the clinical relevance of IgE binding to ubiquitous carbohydrates of *N*-glycans from plants remains in doubt. The paper summarises the knowledge pertaining to the molecular features of these cross-reactive structures and the characteristics of the cross-reactivity patterns and discusses aspects of diagnosis, management and routes of sensitisation. © 1997 Elsevier Science B.V.

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1. Introduction

Cross-reactivity of allergen-specific antibodies is a well-known phenomenon in food allergy. This reactivity appears not only between proteins of phylogenetically closely related, but also between phylogenetically distantly related, species. Examples for the first type of cross-reactions are those between the parvalbumins of different fish species or among the members of the legume botanical family (Bernhisel-Broadbent and Sampson, 1989; Bernhisel-Broadbent et al., 1992). Birch pollen and kiwi may serve as an example for unrelated species expressing cross-reacting allergens (Gall et al., 1994). The latter phenomenon touches upon the important problem of cross-reactions between inhalants and ingestants, which covers a wide range of food allergies most probably being caused by respiratory uptake of inhalant allergens—the so-called ‘bird-egg syndrome’, which designates egg yolk allergy induced by inhalation of serum proteins from birds (De Blay et al., 1991), food allergies to flour components which occur in per-

sons with bakers asthma (De Blay et al., 1991; Leonhardt and Molitor, 1993; Dummer et al., 1994), sunflower seed allergy due to inhalation of food for domestic birds (Axelsson et al., 1994) and all kinds of pollen related food allergies which are the main subject of this article. However, there are several other important examples for food-related cross-reactivities, i.e. the ‘latex-fruit cluster’ (M’Raihi et al., 1991; De Corres et al., 1993; Rodriguez et al., 1993; Blanco et al., 1994; Andre et al., 1995) or shrimp tropomyosins that cross-react not only with those of other crustacea species but also with molluscs and insects (Witte mann et al., 1994, Van Ree et al., 1996).

A common observation in the context of cross-reactivities is that a relatively high number of these seem to be without clinical significance, as known from cross-reactions among the legume botanical family (Bernhisel-Broadbent and Sampson, 1989) and between grass pollen and cereal proteins (Vestergard et al., 1994, Bruijnzeel-Koomen et al., 1995; Jones et al., 1995). More controversial results have been reported in the case of fish. Seven of 11 patients who showed a cross-reactive sensitisation to up to ten fish species had a

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Table 1
Allergy to plant foods in pollinosis patients

Pollen	Food	Reference
Birch	Apple, pear, cherry, peach, nectarine, apricot, plum, kiwi, hazelnut, other nuts, almond, celery, carrot, potato	Eriksson et al., 1982; Calkhoven et al., 1987, Dreborg, 1988; Wüthrich et al., 1990, Helbling et al., 1993; Gall et al., 1994
Birch/mugwort	Celery, carrot, spices	Wüthrich and Dietschi, 1985; Thiel, 1988, Jankiewicz et al., 1996a
Grass	Melon, watermelon, orange, tomato, potato, peanut, swiss chard	Calkhoven et al., 1987; De Martino et al., 1988, Ortolani et al., 1993; Boccafogli et al., 1994, Varela et al., 1994; Garcia Ortiz et al., 1995
Ragweed	Watermelon and other melons, banana, zucchini, cucumber	Anderson et al., 1970; Enberg et al., 1987; Ross et al., 1991

positive challenge to only one species (Bernhisel-Broadbent et al., 1992). In contrast, multiple clinical reactions have been reported from 39 fish-allergic patients with more than 50% of the patients being intolerant to at least four different species (Helbling et al., 1996).

The overwhelming majority of hypersensitivity reactions against fruits, vegetables and certain nuts is highly associated with several pollen allergies (Eriksson et al., 1982; Wüthrich and Dietschi, 1985; Thiel, 1988; Wüthrich et al., 1990; Ortolani et al., 1993). These particular foods belong to the most important elicitors of adverse reactions to food in adults and adolescents (Ortolani et al., 1993; Wüthrich, 1993; Pastorello et al., 1996a). A 2–4% prevalence has been estimated for the adult population of the European countries (Pastorello et al., 1996b).

The attention of this contribution will therefore, be focused on the characteristics of well-known cross-reacting food and pollen allergens which represent the molecular basis of pollen related food allergies. In addition, the data concerning the route of sensitisation will be summarised and critically evaluated. At the molecular level, evidence will be presented that this phenomenon is based on cross-reactions of human antibodies which are directed against pollen allergens.

2. Clinical aspects of pollen related food allergies

Only a very small proportion of allergies to fruits, nuts and vegetables are independent of pollen allergy (Pauli et al., 1985, Wüthrich and Dietschi, 1985; De Martino et al., 1988, Dreborg, 1988; Thiel, 1988; Ortolani et al., 1993, Schwedler et al., 1996). The plant foods that most frequently affect pollinosis patients are listed in Table 1. Typically, patients sensitized to birch pollen are very often hypersensitive to other pollen of trees belonging to the Fagales order and to apple, many sorts of stone fruit, kiwi, various kind of nuts, almond, celery, carrot and/or potato. The latter, however, predominantly causes contact urticaria of the hands or

allergic rhinitis during peeling. In addition, rare cases of unusual food allergies can occur in pollen-allergic patients. Examples for these may be hop allergy related to birch pollinosis (Kalveram et al., 1989) or hypersensitivity to lychee fruit concomitted by cross-reactions to pollen of *compositae*, birch and timothy grass (Fäh et al., 1985).

As will be discussed below, the possibility of such rare events depends on the specific sensitisation pattern of the allergic individual. In areas with birch trees, for example northern and central Europe, typical birch pollen related fruit allergies are most important. In addition, the dominating role of birch and mugwort pollen sensitisation to predispose patients for the expression of food related symptoms is also evident from studies in Italy where grasses and *parietaria* represent the most common allergenic pollen species (Pastorello et al., 1996a,b).

Allergy to celery, carrots and umbelliferous spices has originally been described as being mainly associated with mugwort pollen allergy (Pauli et al., 1985; Wüthrich and Dietschi, 1985). However, more recent studies (Table 1) revealed a co-sensitization to birch pollen in most cases. At the molecular level, no birch pollen-independent food allergens have been identified in celery (see below). Fruit allergy clusters in grass pollen allergic patients have been described by groups from Italy and Spain (Table 1). Tomatoes, potatoes, melons and oranges have been particularly named in this context (De Martino et al., 1988; Ortolani et al., 1993; Boccafogli et al., 1994). In addition to these plant foods, peanut allergy has also been found to be associated with grass pollen hypersensitivity (De Martino et al., 1988). In contrast to birch pollen allergy, only a minor proportion of grass pollen allergies is affected by food hypersensitivities (Dreborg, 1988).

Pollen of ragweed (*Ambrosia*) frequently causes pollinosis in North America, some parts of France, Northern Italy and Austria. Anderson et al. (1970) investigated 1447 pollen-sensitised patients and diagnosed a co-occurring allergy against ragweed pollen,

Table 2

Molecular characteristics of Bet v 1^a related major allergens from foods of plant origin

Food	MW (kDa)	pI	N-terminal sequence identity ^b with Bet v 1 (%)	N-terminal sequence identity ^b with PcPR 1-1 ^c (%)	Reference
Apple (Mal d 1)	17–18	5.5	53	40	Schöning et al., 1995
Pear	16–18	5.1	n.d.	n.d.	Schöning, 1996b
Cherry	18	5.8	67	40	Schöning et al., 1995
Celery (Api g 1)	15–16	4.4–4.6	40	66	Schöning et al., 1995; Ebner et al., 1995a; Vieths et al., 1995b
Carrot	16	4.4	28	57	Schöning et al., 1995; Ebner et al., 1995a
Hazelnut	18	n.d.	n.d.	n.d.	Hirschwehr et al., 1992

Acronyms of named food allergens are given in parenthesis; n.d., not done.

^a Bet v 1: major birch pollen allergen.

^b Calculated from 15 N-terminal amino acid residues.

^c PcPR 1-1: pathogenesis related protein from parsley, sequence data from Somssich et al., 1988. Mol. Gen. Genet. 213, 93.

melon and banana in 90 cases. These results have been confirmed by Enberg et al. (Enberg et al., 1987, 1988), who also showed an extended reactivity to other cucurbitaceae such as cucumber and zucchini and who demonstrated partial cross-reactivity between the food and pollen allergens involved (Table 1). This cross-reactivity was confirmed later by Ross et al. (1991).

Although *parietaria* (*Urticaceae*) and trees from the oleaceae family are found to be common in eliciting pollen allergies in the mediterranean area (D'Amato and Liccardi, 1994), there are no reports relating to specific food allergies associated with these diseases.

Most patients, who are sensitive to fruits and vegetables, suffer from local symptoms at the site of the primary allergen contact, i.e. the oropharynx. Typical phenomena are swelling of the lips, tongue and throat (oral allergy syndrome, OAS). Looking at the patients history reveals that the pollen allergy regularly appears before the occurrence of food related symptoms (Dreborg, 1988). Allergic reactions are usually due to the ingestion of the native foods, but not to the consumption of their heated and processed products (Dreborg, 1988; Ortolani et al., 1993; Gall et al., 1994; Bruijnzeel-Koomen et al., 1995). However, celery and nuts are known to contain a partly thermostable allergenic activity (Dreborg, 1988, Wüthrich et al., 1990). In the case of celery, this stable component seems to be associated with a co-sensitization to mugwort pollen (Wüthrich et al., 1990).

As has been shown for apples, specific IgE can regularly be determined in sensitised patients by serological assays, as well as by skin prick tests providing extracts of high quality are used (Vieths et al., 1995a; Vieths and Schöning, 1996). Unfortunately, these assays do not distinguish between symptomatic patients and patients with latent sensitisations. However, Kleine-Tebbe et al. (1992) demonstrated that the average dose related histamine release is significantly higher in patients who also report symptoms after ingestion of these foods.

A rare example of plant food allergy which is independent of cross-reacting pollen allergens has recently been reported from Italy. A 13 kDa protein from fruits of the *prunoidae* family had a dominating role for patients who were allergic to peach, plum, apricot and cherry, but had no cross-reacting counterpart in grass and birch pollen (Pastorello et al., 1994).

3. Characteristics of pollen related food allergens

In contrast to many allergens from pollen, only a few allergens of related plant foods have been studied in detail. Interestingly, homologues of all these food allergens are present in birch pollen. This is also true for celery allergy in mugwort-sensitive patients and in the case of food allergies in patients with grass pollinosis. No important allergenic structures are known that are exclusively shared by mugwort pollen and food and by grass pollen and food. Thus, the following discussion will be restricted to birch pollen related plant food allergens.

3.1. Allergens related to Bet v 1, the major birch pollen allergen

The data obtained over the last years strengthen the view that adverse food reactions in birch pollen allergic patients are mainly due to a specific family of related proteins. All these proteins seem to possess structural similarities. They share antigenic as well as allergenic epitopes with Bet v 1, the major birch pollen allergen. A considerable number of these allergens appearing in typical birch pollen related foods have been partially characterised. The known molecular properties of these are summarised in Table 2. All these proteins display molecular masses between 15 and 18 kDa which are in the mass range of Bet v 1 (17.4 kDa). Moreover, the known partial sequences of the allergens from apple,

Table 3

Data of Bet v 1 related allergenic food proteins with completely known cDNA sequences

Allergen	Source	Molecular mass (kDa)	Number of amino acid residues	Sequence identity with Bet v 1a (%)	Sequence identity with PcPR1-1 (%)	Reference
Mal d 1	Apple	17.5	158–159	58	40	Vanek-Krebitz et al., 1995, Schöning et al., 1996
Pru a 1	Cherry	17.7	159	59	41	Scheurer et al., 1996
Api g 1	Celery root	16.2	153	40	61	Breiteneder et al., 1995

cherry, celery and carrot show 28–67% sequence identity with the isoform Bet v 1a from birch and 40–60% identity with PcPR1-3, a pathogenesis related protein (PRP) from parsley (Schöning et al., 1995; Schöning, 1996b). Comparable sequence identities can also be found with other PRP occurring in foods such as soya bean, bean, pea or potato. As has been suggested, these PRP may have RNase activity (Moiseyev et al., 1994; Bufe et al., 1996).

Until now, three plant food allergens of the Bet v 1 family, namely those of apple, cherry and celery have been completely sequenced at the cDNA level (Breiteneder et al., 1995; Vanek-Krebitz et al., 1995; Scheurer et al., 1996; Schöning, 1996b; Schöning et al., 1996). The molecular data of these allergens which are compared in Table 3 agree closely with the characteristics listed in Table 2.

In general, food allergens are thought to be highly soluble and relatively small. A considerable number of them are known to resist enzymatic hydrolysis and to contain sequential epitopes (Metcalf, 1985; Taylor et al., 1987; Matsuda and Nakamura, 1993, 1993; Vieths et al., 1996a). However, this view seems to be incorrect in the case of celery and apple allergens since we have observed partial digestibility of Api g 1 in a gastrointestinal model (Jankiewicz et al., 1997b). Additionally, we found that also Mal d 1 can easily be cleaved by several proteases (Son et al., 1997). Immunoreactive fragments of this allergen are only recognised by IgE of $\approx 35\%$ of our positive patient sera (Son et al., 1997).

T cell lines of apple allergic patients are only weakly stimulated by Mal d 1, whereas Bet v 1 induces high proliferation rates of these cells (Fahlbusch et al., 1996). Furthermore, until now IgE specific for Mal d 1 could not be induced in mice, but IgE against Bet v 1 was obtained successfully many times (Hoffmann et al., 1997 and unpublished results). At the antibody level, IgE from apple allergic patients reacts at least 15-fold stronger with Bet v 1, when compared to the apple allergen (Vieths et al., 1995a; Vieths and Schöning, 1996).

Thus, the molecular properties of the food allergens mentioned above seem to be different from 'classical' food allergens (Yunginger, 1990), such as those of milk, egg and mustard. There is strong evidence that Bet v 1

induces the IgE response and that the hypersensitivity to specific plant foods is an epiphenomenon due to cross-reacting antibodies.

3.2. Profilins

Carlsson et al., 1976 described a small protein in calf spleen that inhibited the growth of actin filaments in vitro. Due to the formation of 'profilamentous' complexes with actin, it has been named 'Profilin'. The current knowledge about the functions of profilins and their role as 'plant pan allergens' has recently been summarised in several review articles (Valenta et al., 1992a,b; Theriot and Mitchinson, 1993; Martinez et al., 1995; Vieths et al., 1996b,c). Profilins are involved in the regulation of actin polymerisation, in signal transduction processes of the phosphatidylinositol pathway and may represent important mediators of membrane-cytoskeleton communication. Due to these specific functions in non-muscle cells, profilins are ubiquitously abundant in eukaryotic organisms. Valenta et al. (1991) were the first who identified profilin as an allergen from birch pollen. After sequencing and expression as a recombinant protein, the allergen was named Bet v 2.

In recent years, profilins of many pollen species and from many foods of plant origin (e.g. celery, tomato, potato, apple, peach, lychee fruit) have been identified as allergens (Fäh et al., 1985; Vallier et al., 1992; Van Ree et al., 1992; Ebner et al., 1995a,b; Vieths et al., 1995b; Petersen et al., 1996). The sensitisation to profilins affects $\approx 20\%$ of the pollen-allergic population. As potential plant food allergens, only the profilins of maize (Staiger et al., 1993) and wheat (Rihs et al., 1994) have been cloned and sequenced. The known profilins constitute a heterogenous group of neutral, basic and acidic proteins with a considerable number of isoforms. Their molecular masses range between 12 and 15 kDa. The amino acid sequence identity between known plant profilins is at least 70%, but can be drastically lower between plants and mammals, for example 27% in the case of human and timothy pollen profilin (Vieths et al., 1996b,c). However, the conformational structure of profilins seems to be highly conserved, even between distantly related species such as amoeba and cattle. These conserved structures may be responsible for the

extreme degree of cross-reactivity which can regularly be shown among almost all profilins. Moreover, a recent study indicated the existence of two profilin gene families in monocot and dicot plants. The first being expressed in all major plant organs, whereas the expression of the second seems to be restricted to mature pollen (Huang et al., 1996). Divergence between these two profilin families may also partly explain the higher allergenic potency of pollen profilin in relation to those from cross-reacting plant foods.

When birch pollen were extracted by aqueous protein extraction methods, profilin was released more slowly and in smaller amounts when compared to Bet v 1 (Vrtala et al., 1993). Due to our own, unpublished experiments, profilin is a relatively weak immunogen in mice when compared to Bet v 1. Hence, the use of monoclonal antibodies against important pollen and plant food profilins has not been published until now. Taken together, these data may explain why only a minor proportion of the pollen allergic population is sensitive to profilin. Since food allergy to profilin in patients without pollen allergy has not been described in the literature, the sensitisation may again be initiated via the inhalation of pollen. In contrast to allergy against the 'Bet v 1-family', which is restricted to a limited number of plants, profilins have to be considered as potential allergens in almost all kinds of plants. Moreover, the clinical relevance of a weak IgE autoreactivity to human profilin (Valenta et al., 1991) and the potential of allergenicity of other animal profilins requires further investigations. In areas without birch trees like Spain, profilins can represent important food allergens in patients with combined grass pollen/food allergy and can even induce sensitivity to typical birch pollen related foods such as apple (Van Ree et al., 1995a,b). This study also yielded evidence that profilin can induce stronger symptoms to food than those regularly elicited in patients with Bet v 1 related cross-allergies to food. Within a group of 16 patients allergic to peach and/or apple who predominantly presented IgE specific for profilin, ten of these experienced systemic reactions after ingestion of at least one of these foods (five cases of urticaria, two of gastrointestinal symptoms and three cases of anaphylaxis).

3.3. Carbohydrate epitopes involved in cross reactivity between pollen and food

3.3.1. Introductory remarks

In addition to the peptidic structures that are involved in the cross-reactions of IgE between pollen and food, epitopes can also be created by the carbohydrate moieties of glycoproteins. These structures are usually termed 'cross-reactive carbohydrate determinants' (CCD). The recent review of Aalberse and van Ree (1996) briefly summarises the knowledge about the

involvement of CCD in the allergenic response. CCD are able to bind IgE from pollen allergic patients with a high affinity, are widely distributed in the plant kingdom and moreover, on glycoproteins of invertebrates such as insects and molluscs. As a result of the high abundance in these materials, CCD can mediate a very broad spectrum of cross-reactions, comparable to, if not exceeding those of profilins (Aalberse et al., 1981; Faye and Chrispeels, 1988; Broichmann et al., 1992; Van Ree and Aalberse, 1993; Vieths et al., 1994). Cross-reactions of IgE due to CCD have been demonstrated between grass pollen, buckwheat, potato and honeybee venom (Aalberse et al., 1981), bee venom, mugwort pollen and wheat flour (Broichmann et al., 1992), bee venom phospholipase A₂ (PLA₂) and the plant protease bromelain (Tretter et al., 1993) and between celery, apple, strawberry, orange, lychee fruit, onion, zucchini, Brussels sprouts and several spices (Vieths et al., 1994). As shown for celery, the IgE-reactivity to CCD cannot be eliminated by heating the allergenic source material (Jankiewicz et al., 1996a, 1997a). As demonstrated in Spanish patients suffering from food allergy and grass pollinosis, IgE against CCD and/or profilin can be present in the majority of cases (Van Ree et al., 1995a) when birch pollen/Bet v 1 are absent.

3.3.2. Immunogenic structures

Two structures of asparagine-linked *N*-glycans, which are absent in mammalian glycoproteins, have been found to be highly immunogenic. First, an α 1,3-fucose antenna linked to the innermost GlcNAc can be responsible for the antigenic properties and the binding of IgE (Faye and Chrispeels, 1988; Faye et al., 1993; Tretter et al., 1993). Second, many of such *N*-glycans from plants contain a β 1,2-xylose residue at the proximal mannose (Ishihara et al., 1979; D'Andrea et al., 1988; Hayashi et al., 1990). Invertebrate glycans such as PLA₂ or a sea squirt allergen can carry the fucose, but lack the specifically linked xylose. IgE binding to the latter type of glycan makes the link explainable between sensitisation to bee venom and cross-reactivity to plant foods (Tretter et al., 1993). However, in our own studies we were able to demonstrate the existence of cross-reactive anti-CCD IgE in a group of patients with combined food and pollen allergies who were not sensitive to bee venom (Vieths et al., 1994). In such cases, the binding of IgE may be due to xylose or to other cross reactive plant glycans without fucose.

CCD have been identified on several specific allergens. In addition to PLA₂, a sea squirt allergen, DIIIa (Shigeta et al., 1990), the cedar pollen allergen Cry j 1 (Hijikata et al., 1994; Ogawa et al., 1996), the olive pollen allergen Ole e 1, the grass pollen allergens Lol p 11 and Phl p 1 (Petersen et al., 1995; Van Ree et al., 1995a,b) and an IgE binding β -fructofuranosidase from

tomato (Petersen et al., 1996) have been shown to contain these kinds of determinants. However, the CCD of most of these allergens do not represent major epitopes.

3.3.3. Clinical relevance of CCD

Contrary to Bet v 1 and profilin, the IgE reactivity of CCD is thought to be of minor importance, or even irrelevant, for the symptomatology of patients with combined food and pollen allergies (Aalberse, 1992; Van Ree and Aalberse, 1993; Aalberse and van Ree, 1996). However, symptomatic as well as asymptomatic patients, participated in the studies of Broichmann et al. (1992) and Vieths et al. (1994). The clinical significance can neither be excluded nor confirmed by the results of these and other studies (Weber et al., 1987; Tretter et al., 1993). Moreover, the investigation of the sea squirt allergen yielded evidence that its carbohydrate moiety is involved in the triggering of skin and conjunctival symptoms in allergic patients (Shigeta et al., 1990). A single *N*-glycan, like the structure present on bromelain is a monovalent epitope and thus, can not crosslink IgE if the antibody response is restricted to CCD. However, with a polyclonal and polyvalent antibody population against CCD and peptide epitopes, CCD may be able to participate in this essential event of the type I reaction. Further studies are required to answer this important question.

3.4. Other cross-reactive allergens in pollen and food

On the basis of peer-reviewed journals, there is little evidence that other cross reactive pollen allergens exist which gain comparable importance as the structures described above. Independent of these might be the structural basis of the clinically relevant food allergies in patients with ragweed pollen allergy. However, despite the identification of six IgE-reactive bands in watermelon by isoelectric focusing followed by immunoprinting (Enberg et al., 1987), no molecular data about the allergens of the offending foods is available.

New structures may also exist in the context of kiwi allergy, which seems to be more complex when compared to foods such as apple and celery. First, kiwi participates in the clinically important latex-fruit-cluster (Andre et al., 1995; Pastorello et al., 1996b) which is the subject of many current studies. Second, it is clearly associated with birch pollen allergy (Gall et al., 1994), and Pastorello et al. (1996b) have identified several kiwi allergens and investigated their cross-reactivity to birch and grass pollen. Similar experiments have also been performed by Möller et al. (1997). These authors described two allergen bands in kiwi with masses of 43 and 67 kDa and demonstrated cross-reactivity with a 68 kDa protein of birch pollen. No cross-reactivity was observed between these fruit proteins and Bet v 1.

Recently, Wellhausen et al. (1996) isolated a 35 kDa protein from birch pollen that bound IgE of 9/76 (12%) sera from birch pollen allergic patients. Despite the molecular weight estimated from SDS-PAGE, a pI of 7.4 and the existence of several isoallergens in the pI-range between 6.2 and 7.5, no additional molecular data of this protein is available. However, the allergen cross-reacted with IgE-binding protein bands of comparable size from apple, pear, orange, banana, mango, lychee fruit and carrot. These 35 kDa proteins did not cross-react with Bet v 1. However, the clinical relevance of this observation needs further investigation. Moreover, when looking at the molecular masses, one might suspect the involvement of dimeric structures of Bet v 1, possibly artificial and carrying new epitopes created by the dimerisation process in these uncommon cross-reactivities.

4. Concluding remarks

Oral allergies to plant foods in pollen-allergic patients are based on cross-reactive IgE. Summarising, there remains only little doubt that the immunogenic stimulus is due to inhalation of the pollen allergens. Food related symptoms may occur after exceeding an individual threshold level of IgE specific for the pollen allergens (Ebner et al., 1991). The decision between latent and clinically significant sensitisation to specific kinds of the related plant foods may depend on the epitope specificities of the polyclonal IgE response of the allergic individual, and on nutritional habits. When compared to the 'classical' food allergens, the properties of which have been discussed by Dr Aalberse, pollen related food allergens seem to have some divergent characteristics. Food profilins and food proteins of the 'Bet v 1-family' are relatively sensitive to heat and can be easily cleaved by proteases. Moreover, in the case of Mal d 1 from apple, the sequential epitopes identified so far bind only relatively weakly to specific IgE and contain only little residual activity. This is in contrast to other important non pollen-related food allergens such as bovine casein, β -lactoglobulin or ovalbumin.

The following aspects should be kept in mind when managing pollen related food sensitisation: first, serological assays and skin prick tests allow no distinction between symptomatic and asymptomatic patients. Second, the occurrence of Bet v 1 related proteins is restricted to a specific cluster of plant foods (top of Table 1), whereas profilins are present in all kinds of plants and thus, can cause unlimited cross-reactive sensitisations. Knowledge of the specific sensitisation of individual patients can be obtained by commercial in vitro tests (e.g. CAPTM to Bet v 1 and Bet v 2) and may have consequences on both risk assessment and dietary

management. For example, sensitisation to birch profilin, may indicate a risk of developing allergies against foods that rarely affect pollen allergic patients (e.g. lettuce, eggplant, lychee fruit, etc.). However, fine specificities of the IgE response to divergent pollen profilins may influence sensitisation to foods and the pattern of cross-reactivity. Thus, a mixture of profilins from birch, grass and weed pollen would reveal more reliable *in vitro* results, but is not available as a commercial assay for specific IgE. Positive serological assays should not be taken as indicators for a strict avoidance of foods which are tolerated. However, it is the authors' opinion that excessive consumption of these foods should be avoided by patients with a clinically insignificant sensitisation.

Otherwise, important differences between Bet v 1 and its homologues in food exist at the antibody and at the T cell level. Bet v 1 consists of up to 20 isoallergens with slightly different amino acid sequences (Swoboda et al., 1995). These isoforms differ in both their ability to bind specific IgE from birch pollen allergic patients and in their potency to stimulate IL-4-producing T cell clones from allergic patients (Ebner et al., 1995b; Ferreira et al., 1996). Bet v 1d, for example, is not recognised by IgE, but induces a strong T cell response. Molecules with such properties have been proposed as candidates for an effective low-risk pollen immunotherapy. The IgE reactivity of Bet v 1a depends on a threonine residue at position 10 and decreases strongly by changing this residue into a proline by site-directed mutagenesis (Ebner et al., 1995a,b). However, the food allergens belonging to this family are generally weak IgE binders. No evidence has been published that specific T-lymphocytes of subjects with food related symptoms show a significant proliferative response to these food proteins. Comparison of overlapping peptides representing sequence motifs of Bet v 1 and carrying T-cell epitopes with the corresponding partial sequences of Mal d 1 revealed differences of at least 3/12 residues. The sequence of one immunodominant epitope (Bet v 1 77–92) contained 10/16 exchanges (Vieths and Schöning, 1996). The latter findings support the view of a lower sensitisation potency of the apple allergen.

Despite proteins which carry CCD, the clinical relevance of which is doubtful, there is negligible knowledge about the structures of cross-reactive B-cell epitopes on both Bet v 1 and the related food proteins and on profilins from pollen and food. This kind of data could provide general insights in the properties of epitopes being responsible for eliciting food-related symptoms in patients with pollinosis.

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