

Pathogenesis-related (PR)-proteins identified as allergens

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Abstract

Type 1 allergies are recognized as an important disease affecting around 25 % of the population of industrialized countries of the Northern hemisphere. Allergic patients produce specific IgE antibodies after frequent exposure to either inhaled or nutritive allergens. Of the plant allergens listed in the Official Allergen Database of the International Union of Immunological Societies, approx. 25 % belong to the group of pathogenesis-related proteins (PR-proteins). PR-proteins are defined as proteins that are induced upon stress, pathogen attack and abiotic stimuli. This inhomogeneous group of proteins has been classified into 14 PR-protein families. So far, plant-derived allergens have been identified with sequence similarities to PR-protein families 2, 3, 4, 5, 8, 10 and 14. In general, both protein groups, i.e. PR-proteins and allergens, comprise rather small proteins, which are stable at low pH and resistant to proteolysis. These features, and their level of expression, make PR-proteins good candidates for evoking an immune response in predisposed humans, when coming into contact with mucosal surfaces. The identification of PR-proteins with allergenic potential and their homologues is of importance for the allergic patient and the management of this disease. Firstly, plant foods derived from genetically modified plants could represent new allergen sources, and therefore should be evaluated carefully for their potential allergenicity. Secondly, complex plant-derived foods should be analysed for hidden allergens and labelled accordingly.

Introduction

Plant food allergens can cause symptoms ranging from pruritus, swelling of the lips, tongue and oral mucosa (often accompanied by mild laryngeal symptoms as a sensation of tightness), itching, cough and pruritus of the ear canals to gastro-

intestinal symptoms, rhinitis, asthma, cutaneous reactions, and the most severe reaction, systemic anaphylaxis. Inhaled plant allergens present predominantly in pollen, spores, and plant-derived products such as cosmetics and rubber articles may cause rhinoconjunctivitis, asthma, oedema, urticaria and anaphylaxis.

Among the numerous different proteins present in plant food, only a comparatively small number has been identified as food allergens [1]. It is challenging for the modern allergologist to investigate whether a relationship can be established between primary sequences coding for allergens, their physicochemical properties and their three-dimensional structures, and their potential to act as an allergen when coming into close contact with the human immune system.

To date, a number of identified plant-derived allergens have been classified into defined groups of plant proteins, such as pathogenesis-related proteins (PR-proteins), seed storage proteins and structural proteins. These relationships are based primarily on sequence similarities. In addition, for a number of proteins, this classification has been supported by information on their biological function from *in vitro* and/or *in vivo* assays.

A considerable percentage of identified plant allergens can be grouped into one of the 14 PR-protein families [2]. These proteins are encoded by the host and are induced by various types of pathogens (viruses, bacteria and fungi), or by chemicals such as ethylene and salicylic acid that mimic the effects of pathogen infection [3].

The term PR-proteins encompasses very different plant proteins, such as chitinases, glucanases, endoproteinases and peroxidases, as well as small proteins such as defensins, thionins and lipid transfer proteins (LTPs) (Table 1). Surprisingly, some of the PR-proteins not only are induced *de novo* upon pathogen attack/wounding or other physical or chemical stress, but are constitutively expressed in some organs or during certain developmental stages. So, in strict terms, these forms are not PR-proteins themselves, but are designated 'PR-like'. To date, plant-derived allergens have been identified with sequence similarity to PR-protein families 2, 3, 4, 5, 8, 10 and 14. These proteins share some of the characteristics

Key words: chitinase, IgE, latex, lipid transfer protein, pathogenesis-related protein, plant allergens.

Abbreviations used: LTP, lipid transfer protein; nsLTP, non-specific LTP; OAS, oral allergy syndrome; PR-protein, pathogenesis-related protein; TLP, thaumatin-like protein.

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Table I

Allergens related to PR-proteins

Family	Designation	Source	Allergen name
PR-2	β -1,3-Glucanases	<i>Hevea brasiliensis</i> latex, banana	Hev b 2
PR-3	Class I chitinases	Avocado, <i>H. brasiliensis</i> latex, chestnut, banana	Pers a 1, Hev b 11, Cas s 5
PR-4	Chitinases	<i>H. brasiliensis</i> latex, turnip	Hev b 6
PR-5	TLPs	Cherry, apple, bell pepper, mountain cedar	Pru av 2, Mal d 2, Cap a 1, Jun a 3
PR-8	Class III chitinases	<i>H. brasiliensis</i> latex	Hevamine
PR-10	Unknown; Bet v I homologues	Birch, hazel, alder, hornbeam, chestnut, apple, celery, cherry, peach, apricot, pear, carrot, potato, parsley	Bet v 1, Cor a 1, Aln g 1, Car b 1, Cas s 1, Mal d 1, Api g 1, Pru av 1, Pru p 1, Pru ar 1, Pyr c 1, Dau c 1, STH-2, PcPR-1
PR-14	LTPs	Peach, apple, soybean, apricot, plum, cherry, barley, <i>H. brasiliensis</i> latex, chestnut, hazelnut, walnut, mugwort, ragweed, asparagus, grape, maize, olive	Pru p 3, Mal d 3, Gly m 1, Pru av 3, Art v 3, Amb a 6, Par j 1,2, Cas s 8, Cor a 8, Jug r 1, Aspa o 1, Vit v 1, Hev b 12, Zea m 14, Ole e 7

that are relevant for plant-derived allergens: they are usually rather small proteins (5–70 kDa), stable at low pH and rather resistant to proteolysis. This article provides a brief overview of the relevant PR-protein families with known allergenic members.

PR-2 family: β -1,3-glucanases

Members of the PR-2 family are monomeric β -1,3-glucanases (glucan endo-1,3- β -glucosidases; EC 3.2.1.39), with a molecular mass of 25–35 kDa, which catalyse the hydrolytic cleavage of β -1,3-glucans, the abundant component of plant cell walls. These enzymes are thought to play a role in the response of plants to microbial pathogens, but they are also implicated in a number of physiological and developmental processes in uninfected plants, such as pollen germination, tube growth, fertilization, fruit ripening, seed germination and mobilization of storage products in the endosperm of cereal grains (reviewed in [4]). In addition, they represent a response to wounding, cold, ozone and UV-B radiation [5]. Allergens with similarity to PR-2 proteins have been identified from the latex of the tropical rubber tree *Hevea brasiliensis*, i.e. Hev b 2, a relevant latex allergen [6]. The association between allergy to *Hevea* latex and hypersensitivity to foods, especially avocado, banana, chestnut, fig and kiwi, has been termed latex–fruit syndrome ([6–8]; see also the paper by Wagner and Breiteneder in the current colloquium [8a]). The basic β -1,3-glucanases from *Hevea* latex

are recognized by specific IgEs from food-allergic patients suffering from hypersensitivity to banana, potato and tomato, rather than to latex products [9].

PR-3 family: chitinases (classes I, II and IV)

Plant chitinases are mostly endochitinases which hydrolyse chitin, the major component of the exoskeleton of insects as well as of the cell wall of most fungi and nematodes. Neuhaus et al. [10] have grouped chitinase sequences into seven different classes, and the PR-3 family comprises chitinase classes I, II and IV.

Class I chitinases contain a cysteine-rich 40-amino-acid domain at the N-terminus, the chitin-binding hevein domain, a hypervariable domain (which is a proline-rich hinge region) and a catalytic domain. A signal peptide is removed from the mature protein, and a target sequence directing the protein to the vacuole is located at the C-terminus. The hevein domain is not a targeting signal and does not play a role in the catalytic activity of chitinases, yet its presence seems to be essential for chitin binding and for substrate affinity.

Chitinases have been shown to exert anti-fungal activity *in vitro* [3], which represents the rationale behind attempts to establish transgenic plants expressing class I chitinases [11].

Major allergens of the PR-3-type class I chitinases are known from chestnut (*Castanea sativa*; Cas s 5) and avocado (*Persea americana*).

They have been identified by N-terminal amino acid sequencing and cDNA cloning as class I chitinases containing hevein (chitin-binding) domains [12,13]. A cDNA encoding avocado chitinase has been cloned and expressed in the yeast *Pichia pastoris*, and is now designated Pers a 1 [12]. For this recombinant allergen, antifungal assays could provide the first evidence that a PR-protein indeed exerts allergenic characteristics [12].

Two major IgE-binding proteins of 32 and 34 kDa from banana were identified as class I chitinases with a hevein-like domain, further explaining the cross-sensitization between *Hevea* latex and fruits [14].

PR-4 family: chitinases

Representatives from the PR-4 family, another set of chitinases with allergenic activity, are prohevein and a related protein from turnip. Prohevein is a chitin-binding protein from *H. brasiliensis*, the rubber tree. The sequence of the preproprotein comprises 204 amino acid residues and contains a leader sequence of 17 residues. The mature 20 kDa protein is cleaved into two fragments: a peptide of 4.7 kDa (43 residues), designated hevein, and a protein of 14 kDa at the C-terminus (144 residues), designated the C-terminal domain. Hevein has sequence similarity to chitin-binding proteins, whereas the C-terminus is similar to wound-inducible proteins.

Prohevein represents a major allergen from *Hevea* latex, designated Hev b 6.01. Furthermore, the two domains themselves represent allergens: Hev b 6.02 (hevein) and Hev b 6.03 (the C-terminal domain). Approx. 75–83 % of latex-allergic patients display specific IgEs directed against Hev b 6 [6,15].

Wounding and chemical treatment of turnip (*Brassica rapa*) plants induces the expression of an 18.7 kDa allergen that was recognized by the IgE of individuals allergic to natural rubber latex [16]. This protein has 70 % sequence identity to Hev b 6.01, as well as high sequence similarities to wound-induced proteins from tomato (74 %) and potato (71 %).

PR-5 family: thaumatin-like proteins (TLPs)

Thaumatococcus, an intensely sweet-tasting protein, originates from the African shrub *Thaumatococcus*

daniellii [17]. Based on sequence similarity, all PR-5 proteins are designated TLPs, although none of the other proteins have been described to have a sweet taste. TLPs have been detected in the leaves of young plants, but they accumulate rapidly to high levels upon biotic or abiotic stress. TLPs contain 16 cysteine residues which are involved in the formation of eight disulphide bridges. The locations of the cysteine residues are highly conserved between other high-molecular-mass members of the PR-5 family.

One hypothesis is that PR-5 proteins are inserted directly into fungal membranes, forming a transmembrane pore and causing influx of water followed by osmotic rupture [18].

Several attempts have been undertaken to investigate whether transgenic plants over-expressing PR-5 proteins display enhanced disease resistance. Up to now the results have been conflicting [19].

Members of the PR-5 family represent food allergens that are present in various plant-derived foods. An apparent 31 kDa major apple allergen whose N-terminal sequence shares 46 % identity with PR-5 proteins was the first TLP to be described as an allergen [20]. The full cDNA sequence has been obtained and the allergen has received the designation Mal d 2 from the international nomenclature committee (<http://www.allergen.org>). In sweet cherry (*Prunus avium*), a 23.3 kDa TLP was identified as a major allergen, designated Pru av 2, and its cDNA was determined [21]. In bell pepper a 23 kDa protein was identified as an important allergen and designated Cap a 1 [22]. The N-terminal sequence of this protein was found to be identical to a corresponding portion of the osmotin-like protein P23 from tomatoes. Recently, a TLP from mountain cedar pollen has been identified as an airborne allergen.

PR-8 family: chitinases (class III)

PR-8 proteins are chitinases of class III, originally described as lysozymes [23]. One of the major latex proteins from *H. brasiliensis*, hevamine, displays lysozyme and chitinase activity. Hevamine, a 30 kDa basic protein from the luteoids of *Hevea* latex, is involved in plugging the latex vessels and stopping latex flow. It has been identified as an allergen present in latex products, but it is regarded as a minor allergen from

H. brasiliensis, and is without an official allergen designation at present [6].

PR-10 family: intracellular proteins with unknown enzymic function

A large number of intracellular, possibly cytosolic, proteins has been isolated from various species such as asparagus, parsley, bean, pea, potato and apple [24–28]. No signal peptide has been found for these proteins. Due to their sequence similarities and uniform size, they have been grouped together into the PR-10 family. Proteins from ginseng have been shown to display ribonuclease activity [29], but for other members no or rather weak activity has been shown [30]. It is noteworthy that all of these proteins are encoded by multiple genes (designated *Ypr10* by van Loon and van Strien [2]). Most of the genes have been shown to be induced upon microbial attack [25], and by fungal elicitors [25,26], wounding [24] and stress stimuli [31]. As is the case with most of the other PR-protein families, PR-10-type proteins are also expressed in a tissue-specific manner during development.

The most frequent clinical syndrome caused by cross-reactive IgE antibodies is the oral allergy syndrome (OAS), an association of food allergies to fruits, nuts and vegetables in patients with pollen allergy. In the majority of cases, OAS in individuals allergic to tree pollens is caused by IgE cross-reactivity of Bet v 1 (the major allergen of birch) and related proteins. About 90 % of patients allergic to birch pollen react to this major pollen allergen, and they frequently display cross-reactivity to pollen from related trees, such as alder, hazel, hornbeam, beech and European chestnut [32]. Proteins with significant high sequence similarity to Bet v 1 have been identified in all these species.

Mal d 1, the major allergen from apple, was the first Bet v 1-related fruit allergen to be cloned and produced as a recombinant allergen by Vanek-Krebitz and co-workers [33]. Induction of Mal d 1 by pathogen and abiotic factors has been shown by Pühringer and co-workers [28]. A number of Bet v 1-related allergen sequences have been isolated and cloned from fruits, including cDNAs encoding Pru av 1 from sweet cherry [34], Pru ar 1 from apricot (AF020784; AF134731) and Pyr c 1 from pear (AF057030). In vegetables, allergen-encoding cDNA sequences are known from celery (*Api g 1* [35]) and from carrot (*Dau c 1* [36]). Additional Bet v 1-related proteins capable of

binding anti-Bet v 1 IgE have been described as pcPR-1 and pcPR-2 from parsley and pSTH-2 and pSTH-21 from potato [37]. The N-terminal sequence of the major hazelnut allergen was found to be 72 % identical with that of the major hazel pollen allergen Cor a 1, another Bet v 1 homologue [38].

PR-14 family: LTPs

Plant non-specific (ns)LTPs are small proteins (9 kDa) which facilitate the transfer of phospholipids and other lipids across membranes. These proteins are widely distributed throughout the plant kingdom. nsLTPs can take part in plant defence, as some nsLTPs have potent antifungal and antibacterial activities ([39]; see also the paper by van Ree in this colloquium [39a]).

The subcellular location of these proteins is unknown, but they may play a major role in membrane biogenesis by conveying phospholipids such as waxes and cutin from their place of synthesis to membranes that are unable to form these lipids. nsLTPs contain eight conserved cysteine residues forming four disulphide bridges, which makes them highly resistant to harsh temperature and pH changes [40].

nsLTPs are the most important allergens of the Prunoideae (e.g. peach, apricot, plum and cherry) when no pollinosis is involved [41,42]. An 8–10 kDa protein doublet, exclusive to peach skin extracts, which largely accounts for the allergenicity of that fruit, was tentatively named Pru p 1 [43]. The nsLTP of peach was granted the designation Pru p 3 [44–46], and the nsLTP of apple was called Mal d 3 [47], by the International Allergen Nomenclature Committee. An IgE-mediated allergy to beer can be caused by the nsLTP from barley, a certain percentage of which is found intact in beer after the malting and brewing process, and which is involved in beer foam formation [48].

A low-molecular-mass allergen (~8 kDa) localized in soybean hulls was identified as the main protein responsible for several asthma outbreaks in Spain [49]. The allergen Gly m 1 consists of two isoforms, 1A and 1B. The number of nsLTPs identified to have allergenic activity has increased dramatically in recent years. They have been characterized from, for example, pollen (mugwort; *Art v 3*), ambrosia (*Amb a 6*), olive (*Ole e 7*), hazelnut (*Cor a 8*), fruits (grape; *Vit v 1*), maize (*Zea m 14*), asparagus (*Aspa o 1*) and *H. brasiliensis* latex (*Hev b 12*).

Conclusions

A large number of proteins with different (or unidentified) biochemical and enzymic activities are encompassed by the term PR-proteins. The only unifying feature is that all of these proteins are induced upon pathogen attack, by either abiotic or biotic factors. In addition, certain isoforms of PR-proteins are expressed constitutively at certain stages of development.

New complications may arise from genetically modified plant foods. Since one major goal is to improve disease resistance in economically useful plants, insertion of genes encoding PR-proteins or enhancing their level of expression is the method of choice. Since a number of allergens are PR-like proteins, the potential allergenic features of newly introduced proteins have to be carefully evaluated. Thus the U.S. Food and Drug Administration has already recommended a decision tree approach to risk assessment of allergens to be used, especially for transgenic plants [50].

A number of plant-derived allergens and PR-like proteins can be found in various species throughout the plant kingdom. These proteins are responsible for cross-reactions between different allergen sources and represent, at least in part, the molecular basis for syndromes such as the pollen-related food syndrome, the latex–fruit syndrome and the birch–mugwort–celery–spice syndrome. Therefore new insights into plant cell metabolism and the defence-related strategies that plants have developed may contribute to a better understanding of allergy syndromes. Furthermore, based on this knowledge, improvements in allergy diagnosis are conceivable.

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The latex–fruit syndrome

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Abstract

Approximately 30–50% of individuals who are allergic to natural rubber latex (NRL) show an associated hypersensitivity to some plant-derived foods, especially freshly consumed fruits. This association of latex allergy and allergy to plant-derived foods is called latex–fruit syndrome. An increasing number of plant sources, such as avocado, banana, chestnut, kiwi, peach, tomato, potato and bell pepper, have been associated with this syndrome. The prevailing hypothesis is that allergen cross-reactivity is due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or represent evolutionarily conserved structures. Several types of proteins have been identified to be involved in the latex–fruit syndrome. Two of these are plant defence proteins.

Class I chitinases containing an N-terminal hevein-like domain cross-react with hevein (Hev b 6.02), a major IgE-binding allergen for patients allergic to NRL. A β -1,3-glucanase was identified as an important latex allergen which shows cross-reactivity with proteins of bell pepper. Another important NRL allergen, Hev b 7, is a patatin-like protein that shows cross-reactivity with its analogous protein in potato. Furthermore, patients with allergy to plant-derived foods and associated pollinosis show a high frequency of IgE reactivity to the pan-allergen profilin, which may cause positive serum IgE determinations to NRL. Although there is much information about the plant-derived foods and some data about the allergens involved in the latex–fruit syndrome, it is not always clear whether latex sensitization precedes or follows the onset of food allergy.

Key words: cross-reactive allergen, food allergy, latex allergy.

Abbreviations used: NRL, natural rubber latex; PR, protein, pathogenesis-related protein; SPT, skin prick test.

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Introduction

Allergy to natural rubber latex (NRL) continues to be a feature of allergy practice world-wide. IgE-