

Allergies to Cross-Reactive Plant Proteins

Latex-Fruit Syndrome Is Comparable with Pollen-Food Allergy Syndrome

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Key Words

Latex-fruit syndrome · Oral allergy syndrome · Pollen-food allergy syndrome · Protein, defense-related · Protein, pathogenesis-related · Cross-reactive carbohydrate determinant · Sensitization · Elicitation · Food allergen, complete · Food allergen, incomplete

Abstract

Both latex-fruit syndrome and oral allergy syndrome concomitant with pollinosis (pollen-food allergy syndrome) are considered to be caused by cross-reactivity between sensitizers and symptom elicitors. The cross-reactive food allergens relevant to these syndromes are mostly sensitive to heat and digestive enzymes. Such a vulnerable antigen cannot sensitize people perorally but provokes allergic reactions in already sensitized patients based on its cross-reactivity to the corresponding sensitizer. These types of food allergens are often called incomplete food allergens or nonsensitizing elicitors. Their features contrast with those of complete food allergens that have the capacity for peroral sensitization as well as symptom elicitation. Although highly antigenic and cross-reactive, carbohydrate epitopes do not generally elicit allergic reactions and often disturb in vitro IgE tests. Recent research has revealed that some of the cross-reactive allergens responsible for the two syn-

dromes are proteins related to the defense responses of higher plants. Plant defense-related proteins are relatively conserved in the course of evolution and can supply cross-reactive epitopes. It is important to note that various stresses can stimulate the expression of these proteins, which implies that allergens increase in plants under stressful conditions like severe growing situations and exposure to some kinds of chemicals. Because defense-related proteins usually provide a plant with resistance to stresses, varieties that are apt to intensively induce such proteins are agriculturally valuable. Less toxic substances that cause crops to express defensive proteins are being investigated as a new type of agrochemical. Moreover, some defense-related proteins are going to be constantly produced in genetically modified plants. Even though these proteins can be useful agriculturally, their allergenicity should be evaluated carefully.

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Introduction

It is reported that more than half of latex-sensitized people had specific IgE antibodies to proteins from some kinds of fruits and vegetables [1]. About one third of these patients experience immediate-type reactions when they ingest vegetable foods such as avocado, banana, chestnut,

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1018–2438/02/1284–0271\$18.50/0

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kiwi and potato [2, 3]. This cross-reactivity is often called 'latex-fruit syndrome' [1]. It has become evident that the latex-fruit syndrome is based on the cross-reactivity between latex allergens and antigens in the causative foods [4–6].

On the other hand, it is well known that some pollen-allergic patients also become allergic to certain kinds of fresh fruits and vegetables as time passes. The offensive vegetable foods are usually not notorious for their allergenicity. Because the specific symptoms are usually restricted to the oral cavity, this type of food allergy has been collectively called 'oral allergy syndrome' (OAS) [7, 8]. It has also been proposed that this particular food allergy should be called 'pollen-food allergy syndrome' [9], because OAS is a general term for allergic symptoms limited to the oral cavity, and some patients experience OAS without pollinosis. Recent research has made it clearer that food allergies concomitant with pollinosis are based on the cross-reactivity between pollen allergens and antigens in vegetable foods [10–13].

Latex-fruit syndrome is comparable to pollen-food allergy syndrome in several respects, including the processes from sensitization to symptom elicitation and the relevant cross-reactive antigens. However, the severity of the allergic reactions in these syndromes is different to some extent. In this article, the similarity of the two syndromes will be described from the viewpoint of the cross-reactive antigens and their mode of action in symptom manifestation.

Cross-Reactive Antigens

Immediate-type reactions are considered to be triggered by antigen-mediated cross-linking of IgE antibodies attached to the specific receptor on the surface of a sensitized cell [14]. Without this cross-bridge formation between the IgE antibodies, allergic symptoms are not provoked, even if an antigen is recognized by an IgE antibody on the membrane. The variable region of an IgE antibody does not interact with the whole of an antigenic protein. The variable region recognizes the partial structure (epitope) of an antigen that generally exists on the exterior. Therefore, an IgE antibody may not be able to distinguish structurally different antigens if they share the same epitope. This phenomenon underlies the cross-reactivity of IgE antibodies.

As candidates of antigens containing a common epitope, we can imagine genetically conserved enzymes and proteins with interactive or binding properties [15]. The

partial structures important for their enzymatic or binding activities tend to exist on the outside of a molecule. Moreover, these structures would not be mutated and therefore conserved in the course of evolution, regardless of the species. Extensive cross-reactivity is expected when such a conserved structure supplies epitopes for IgE antibodies [16].

At this stage, it is essential to differentiate peptidic epitopes from carbohydrate epitopes on glycoproteins. A protein or glycoprotein with peptidic epitopes most likely acts as a multivalent antigen and forms a cross-bridge between the specific IgE antibodies attached to the surface of a sensitized cell [14]. Allergic reactions are actually triggered by this event. In contrast, carbohydrate epitopes, except for some special cases [17, 18], act as monovalent antigens. Monovalent antigens cannot form the cross-bridge that is necessary for the occurrence of ensuing allergic symptoms. In other words, carbohydrate epitopes do not usually result in actual symptoms, even though they are specifically recognized by IgE antibodies [19, 20]. In particular, we must pay attention to the cases where carbohydrate structures called complex-type glycans provide epitopes for IgE antibodies [21, 22]. These epitopes (carbohydrate cross-reactive determinants) are often seen on glycoproteins from plant and invertebrate tissues and probably bring about false-positive results on in vitro IgE tests that check cross-reactivity [23, 24]. The functional difference between the peptidic epitopes and carbohydrate epitopes described above sometimes confuses the interpretation of in vitro IgE tests that are applied daily in the diagnosis of immediate-type allergies [19–24].

In in vitro IgE tests of a patient's sera, the amount of IgE antibodies that specifically recognized antigens, which are fixed on a plate or disk, is determined. In particular, it is not the specific IgE antibodies attached to the receptor of a sensitized cell that are being measured, but rather the free IgE antibodies in the sera. Antigen recognition by the free IgE antibodies in a patient's serum does not directly reflect the following allergic reactions, even if the recognized antigen is multivalent. Moreover, we cannot distinguish the specific IgE antibodies to monovalent antigens from those to the multivalent antigens that are actually responsible for allergic reactions. If glycoproteins occupy part of the fixed antigens, IgE antibodies specific to the monovalent carbohydrate epitopes are detected simultaneously and bring about false-positive results. To make matters worse, IgE antibodies specific to carbohydrate cross-reactive determinants will result in a false-positive outcome with respect to cross-reactivity to various

glycoproteins from plants and invertebrates [19, 23, 24]. These IgE tests might also show false-negative responses if the fixed antigens are unstable and easily lose their antigenicity, as described in the following section. In this way, in vitro IgE tests involve the inherent drawbacks of false-positive or false-negative results, even though they are very convenient.

We can investigate the relevance of an antigen to particular allergic reactions more directly using the skin prick test or the histamine release test. These diagnostic tests are not distorted by the specific IgE antibodies to monovalent antigens. Symptomatic cross-reactivity can also be evaluated by these methods without significant disturbances. However, the standardized antigen solution necessary for these tests is unavailable at present for many kinds of allergic sources. Moreover, allergens in fresh fruits and vegetables are usually unstable and easily lose their antigenicity during storage [12, 25, 26]. False-negative results may be brought about by such expired antigens. Thus, each diagnostic test involves the inherent strong points and weak points. From the characteristics of each method, we can conclude that it is probably reasonable to reconfirm the results of in vitro IgE tests by the skin prick test or the histamine release test if there are uncertainties in the former test.

In vitro IgE tests are often applied to the diagnoses of vegetable food allergies concomitant with latex allergy or pollinosis. We must always take into consideration the possible false-positive or false-negative results in such a test, because antigens extracted from plant tissues ordinarily include glycoproteins and are inclined to readily lose their antigenicity [12, 26]. In addition, the antigen solution used in the skin prick test and the histamine release test should be prepared just before diagnosis to ensure the relevance of the suspected vegetable foods to the allergic reactions.

Pan-Allergens

Allergenic proteins responsible for extensive cross-reactivity are often called 'pan-allergens'. Profilin is a representative pan-allergen [27, 28]. It has an actin-binding property, and every eukaryotic cell contains structurally related profilin. Because of its structural conservatism, profilin can provide common epitopes that are at the root of the extensive cross-reactivity. One of the reasons for the marked cross-reactivity of pollen-allergic patients to various vegetable foods is the profilin present both in the pollen and in the offensive foods [12, 28]. Profilin in natu-

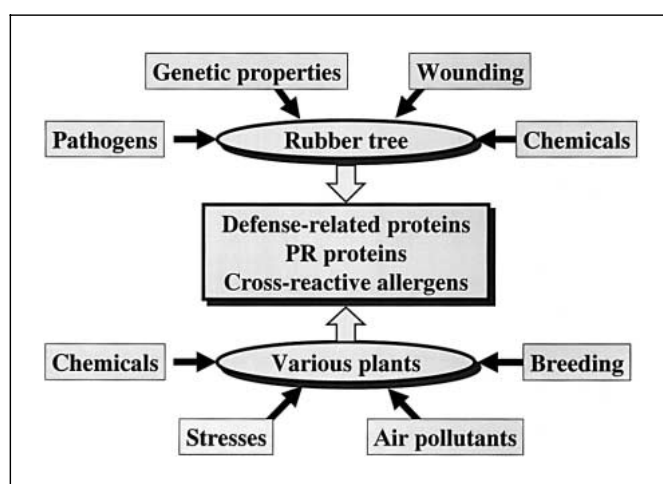


Fig. 1. Defense-related proteins form families of cross-reactive plant allergens.

ral rubber latex, which is a cause of latex-fruit syndrome, was also officially registered as latex allergen Hev b 8 [29]. Similarly, calcium-binding proteins from plants contain a conserved structure. They were actually assigned to a family of cross-reactive plant allergens [30].

Recently, it has been confirmed that a series of proteins related to the defense responses of higher plants organize new families of pan-allergens (fig. 1) [31–33]. The defense mechanisms of higher plants are relatively conserved in the course of evolution, and structurally related proteins are induced or accumulated in taxonomically distant plants [34–37]. Some of the defense-related proteins strengthen the cell walls to protect the plant, and others are necessary for the biosynthesis of a low-molecular-weight antibiotic called phytoalexin [34]. For example, isoflavone reductase, which was reported as a minor cross-reactive allergen for birch-pollen-allergic patients [38, 39], is a defense-related protein that plays a part in the biosynthesis of phytoalexin [34]. Some kinds of lectin and storage albumin have antifungal activity and are also considered members of the defensive array of a plant [34, 40, 41]. Moreover, it is becoming more and more evident that pathogenesis-related (PR) proteins form novel families of cross-reactive plant allergens [32, 33, 42–45]. They are a group of defense-related proteins that are specifically expressed following an attack of phytopathogens [46, 47].

PR proteins are now classified into fourteen groups based on their sequence homology, serological or immunological relationships, and enzymatic activity [48, 49]. Class I endochitinases, which are a major cause of cross-

reactivity between latex and vegetable foods [6], belong to the PR-3 family. They commonly contain a hevein-related region in their N-termini [50, 51]. Hevein is an important latex allergen (Hev b 6.02) and provides several cross-reactive epitopes [52, 53]. On the other hand, proteins in the PR-4 family are homologous to the C-terminal region (Hev b 6.03) of prohevein (Hev b 6.01) [54, 55]. Therefore, proteins classified into the PR-4 families as well as into the PR-3 family would participate in latex-fruit syndrome [6, 56]. Nonspecific lipid transfer proteins (LTPs) occupy the PR-14 families [49]. An LTP from natural rubber latex was officially registered as latex allergen Hev b 12. Some vegetable food allergies without concurrent pollinosis are due to the cross-reactivity of LTPs in causative foods [57, 58].

Proteins belonging to the PR-10 family are a key to understanding OAS concomitant with pollinosis (pollen-food allergy syndrome). A major cross-reactive allergen (Bet v 1) in birch-pollen is induced by stresses and is classified as a member of this family [59–63]. Pollen from other trees such as elder, oak and chestnut also contains allergens with sequences that are homologous to those of PR-10 proteins [12, 33]. Furthermore, vegetable foods that often irritate birch-pollen-allergic patients produce and accumulate defensive proteins that may also be members of this family [64, 65]. By considering the homology among the antigens in pollen and vegetable foods, we can easily understand why pollen-allergic people, especially Bet v 1-sensitized patients, often cross-react to various taxonomically unrelated vegetable foods and pollen [66, 67].

Induction of Novel Plant Allergens

Important cross-reactive allergens that are responsible for latex-fruit syndrome or pollen-food allergy syndrome are related to the defense responses of higher plants [33]. Some of the defense-related proteins are accumulated in seeds or fruit, and others are newly induced under stressful conditions [34]. Proteins in a storage organ usually change quantitatively and qualitatively according to the maturity of the organ. On the other hand, the defense responses are triggered by various factors such as chemicals, heavy metals, pathogens, air pollutants, ultraviolet rays and severe growing conditions. It is reasonable to speculate, then, that antigens in a plant tissue are changeable quantitatively and qualitatively (fig. 1) [68–74]. If this is the case, environmental pollution could be partly blamed for the increase in allergic disorders to plants

because some kinds of chemicals and air pollutants stimulate the defense responses. In fact, one report suggests the induction of a cross-reactive allergen (Bet v 1) in birch pollen by ozone and nitrogen dioxide [75, 76]. Another study revealed that the amounts of IgE-reactive antigens were increased up to 10 times by treating *Brassica rapa* with salicylic acid or ethephon, which are representative chemicals that stimulate the defense responses [77]. This finding is especially notable because such defense-response activating chemicals are being intensively investigated as a new type of agrochemical with less toxicity to humans. The application of such substances might augment the amount of allergen in a plant. Extensive studies are urgently required to establish whether various chemicals and environmental pollutants have something to do with the recent prevalence of immediate-type allergies to vegetable foods and pollen.

Given the functions of defense-related proteins, it is clear that a plant producing a large amount of such proteins would be resistant to stresses and therefore agriculturally advantageous [41, 47]. One aim of conventional plant breeding is actually to develop a new variety highly resistant to environmental stresses. However, a variety that produces a large amount of allergens might inadvertently be selected through such improvements. The variety dependencies of IgE-reactive proteins have already been reported for apple, paprika, rice and other food crops [65, 78–80]. Unfortunately, no exhaustive research has yet been done on the possible increase in allergens accompanying conventional plant breeding.

Additionally, many researchers are trying to develop a stress-resistant variety by constantly expressing some kind of defense-related proteins using biotechnology [37, 81, 82]. Again, one can readily imagine the increased allergenicity of the genetically modified plant [33]. These are remarkable examples where potentially allergenic proteins were intentionally expressed in a plant [41, 47, 83, 84]. It is important that newly developed plants should be carefully evaluated for their safety. The allergenicity of a deliberately expressed protein must be evaluated from various points of view [85, 86]. As will be discussed in the next section, people cannot fully determine the allergenicity of a protein based solely on its stability to digestive enzymes [87]. An international consensus for the evaluation of the allergenicity of genetically modified plants must be established [88].

Complete Food Allergens and Incomplete Food Allergens

It has been generally believed that food allergens are proteins that are resistant to heat and digestive enzymes. In actuality, significant stability in an artificial gastric fluid was reported for the major allergens in milk, eggs, soybeans, peanuts and others [89–91]. However, many of the allergens responsible for latex-fruit syndrome or pollen-food allergy syndrome are sensitive to heat and digestive enzymes [12, 92, 93]. The author's group showed that most IgE-reactive antigens extracted from natural rubber latex and vegetable foods were digested in an artificial gastric fluid within a few minutes [87]. As a matter of fact, many patients suffering from pollen-food allergy syndrome can eat cooked vegetable foods without any allergic reaction [94]. It also has to be mentioned that the number of patients who are allergic only to fresh fruits or vegetables is significantly smaller than the number of people suffering from latex-fruit syndrome and pollen-food allergy syndrome [16]. From these findings, we can rationally speculate that the food allergens responsible for these syndromes have considerably different properties from the conventional food allergens [33].

It is traditionally postulated that only special food proteins unaffected by cooking and digestive enzymes are absorbed from the intestine and recognized by the immune system to be a peroral sensitizer. After the establishment of peroral sensitization, generalized symptoms are expected to be provoked whenever the patient ingests the same protein. In this sequential process of food allergy manifestation (type I food allergy), the same antigen plays a crucial role in both the sensitization and the symptom elicitation (fig. 2). Such a food allergen that has the potential to cause peroral sensitization as well as peroral elicitation is often called a 'complete food allergen' [95, 96].

In contrast to the conventional food allergies, sensitization is established through direct contact with latex products or through the inhalation of allergen-containing particles in the latex-fruit syndrome and the pollen-food allergy syndrome [11, 13, 57, 97]. Upon the completion of sensitization, allergic symptoms are expected to be provoked by not only the second exposure to the same allergens but also by ingestion of vegetable foods containing the cross-reactive antigens (type II food allergy). In this sequential process, different antigens (a sensitizer and an elicitor) play a crucial role in the sensitization and the symptom elicitation, respectively (fig. 2). The cross-reactive antigens in foods are responsible only for the symptom elicitation, and they have nothing to do with the sen-

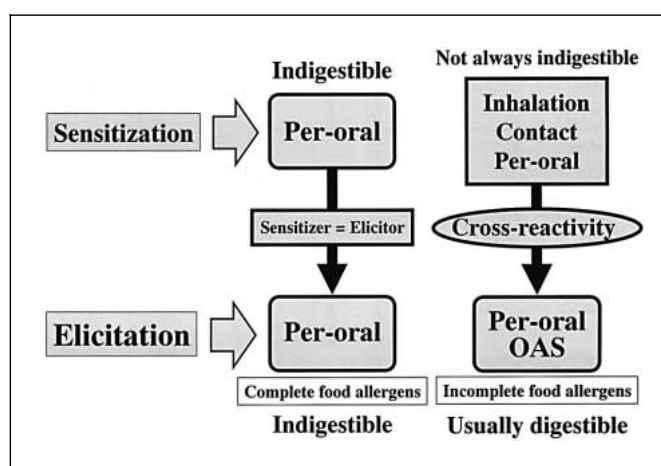


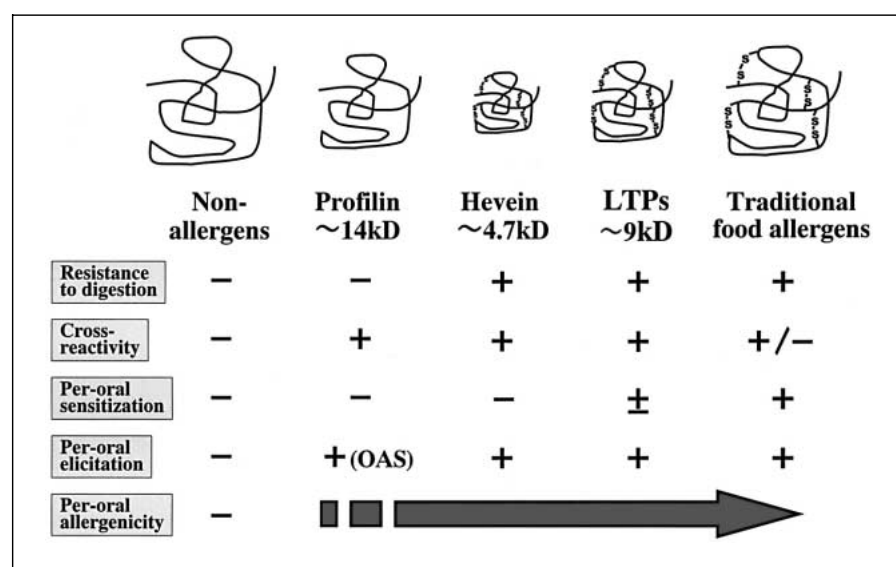
Fig. 2. Traditional food allergies (left) and food allergies based on the cross-reactivity between sensitizers and symptom elicitors (right). Digestible food proteins rarely establish peroral sensitization. However, they can cause allergic symptoms, mainly OAS, in already sensitized patients based on their cross-reactivity to the corresponding sensitizers.

sitization. Accordingly, these cross-reactive allergens do not usually have the properties required to establish peroral sensitization. Such a food allergen having the potential only to cause peroral elicitation is often called an 'incomplete food allergen' or a 'nonsensitizing elicitor' [95, 96]. Incomplete food allergens provoke allergic reactions in already-sensitized patients based on their cross-reactivity to the corresponding sensitizers (fig. 2).

By considering the mode of action of incomplete food allergens, we can easily explain why allergic reactions around the oral cavity (OAS) are the dominant manifestation of latex-fruit syndrome and pollen-food allergy syndrome [33]. Incomplete food allergens are mostly digestible [87]. Therefore, they rapidly lose their antigenicity after reaching the digestive organs, although they retain it in the oral cavity (fig. 3). The instability of incomplete food allergens to heat also accounts for the declined allergenicity of cooked vegetables [26, 74, 94].

The most noticeable difference between latex-fruit syndrome and pollen-food allergy syndrome is the severity of the symptoms caused by offensive foods. The majority of food allergies concomitant with pollinosis are limited to the oral cavity (OAS), but latex-sensitized patients sometimes experience generalized symptoms in addition to OAS [2, 3]. The author's group showed that hevein (4.7 kD) was exceptionally stable in an artificial gastric fluid [87]. Hevein includes common epitopes relevant to

Fig. 3. Diverse allergenicity of food antigens. For efficient peroral sensitization, stability to digestive enzymes and a molecular weight larger than LTPs would be required. Profilin and the hevein-related regions of class I endochitinases are most likely incomplete food allergens (nonsensitizing elicitors). They are expected to cause symptoms from OAS to anaphylaxis in already sensitized patients, depending on their stability to heat and digestive enzymes. Drawings show the representative features of each group.



the cross-reactivity between latex and vegetable foods such as avocado, banana and chestnut [6, 53]. However, few people claim to have allergic reactions only to these vegetable foods without a concomitant latex allergy [98]. Taken together, these findings suggest that the hevein-related regions of cross-reactive food allergens are resistant to digestion and are absorbed from the intestine, but they are too small to sensitize people. Nevertheless, they can cause generalized symptoms for a patient who has already been sensitized by hevein or a protein containing a hevein-related region through inhalation or direct contact (fig. 3) [33].

Here it must be emphasized that the differentiation between complete food allergens and incomplete food allergens mentioned above is relative and presupposes the digestion of healthy adults. For patients with gastrointestinal disease and for young children, even food proteins that are easily digested in the normal adult gut may act as peroral sensitizers and elicitors of generalized symptoms [95]. In addition, manifestations of allergic reactions may be modified by the physiological stresses of a patient and concurrent medication. It is well-known that some people experience food-dependent exercise-induced anaphylaxis [99] and others suffer from food allergies following the administration of certain medicine [100, 101]. The actual allergenicity of an antigen, therefore, depends not only on the nature of the protein but also on the status of the individual.

Perspectives

Researchers have accepted the general concept that there are allergens specific to each exposure route and that they cause allergic reactions independently. This concept presupposes the identity of the antigens responsible for sensitization and for symptom elicitation. In latex-fruit syndrome and pollen-food allergy syndrome, however, the elicitors are molecules that are distinct from the sensitizers and provoke allergic symptoms based on their cross-reactivity to the corresponding sensitizers. Because the cross-reactivity is the sole prerequisite for becoming a symptom elicitor, we must take into consideration cases where the exposure routes to a sensitizer and an elicitor are different (fig. 2) [33]. The advent of the idea that allergic reactions caused by the cross-reactivity between a sensitizer and an elicitor might bring about discussions of which antigens should be called allergens: sensitizers, symptom elicitors, or both.

Many proteinaceous allergens have been identified from various sources in recent years. However, no decisive common features can be drawn from the official list of proteinaceous allergens [96]. This implies that most proteins can become allergens if specific conditions are met, including exposure routes, amounts of antigens, frequency of exposure or cross-reactivity. Conventional food allergens were, indeed, confined to proteins that are stable to heat and digestive enzymes (complete food allergens) [89, 90]. We can now interpret this historical fact as meaning that ingestion was the only important exposure

route to the sensitizers. If a person is sensitized through other exposure routes, for example, through the inhalation of pollen and allergen-adsorbing powder, many cross-reactive food proteins become candidates for novel food allergens (incomplete food allergens) [33]. It is possible that the recent prevalence of vegetable food allergies in the adult population is attendant on the increasing tendency toward pollinosis [86].

Some defense-related proteins in plants are responsible for latex-fruit syndrome and pollen-food allergy syndrome [33]. They can be induced by conventional or biotechnological plant breeding as well as by chemicals and environmental pollutants (fig. 1). On the other hand, we are exposed to proteinaceous sensitizers through various

routes including ingestion, inhalation and direct contact. Allergic disorders have steadily been increasing for a long time, but the real reason for this increment is still obscure. The changes in the susceptibility of human beings have been well documented; however, the quantitative increase and the changes in allergenic proteins as well as the expansion of exposure routes to sensitizers may be other factors that have been overlooked.

Acknowledgment

The author thanks Dr. Hirohisa Saito (National Research Institute for Child Health and Development, Japan) for his helpful comments and encouragement.

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