

Features and Mode of Action of Cross-reactive Plant Allergens Relevant to Latex-fruit Syndrome

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Immediate-type reactions to articles made from natural rubber latex are collectively referred to as latex allergy. Some latex-sensitized patients also experience allergic reactions to various fruits and vegetables. This phenomenon is called latex-fruit syndrome. Recent research revealed that several proteins related to the defense mechanisms of plants are responsible for latex allergy and the accompanying cross-reactivity. Protective systems of higher plants are relatively conserved in the course of evolution, and therefore homologous defense-related proteins are produced regardless of the species. Once sensitized by such a conserved protein, the patient is expected to cross-react to taxonomically unrelated plants. Remarkably, cross-reactive antigens in the causative foods are generally sensitive to heat and digestive enzymes. Per-oral sensitization is not commonly established by such food antigens. They are instead considered to elicit allergic reactions in latex-sensitized patients based on their cross-reactivity to the corresponding sensitizers. Defense-related proteins in higher plants are agriculturally useful, and various environmental stresses up-regulate their production. These proteins are also suspected to be relevant to the increasing allergies to plants.

Keywords: Latex allergy, cross-reactivity, epitope, pan-allergen, conserved protein, oral allergy syndrome, defense-related protein, pathogenesis-related protein, incomplete food allergen, class II food allergy

RESEARCH ON ALLERGENS

There have been recent surprising advancements in immunology, and we expect it to progress even more rapidly and steadily in the future using the genomic information of the human being. By contrast, research on allergenic substances (allergens) is far behind the times. The accumulation of scientific knowledge about the features and modes of action of allergens is

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TABLE 1. Characteristics of latex allergy

Causes	Gloves, catheters, rubber dam, balloons, etc.
Prevalence	5 to 15% of medical personnel are IgE positive
Symptoms	Local to generalized urticaria, anaphylaxis
Allergens	Proteins in natural rubber latex and their derivatives
Cross-reaction	Vegetable foods, pollen, medical plants, etc.

indispensable for realizing preventive measures against allergies and for improving the lifestyle of patients suffering from allergic diseases. In this mini-review, the characters and modes of action of proteinous cross-reactive allergens from plants are described, mainly with reference to latex allergy.

LATEX ALLERGY

Immediate-type reactions that are caused by any product made from natural rubber latex are collectively called latex allergy (Turjanmaa *et al.*, 1996; Poley & Slater, 2000; Levy & Leynadier, 2001). The causative articles containing natural rubber latex are ubiquitous: from medical devices and dental materials to household products (Table 1). As would be expected, people who are apt to repeatedly come into contact with latex products form a group at high risk for this allergy. About 5 to 15% of healthcare workers were reported to have IgE antibodies against antigens in natural rubber latex; they routinely use latex gloves in their daily tasks. More prominently, spina bifida patients who have undergone multiple operations since just after birth are sensitized at 30 to 60%. In addition to direct contact with latex products, inhalation of allergen-adsorbing donning powder that was applied to the surface of latex gloves is recognized as a major route for the sensitization of and symptom elicitation from latex-allergic people (Miguel *et al.*, 1996; Allmers *et al.*, 1998).

Symptoms of latex allergy are relatively mild in many cases and are restricted to the affected localities. However, they sometimes extend to generalized urticaria and anaphylaxis. Even lethal cases have been reported in America. The causatives of this allergy have already been proven to be plural proteins existing in natural rubber latex (Nel & Gujuluva, 1998; Breiteneder & Scheiner, 1998; Posch *et al.*, 1998). Nevertheless, their biochemical properties and their physiological roles in rubber trees remain to be elucidated.

One of the notable features of latex allergy is the patients' cross-reactivity to various sorts of fruits, vegetables, and pollen (Lavaud *et al.*, 1997; Raulf-Heimsoth *et al.*, 1997). It was pointed out early in the research on this allergy that some latex-sensitized patients cross-react to avocado, banana, and chestnut. This phenomenon later came to be called 'latex-fruit syndrome' (Brehler *et al.*, 1997). In the meantime, the kinds of fruits and vegetables that demonstrated their cross-reactivity to natural rubber latex increased rapidly (Kim & Hussain, 1999). Cross-reactivity of latex-sensitized people to some kinds of tree pollen and medical plants has also been documented (Pfützner *et al.*, 1998). Because patients experience immediate-type reactions to diverse sorts of plants, it might be more appropriate to recognize latex-fruit syndrome as one cross-section of a border-less plant allergy (Yagami, 2000). Allergenic proteins that are universally produced in plants regardless of the species must be responsible for such extensive cross-reactivity.

CROSS-REACTIVE PLANT ALLERGENS

Immediate-type allergies are a result of chemical reactions that follow the interaction of antigenic proteins with IgE antibodies attached to the receptor on the surface of a sensitized cell (Huby *et al.*, 2000). An antigenic molecule is recognized by the specific IgE antibodies. However, the antibodies do not recognize the whole of the antigenic protein. The variable

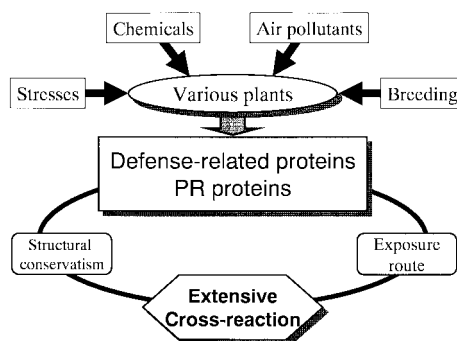


FIG. 1. Defense-related proteins form groups of cross-reactive plant allergens.

region of an antibody interacts with a confined structure generally existing on the surface of an antigenic molecule. Such a partial structure that determines the specificity of antigen-antibody recognition is called an 'epitope' or a 'determinant'. Suppose that two distinct antigenic proteins happen to contain an epitope in common. It is then possible that an antibody specific to this epitope cannot distinguish between the two antigenic molecules. This phenomenon underlies the cross-reactivity of IgE antibodies.

Antigenic proteins responsible for the extensive cross-reactivity of IgE antibodies are often referred to as 'pan-allergens' (Valenta *et al.*, 1992). It is assumed at the moment that conserved proteins with binding or enzymatic capacities can form a group of pan-allergens (Vuitton, 1997). The partial structures necessary for the binding or enzymatic activity tend to reside on the surface of the molecule. They are not significantly mutated in the course of evolution, and therefore taxonomically distant plants produce functionally the same proteins containing these highly conserved motifs. The advent of extensive cross-reactivity is rationally predicted when such a conserved partial structure provides an epitope to IgE antibodies (Sicherer, 2001). In theory, any proteins that are conserved in the course of evolution can provide cross-reactive epitopes to IgE antibodies.

Profilin is a representative plant-derived pan-allergen (Valenta *et al.*, 1992). It is an actin-binding protein, and every eukaryotic cell produces structurally related profilin. One of the causes of the oral allergy syndrome (OAS) that pollen-allergic patients often experience in response to various kinds of fruits and vegetables (Sloane & Sheffer, 2001) is the presence of homologous profilin in both the pollen and the offending foods (Deviller & Pauli, 1997; Fritsch *et al.*, 1997; Vieths, 1997). Because it is conserved in the course of evolution, profilin can offer common epitopes to IgE antibodies. Likewise, proteins with calcium-binding capacities include a conserved motif in common. These proteins were indeed proved to form a group of pan-allergens (Valenta *et al.*, 1998). What, then, is the pan-allergen responsible for latex-fruit syndrome? One possibility is profilin, which is present in both natural rubber latex and vegetable foods (Ganglberger *et al.*, 2001). Latex profilin was actually registered as a latex allergen (Hev b 8). However, it is a minor allergen and can explain only a limited part of the cross-reactivity of latex-allergic people (Vallier *et al.*, 1995). The author of this article has hypothesized that proteins that participate in the defense mechanisms of higher plants are the pan-allergens pertinent to latex allergy and the accompanying cross-reactivity (Figure 1) (Yagami, 1998, 2000; Yagami *et al.*, 1994, 1995a, b, 1996, 1998).

DEFENSE-RELATED PROTEINS IN HIGHER PLANTS

Most plants have defense mechanisms that correspond to the immune systems of animals. We can simply understand the defensive regime of a higher plant by roughly dividing it into two

TABLE 2. Recommended classification of pathogenesis-related proteins (PR proteins)

Family	Type member	Properties
PR-1	Tobacco PR-1a	Antifungal?, 14–17 kD
PR-2	Tobacco PR-2	Class I, II, and III endo- β -1,3-glucanases, 25–35 kD
PR-3	Tobacco P, Q	Class I, II, IV, V, VI, and VII endochitinases, about 30 kD
PR-4	Tobacco R	Antifungal, <i>win</i> -like proteins, endochitinase activity
PR-5	Tobacco S	Antifungal, thaumatin-like proteins, osmotins, zeamatin, permealins
PR-6	Tomato inhibitor I	Protease inhibitors, 6–13 kD
PR-7	Tomato P ₆₉	Endoproteases
PR-8	Cucumber chitinase	Class III endochitinases, chitinase/lysozyme
PR-9	Lignin-forming peroxidase	Peroxidases, peroxidase-like proteins
PR-10	Parsley PR1	Ribonucleases, Bet v 1-related proteins
PR-11	Tobacco class V chitinase	Endochitinase activity
PR-12	Radish Ps-AFP3	Plant defensins
PR-13	<i>Arabidopsis</i> THI2.1	Thionins
PR-14	Barley LTP4	Nonspecific lipid-transfer proteins (ns-LTPs)

categories: the static system and the dynamic system. The static defense system is interpreted as a peacetime precaution against infectious pathogens, insects, herbivores, and so forth. Reinforcement of the cell walls by depositing polyphenolic compounds is an obvious example of static defense. Storage proteins in seeds and fruits are also considered to take defensive roles in addition to their function of accumulating necessary nutrients. In actuality, several storage proteins were confirmed to have antifungal activity to potential phytopathogens (Shewry & Lucas, 1997; Yun *et al.*, 1997). The storage organs of a plant are usually rich in nutrients and therefore prone to be attacked by invaders, including fungi. Some kinds of lectins with antifungal activity are also believed to be a member of the defensive array of a plant (Chrispeels & Raikhel, 1991; Peumans & van Damme, 1995).

On the other hand, the dynamic defense system involves inducible resistance to various stresses from the outside world. At the affected localities of a plant, a series of 'defense-related proteins' (Bowles, 1990) are expressed following the rapid and intense reactions called hypersensitive response (Kombrink & Somssich, 1995; Fritig *et al.*, 1998; Maleck & Lawton, 1998). Some defense-related proteins force the cell walls to confine the infectious pathogens to the locality, and others catalyze the biosynthesis of the low-molecular-weight antibiotic called phytoalexin (Bowles, 1990). In particular, groups of defense-related proteins that are specifically induced in response to a pathogen's attack are collectively called 'pathogenesis-related proteins' (PR-proteins) (Bol *et al.*, 1990; Linthorst, 1991; Ohashi & Ohshima, 1992; Stintzi *et al.*, 1993; van Loon, 1997). Many plant-derived allergens are now known to have sequence homologies to certain families of PR proteins (Salcedo *et al.*, 1999; Hoffmann-Sommergruber, 2000; Breiteneder & Ebner, 2000; Yagami, 2000; Breiteneder & Ebner, 2001; Ebner *et al.*, 2001; Midoro-Horiuti *et al.*, 2001).

It is worth mentioning that PR-proteins found in various species of plants are, at present, classified into 14 families based on their sequence homologies, serological or immunological relationships, and enzymatic properties (Table 2) (van Loon *et al.*, 1994; van Loon & van Strien, 1999). This classification automatically means that the structure and function of each family of PR-proteins have been conserved in the course of evolution. Such conservatism is not limited to PR-proteins. Other groups of defense-related proteins also show sequence similarities, more or less regardless of the original plant species. From their structural conservatism, we can suspect the potential of defense-related proteins to form groups of plant pan-allergens (Figure 1) (Yagami, 1998, 2000). A recent example supporting this idea is isoflavone reductase, which is a defense-related protein that plays a role in the biosynthesis

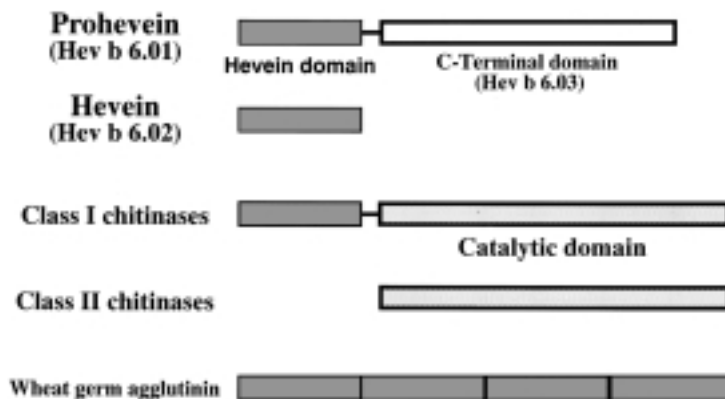


FIG. 2. Hevein-related domain is conserved in the course of evolution.

of phytoalexin (Bowles, 1990). This enzyme and its homologues were documented as a minor cross-reactive allergen for subjects sensitized by birch-pollen (Vieths *et al.*, 1998; Karamloo *et al.*, 1999).

The question arises as to whether rubber trees cultured in plantations are receiving stresses that are sufficient to bring about the induction of defense-related proteins. Latex is the milky cytoplasmic fluid of a rubber tree (*Hevea brasiliensis*) (d'Auzac *et al.*, 1982, 1995). It is harvested by cutting the bark of the tree. This operation (tapping) is repeated regularly. In addition, an ethylene precursor (ethephon), which stimulates the biosynthesis of the latex (Audley *et al.*, 1978), is sometimes administered to rubber trees for economic latex production. All of these treatments can bring about intensive production of defense-related proteins by the rubber trees (Broekaert *et al.*, 1990; d'Auzac *et al.*, 1993). Moreover, it is suspected that the propensity to express defense-related proteins intensively is unconsciously selected with the breeding of *Hevea brasiliensis* aiming at cost-effective latex production (Kush *et al.*, 1990; Chrestin *et al.*, 1997). From the circumstantial evidence mentioned above, we can speculate that the latex collected from such rubber trees contains a large amount of defense-related proteins produced as just described (Yagami, 1998, 2000). If these conserved proteins are present in the final products, they may become cross-reactive latex allergens (Figure 1).

DEFENSE-RELATED PROTEINS AS LATEX ALLERGENS

Several of the latex allergens that have been officially registered to date, namely, β -1,3-glucanase (Hev b 2), microhelix component (Hev b 4), hevein-related allergens (Hev b 6), patatin homologues (Hev b 7), latex endochitinase (Hev b 11), and lipid transfer protein (Hev b 12), actually have something to do with the defense mechanisms of a rubber tree (Sunderasan *et al.*, 1995; Beezhold *et al.*, 1997; Kostyal *et al.*, 1998; Sowka *et al.*, 1998b; O'Riordain *et al.*, 2002). The importance of hevein (Hev b 6.02) as a cross-reactive latex allergen must be especially emphasized (Alenius *et al.*, 1996; Chen *et al.*, 1997). Hevein is a small antifungal protein (4.7 kD) in natural rubber latex (van Parijs *et al.*, 1991). It is biosynthesized as a precursor (prohevein) and post-translationally cleaved into the small N-terminal region (hevein) and the C-terminal domain (Hev b 6.03) (Lee *et al.*, 1991; Soedjanaatmadja *et al.*, 1995). Interestingly, every class I endochitinase that is classified into the PR-3 family (Table 2) includes a hevein-like domain in its N-terminus (Figure 2) (Raikhel *et al.*, 1993; Beintema, 1994; Graham & Sticklen, 1994). Patients sensitized to hevein (Hev b 6.02) or the N-terminal region of prohevein are therefore predicted to show cross-reactivity

to class I endochitinases in various fruits and vegetables. Class I endochitinases in avocado, banana, and chestnut were indeed confirmed as cross-reactive allergens for hevein-sensitized patients (Chen *et al.*, 1998; Diaz-Perales *et al.*, 1998; Mikkola *et al.*, 1998; Sowka *et al.*, 1998a; Blanco *et al.*, 1999; Diaz-Perales *et al.*, 1999; Posch *et al.*, 1999; Sánchez-Monge *et al.*, 1999, 2000). The hevein-like domains of class I endochitinases are supposed to have a binding capacity to chitin, which is a major component of the external walls of pathogenic fungi (Raikhel *et al.*, 1993; Beintema, 1994). These conserved domains must supply common epitopes to the IgE antibodies and bring about the extensive cross-reactivity among the taxonomically unrelated plants. On the other hand, the C-terminal domain of prohevein (Hev b 6.03) is homologous to proteins belonging to the PR-4 family (Figure 2) (Friedrich *et al.*, 1991). Patients sensitized by Hev b 6.03 may accordingly cross-react to the members of the PR-4 family in various plants (Beezhold *et al.*, 1997; Hänninen *et al.*, 2000). The cross-reactivity of the other defense-related latex allergens is also expected to be established (Yagami, 2000).

INDUCTION OF CROSS-REACTIVE PLANT ALLERGENS

Some cross-reactive plant allergens like profilin and calcium-binding proteins are constitutively expressed in a cell, whereas many defense-related proteins, especially PR proteins, are induced in response to environmental stimuli (Bowles, 1990; Stintzi *et al.*, 1993; van Loon, 1997; Pühringer *et al.*, 2000). The stresses that can trigger defense responses of a plant are variable: infection by pathogens, application of chemicals, heavy metals, air pollutants like ozone, ultraviolet rays, temperature stresses, drought, salt stresses, etc. Additionally, some PR-like proteins are transiently expressed at the specific site of a plant in a developmental stage, and others are accumulated in the storage organs as they become mature (van Loon *et al.*, 1994). From these facts, we can project that the amount of cross-reactive allergens in plant tissue is changeable depending on the surroundings and the tissue's maturation (Yagami, 2000). A cross-reactive endochitinase in avocado (Pers a 1) was actually induced by infectious pathogen and ethylene treatments (Sánchez-Monge *et al.*, 2000). Similarly, a cross-reactive allergen in a turnip was increased up to 10 times by treating the plant with salicylic acid or ethephon (Hänninen *et al.*, 1999). The sequence of the induced turnip allergen was similar to those of prohevein (Hev b 6.01) and proteins belonging to the PR-4 family. The authors of this study concluded that activating the defense mechanisms of plants may considerably increase their allergen content (Hänninen *et al.*, 1999). There is also a potential for the induction of cross-reactive plant allergens by environmental pollutants (Masuch *et al.*, 1997; Midoro-Horiuti *et al.*, 2000, 2001). It is intriguing to speculate on the contributions of air pollution to the recent prevalence of pollinosis in industrialized countries (Figure 1).

Once people understood the biological functions of defense-related proteins, it became easy to conjecture that the plant varieties that are inclined to produce such proteins intensively are resistant to stresses and are therefore agriculturally valuable (Yun *et al.*, 1997). One aspect of conventional plant breeding is actually aiming to develop new varieties that are compatible with stressful surroundings. The question arises, however, as to whether an allergen-inducing propensity is unconsciously intensified along with the development of new varieties (Yagami, 2000). In actuality, there are some reports that describe the cultivar dependency of the amount of allergens in plant-derived foods (Hsieh *et al.*, 1995; Jensen-Jarolim *et al.*, 1998; Son *et al.*, 1999; Kwaasi *et al.*, 2000). Rubber trees cultured in plantations are also varieties that have been improved for the purpose of economic latex production (Kush *et al.*, 1990; Chrestin *et al.*, 1997).

In addition to conventional plant breeding, biotechnologies are also being used to develop agriculturally useful varieties (Lamb *et al.*, 1992; Shah, 1997). By constitutively expressing defense-related proteins in quantity, the genetically modified plants are expected to become tolerant to a certain stress (Shewry & Lucas, 1997; Yun *et al.*, 1997; García-Olmedo *et al.*,

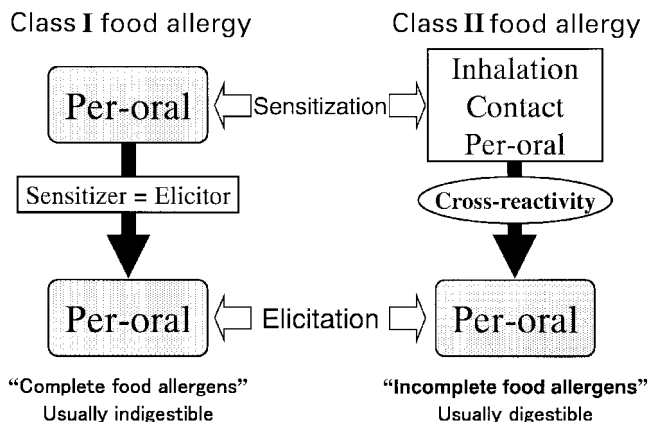


FIG. 3. Comparison of class I food allergy (left) and class II food allergy (right). Class I food allergy is caused by complete food allergens that function as a per-oral sensitizer as well as a symptom elicitor. Complete food allergens are usually resistant to heat and digestive enzymes. Class II food allergy is caused by incomplete food allergens, which cannot easily establish per-oral sensitization because of their sensitivity to heat or digestion. These incomplete allergens provoke allergic reactions in already-sensitized patients based on their cross-reactivity to the corresponding sensitizers.

1998). However, the modified plant could also be more allergenic than the original one (Yagami, 2000). There is the surprising example of a genetically modified tomato that is constitutively expressing prohevein (Lee & Raikhel, 1995), which is a major allergen in natural rubber latex (Alenius *et al.*, 1995). Although the transformed tomato exhibited significant resistance to some kinds of phytopathogens, as expected, we are concerned that latex-allergic patients may hypersensitively react to this tomato. Likewise, antifungal endochitinases are going to be intentionally expressed in crops to enhance their resistance to infections fungi (Graham & Sticklen, 1994; Yun *et al.*, 1997). Again, we should remember that class I endochitinases in vegetable foods as well as hevein have already been registered as cross-reactive allergens (Sowka *et al.*, 1998a). Synergistic effects of endochitinases and β -1,3-glucanases against fungal infection have also been reported (Zhu *et al.*, 1994; Jongedijk *et al.*, 1995). Although these novel plants must be useful from an agricultural perspective, their potential to provoke allergic reactions should be carefully evaluated. As will be discussed in the next section, we cannot predict the allergenicity of a protein solely from its stability in an artificial digestive fluid (Yagami *et al.*, 2000). Together with other properties of known allergens, namely, sequence homology (Gendel, 1998), structural conservatism (Vuitton, 1997), and reactivity to the IgE antibodies of appropriate patients (Wal & Pascal, 1998), the allergenicity of an intentionally expressed protein must be assessed individually and cautiously (Wal, 1999; Taylor, 2002).

FROM SENSITIZATION TO SYMPTOM ELICITATION

Latex-fruit syndrome is comparable with food allergy that is concomitant with pollinosis, which some have now proposed to call 'pollen-food allergy syndrome' (Kelso, 2000). Oropharyngeal symptoms (OAS) are the dominant manifestation of food allergy observed in either syndrome, although some latex-sensitized patients experience generalized reactions (Poley & Slater, 2000; Sloane & Sheffer, 2001). A notable feature common to latex-fruit syndrome and pollen-food allergy syndrome is the relevance of many kinds of fruits and vegetables that are not notorious for their allergenicity (Sicherer, 2001). It is very difficult to conclude that the patients were sensitized concurrently by antigens in each

offending food (Aalberse, 1992). The author's group and others showed that most IgE-binding antigens extracted from fruits, vegetables, and natural rubber latex were proteins that were easily digested in an artificial gastric fluid (Vieths *et al.*, 1999; Wigotzki *et al.*, 2000; Yagami *et al.*, 2000). Per-oral sensitization is rarely established by ingesting such a digestible protein (Astwood & Fuchs, 1996; Astwood *et al.*, 1996). Accordingly, food allergy concomitant with latex allergy or pollinosis is attributable to the cross-reactivity between the sensitizers and symptom elicitors in the causative foods (Figure 3) (Yagami, 2000). That is to say, people are first sensitized through direct contact with latex products or inhalation of allergen-containing particles such as pollen or donning powder. Allergic symptoms are then elicited not only by the second exposure to the sensitizer but also by ingesting any food that contains the antigens that are cross-reactive to the corresponding sensitizers (Valenta & Kraft, 1996; Pastorello *et al.*, 1997; Kazemi-Shirazi *et al.*, 2000). This type of food allergy based on the cross-reactivity between sensitizers and symptom elicitors is called 'class II food allergy', and the causative food antigens are referred to as 'incomplete food allergens' or 'cross-reactive elicitors' (Aalberse, 1997, 2000). By contrast, symptom elicitors correspond to the per-oral sensitizers in traditional food allergy (class I food allergy). The food proteins responsible for class I food allergy (complete food allergens) are usually stable to heat and digestive enzymes (Astwood & Fuchs, 1996; Astwood *et al.*, 1996; Becker, 1997), because they are supposed to be absorbed from the intestine and recognized by the abdominal immune system (Figure 3).

PERSPECTIVES

It has long been believed that immediate-type reactions are independently caused by allergens specific to exposure routes like ingestion, inhalation, and direct contact. Therefore, only the antigens in pollen were blamed when the pollen provoked allergic reactions, and only the antigens in a food were blamed when the food provoked allergic reactions. The presupposition for such a simple relation between cause and effect is that the symptom-eliciting antigens and the sensitizing antigens are identical. In latex-fruit syndrome and pollen-food allergy syndrome, however, food allergy is caused by cross-reactive elicitors that rarely sensitize people per-orally (Yagami, 2000). The responsible sensitizers are proteins that are distinct from the symptom elicitors, but which contain common epitopes to IgE antibodies (Figure 3). The recent prevalence of allergies to fruits and vegetables in the adult population may also be interpreted as a secondary phenomenon following the increasing tendency toward pollinosis (Pastorello *et al.*, 1998; Wal, 1999). In future research on allergens, therefore, it will be important to differentiate the establishment of sensitization from the symptom elicitation. Researchers should evaluate whether an IgE-reactive antigen is relevant only to the sensitization process, only to the symptom-elicitation process, to both, or to neither.

Any decisive features that may be shared by allergenic proteins cannot be extracted from the updated official list of proteinous allergens (Aalberse, 2000). This fact implies that many proteins have the potential to become allergens if certain conditions are arranged by chance, for example, exposure routes, the amount of the protein, frequency of exposure, and the cross-reactivity of the protein (Yagami, 2000). On the other hand, proteins that are recognized by the IgE antibodies from individual patients who are sensitive to the same article are not always uniform. This experimental fact often disturbs the consistent interpretation of the cause of the allergy to the article in question. However, the pertinence of each IgE-reactive protein to the allergy must be clarified by carefully inspecting how the individual patient was sensitized and under what situations the symptoms were elicited. In order to pursue such an investigation, cooperation between basic researchers dealing with substances and clinical allergologists is indispensable. As scientific knowledge about allergens is accumulated, it will be best applied to clinical practice with respect to prevention of sensitization and symptom elicitation, more accurate diagnosis, and improvement of patients' lifestyles.

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