

Crossreactions Involving Natural Rubber Latex

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Introduction

Latex allergy has become an international health problem that is increasing both in frequency and in the severity of its clinical manifestations. Four high risk groups have been identified: atopic individuals, health care workers, certain patients with a history of multiple surgical operations, especially children with spina bifida, and people working in factories where latex goods are manufactured.

Natural rubber latex (NRL) from the rubber tree *Hevea brasiliensis* contains more than 200 polypeptides, many of which have been identified as allergens; that is, they are capable of inducing and binding to IgE antibodies. Latex is a complex mixture in which its allergenicity depends on botanical, technical, immunological, and epidemiological variables (1–4).

Despite extensive investigation, no unique major latex allergen has yet been identified, and none is available for in vivo and in vitro diagnosis. Among the most likely candidates for major allergens are hevein and its precursor, prohevein, and rubber elongation factor; hevamine and β -glucosidase are additional candidates.

It is now well-known that many patients who are allergic to NRL are also allergic to certain plant-derived foods—especially fruits. Clinical observations have implicated a large and growing number of plant-derived foods from phylogenetically different sources; banana, avocado, kiwi fruit, and chestnut are at the top of the list. This is a list that appears to be growing every month. It is now believed that these concurrent allergic sensitivities are the result of crossreactions, at least to some degree, and immunologic studies have identified the allergens respon-

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sible for some of them. This leads us to add a fifth group of individuals to those at risk for latex allergy—namely, patients with “a history of allergy to fruits” (5).

Clinical Aspects of Latex Allergy

The Role of Atopy

Atopy is perhaps the most important predisposing factor for latex sensitization. Turjanmaa reported that 67% of the latex-sensitive hospital personnel that she studied were atopic (6). Among randomized atopic women, 15% are sensitized to NRL (7). In a prospective study of hospital personnel performed in France (8), it was found that 14 out of 24 subjects (58%) with a positive latex skin test were atopic. The proportion of atopic individuals among those who are latex sensitive may be as high as 85% (9). It has been estimated that the presence of atopy increases the risk of latex sensitization by from 4.4 (10) to 25 (9) times, depending on the definition of atopy that is used.

Clinical Expression of Latex Allergy

The clinical expression of latex allergy encompasses the classical spectrum of immediate hypersensitivity reactions, including contact urticaria, rhinoconjunctivitis, angioedema, asthma, and varying degrees of anaphylaxis. Since contact with rubber goods is usually via the skin or mucous membranes, it might be expected that the cutaneous manifestations of this condition would occur most frequently. However, this is not always the case. For example, health care workers have contact with NRL allergens not only on the skin when they wear latex gloves but also in the respiratory tract, when the allergens bound to the glove-lubricating corn starch powder becomes airborne as gloves are changed. Thus, upper and lower respiratory symptoms may be more frequent than cutaneous symptoms in this risk group. Wrangsjö et al. (11) reported that allergic respiratory symptoms were more frequent than cutaneous ones in her patients—88% vs 72%. In Turjanmaa's group of 15 latex-allergic patients, 8 had rhinoconjunctivitis, 3 had asthma and 7 had contact urticaria (6). We would also add that the existence of atopic eczema or contact dermatitis on the hands caused by the chemicals in medical-use gloves, for example, have been identified as lesions that facilitate the transcutaneous passage of latex proteins and, consequently, the induction of latex-specific IgE (6,9).

Association with Food Allergy

Patients with allergy to latex are frequently reported to have an associated skin sensitivity and/or clinical allergy to one or more foods, although the particular food or foods is not always specified. Of the

30 patients studied by Wrangsjö et al. (11), 25 reported food intolerance; and in the study reported by Moneret-Vautrin et al. (9), one-third of the latex-sensitive patients had a food allergy. Based on a number of reports, it appears that about 50% of NRL allergic patients have a concomitant food allergy, with extremes from 30–80% (5,12–15). The frequency differs according to the selection of patients, the clinical data obtained, and the test methods utilized. For example, in the recent study of Beezhold et al. (16), among 47 subjects with a positive skin test to NRL (of whom only 17 [36%] reported an actual clinical reaction to latex), 33 (70%) of them reported an allergy to food. In another recent study (17), Mounedji et al. found that of 28 patients who were clinically allergic to latex and who also had a positive skin-prick test to latex, 21 (61%) were skin-test positive to one or more foods, and 13 of these 21 patients (62%) had a clinical reaction to the food(s) to which they were skin-test positive. These sorts of data indicate that there is a discrepancy between allergic sensitization, as revealed by skin-and/or serological tests, and the clinical manifestation(s) of that sensitization, as has long been known.

Food Allergies that Have Been Associated with Latex Allergy

Nearly all of the suspected crossreactions reported in association with latex allergy as a result of allergens of plant origin. The few reports incriminating nonplant foods, such as milk (16) or fish (11,18), would seem to be coincidental in atopic individuals. Leynadier et al. (18) first called attention to the occurrence of food allergy in latex-sensitive patients. Four of their five patients had a positive skin test to banana, avocado, passion fruit, pear, grapefruit, tomato, mushroom, and/or bell pepper. Many reports have confirmed the fact that banana, avocado, kiwi fruit, and chestnut are the food sensitivities and/or clinical allergies most frequently detected in latex-sensitive patients. For example, Pecquet et al. (15) reported that 34% of their latex-sensitive patients were sensitive to banana, 25% to avocado, and 20% to kiwi fruit. Blanco et al. (5) reported that, of 25 latex-sensitive patients, 9 were sensitive to avocado, 7 to banana, and 5 to kiwi fruit. Mounedji et al. (17) recently reported that among 28 patients who were clinically allergic to latex, 21 were skin-test positive to at least one fresh food, including 18 who reacted to banana, 16 to chestnut, 14 to avocado, and 13 to kiwi. In this study, among the other foods that induced a positive skin-test reaction in these patients were peach (20), tomato (21), mango (21), pineapple (22), celery (22), cantaloupe (23), apple (24), and papaya (25). Thirteen (62%) of the patients with a positive skin test to at least one food had experienced clinical manifestations of food allergy; the foods

reported most frequently were avocado, banana, chestnut, and kiwi in these patients. Eighteen patients had a positive skin test to more than four different foods, and, of these patients, 15 were also allergic to at least one pollen. Pollinosis, present in 61% of the 28 patients, had preceded the onset of latex allergy; in most of those affected, pollinosis had preceded the onset of the clinical manifestations of their food allergy.

M'Raihi et al. (26) were the first to describe the occurrence of a systemic allergic reaction caused by banana in a latex-allergic patient. Mäkinen-Kiljunen et al. (14,27,28) reported that 16 (52%) out of a group of 31 latex-allergic patients had allergic symptoms induced by eating bananas, including some who had systemic reactions. The same proportion was found by Guilloux et al. (12), while Beezhold et al. (16) found that a slightly lower frequency (38%) of latex-sensitive patients had a positive skin-prick test to banana. In many other reports, sensitivity to banana, with or without clinical symptoms, is among the food allergies most frequently found to be associated with NRL allergy.

We reported the occurrence of allergy to avocado in patients with allergy to latex and banana (29). Blanco et al. (30) described allergy to avocado in 17 patients, 10 (59%) of whom reported having had immediate allergic reactions to latex. In that report, a skin-prick test with fresh avocado was positive in all 17 patients, but the size of the reaction varied with the variety of avocado; the strong variety induced larger reactions than the hass avocado variety. So, as with apple allergy (31), the variety of the fruit as well as its maturity and the conditions of culture seem to play a role. In another study (32), 7 of 11 latex-allergic patients were found to have a positive skin-prick test to fresh avocado. The serum of some of these patients was shown to contain IgE antibodies that react with several allergens present in avocado extract and in fresh latex. Based on the additional evidence that some of the sera reacted only with avocado allergens and others only with latex allergens, it was suggested that there are multiple epitopes in both substances—some that are shared and others that are specific to each substance (30).

Kiwi fruit, the edible fruit of the Chinese gooseberry vine, first appeared in western markets only about two decades ago but was soon recognized as being allergenic. Soon thereafter, it was associated with latex allergy. Gaignon et al. (33) described the case of an 8-yr-old boy who experienced rhinoconjunctivitis and edema of the lips upon contact with latex objects and after eating kiwi fruit and bananas. Among 47 latex-allergic patients, Beezhold et al. (16) found 8 with a positive skin-prick test to kiwi fruit, one of whom had had a systemic reaction to the fruit. Blanco et al. (30) described four latex-sensitive patients who also reacted to kiwi fruit, in addition to being allergic to avocado. A

weak correlation between kiwi fruit and avocado sensitivities has also been reported in patients with pollen allergies (34). It should be noted that the kiwi allergen crossreacts with birch pollen-specific IgE antibodies (35). The main kiwi allergen is thermolabile; its reactivity with IgE disappears upon heating at 80–90°C (35).

Spanish authors were the first to describe allergy to chestnuts in latex-allergic patients (22,36,37). Symptoms have followed ingestion of raw chestnuts and sometimes even occur when the patient is peeling these nuts. It was not mentioned whether or not cooked chestnuts might have caused symptoms in their patients.

In addition, there are a growing number of publications containing reports of associations between sensitivity to latex and to various fruit and vegetable foods (11,18–20,38–46). When this review was written, the list included, in addition to those mentioned above: almond, apple, bread fruit, buckwheat, celery, citrus fruits, fig, grapefruit, hazelnut, lettuce, peach, peanut, pear, strawberry, sweet pepper, tomato, walnut, and watermelon. Also reported are condurango bark and passion fruit medicinal plant extracts that are used as infusions (47–49). The enzymes papain and bromelain, present in papaya and pineapple, respectively, have recently been shown to crossreact with latex specific IgE (50–52).

The symptoms of food allergy are, in most cases, induced by uncooked foods, as cooked foods usually are well tolerated. This fact argues for the thermolability of most food allergens, which is in contrast to most latex allergens; latex goods retain their allergenicity in spite of the inclusion of a heating step during their production. Foods of plant origin are known to induce all the classical forms of clinical allergic reactions. Once food is in the mouth, the reaction may be localized there, producing the oral allergy syndrome. Otherwise, it may be expressed systemically in the gastrointestinal tract, the respiratory tract, or in the skin. As with latex allergy, skin contact with the offending food, such as when peeling potatoes, may, in some cases, lead to contact urticaria (16).

Over the years, the value of skin testing in the diagnosis of food allergies has been the subject of much debate. Food extracts are not standardized, and their validity and reliability have not been established. Many allergists use fresh foods or extracts thereof that they prepare themselves, thus making it difficult to compare results obtained by one group of allergists with those obtained by another. It is now clear that, to be confident of the clinical history and the results of skin tests, additional diagnostic steps are often necessary (53). This leads us to inject a word of caution concerning the accuracy of some of the figures on the prevalence of various food allergies referred to above.

The diagnostic approach to latex allergy, sometimes also difficult to establish with certainty, is well-described by Turjanmaa (54,55).

Given the limitations of the skin-test reagents and the serological assays that have been employed in the diagnosis of latex allergy, a similar word of caution is in order with respect to certain statistics cited above.

Other Plant Allergens That Have Been Associated with Latex Allergy

It is not very surprising that latex from the common house plant *Ficus benjamina*—the weeping fig—can induce immediate hypersensitivity reactions in latex-allergic patients. Although *F. benjamina* is not phylogenetically close to *H. brasiliensis*, their latexes do have similar properties (56). Bircher et al. (57) showed that the allergens of the weeping fig are present not only in its latex but also on the surface of its leaves, which implies that they can become airborne. Although the prevalence of allergy to *F. benjamina* has not been determined, it nevertheless appears that most patients who are allergic to this plant are not at the same time allergic to *H. brasiliensis* latex. Bircher et al. reported that only one out of a study of 15 patients allergic to ficus allergens had a positive skin-prick test to NRL, and this patient did not experience symptoms upon contact with latex goods. Latex from other ficus species have not yet shown allergenicity (58). Cannabis, like the weeping fig, belongs to the Moraceae family of plants, and appears to contain allergens that can cause an allergic reaction in NRL allergic patients (59).

Serologic crossreactivity has been reported between NRL allergens and allergens from ragweed and Kentucky blue grass pollens (60), with a high frequency of NRL specific IgE antibodies in sera from ragweed-sensitive patients (61). Merrett et al. (62) found that the latex-reactive IgE, which was detected in 7% of a large set of sera from English blood donors, would in most cases also bind grass pollen allergens. Unfortunately, none of these reports included information on the clinical significance of these crossreacting antibodies. In contrast, Mäkinen-Kiljunen found no correlation between latex RAST and birch pollen RAST results in sera from 47 NRL allergic patients (14). Mounedji et al. (17) recently reported that, among 28 patients who were clinically allergic to latex, 17 (61%) had a history of pollinosis and a positive skin-prick test to at least one pollen. Because the majority of latex-sensitive individuals are atopic, we question whether the coexistence in an individual of allergy to pollen and to latex signals a true crossreactivity.

There is information on the sequence of sensitization to latex and other allergens in patients with multiple allergies in only a limited number of reports. We have described patients who were first sensitized to banana, then to chestnut and avocado and then, after repeated exposures, to latex (29). Blanco et al. (5) described latex allergy preceding allergy to avocado in four patients, the reverse in two patients, and con-

comitant development of the two allergies in four other patients. At least in the case of food allergies, it is evident that any sequence is possible. On the other hand, in the series of patients described by Mounedji et al. (17), pollinosis had preceded the onset of latex allergy in most cases. We suggest that the solution to this riddle might yield some important insights into the control of the IgE response.

Immunological Studies

Determination of Specific IgE

It is generally agreed that the sensitivity of serological assays (the proportion of individuals with a positive test result in an affected population) is lower than the sensitivity of skin tests. This holds true for both latex and food allergens—even more so when fresh foods, rather than commercially prepared food extracts, are used for in vivo testing. As a result, the concordance between the results of in vivo and in vitro tests, as well as either of these with the clinical history, is less than perfect.

The sensitivity of serological tests for latex- and food-specific IgE varies widely. Mäkinen-Kiljunen (14) found that 31 (66%) of a series of 47 patients clinically allergic to latex had a positive latex RAST, and 55% of them had a positive banana RAST. The 31 latex RAST-positive patients were questioned for possible reactions after eating bananas and skin-prick tested with banana. Twenty-five (81%) were also banana RAST-positive, and the latex RAST results correlated significantly with those of the banana RAST ($p < 0.001$). Banana skin-prick test results were positive in 11 (35%) of the 31 latex RAST-positive patients tested. Symptoms after eating bananas were reported by 16 (52%) of these 31 patients. Blanco et al. (5) reported that the avocado RAST had a sensitivity of 70%, banana, 29%, and chestnut only 11%. DeCorres et al. (36) reported that the chestnut RAST had a sensitivity of 83% but almost none for banana allergy. Many patients allergic to the weeping fig, although not clinically allergic to NRL, have latex-specific IgE detectable by RAST: 4 out of 20 in the series reported by Axelsson et al. (56), 5 out of 8 in the series reported by Bircher et al. (57), and 4 out of 10 in the study reported by Bessot et al. (63). Kurup et al. (64) measured specific IgE to banana, potato, and wheat in the sera of latex-sensitive patients (only one of whom was clinically allergic to food) and in sera from a series of normal controls; and they found no major differences in specific IgE titers between the latex-allergic and the normal subjects. We suggest that the difference between these results and those of other publications could be owing to differences in methods, including the reliability of the clinical histories, the quality of the reagents used, and/or to the test methods used, or to a combination of all of these factors.

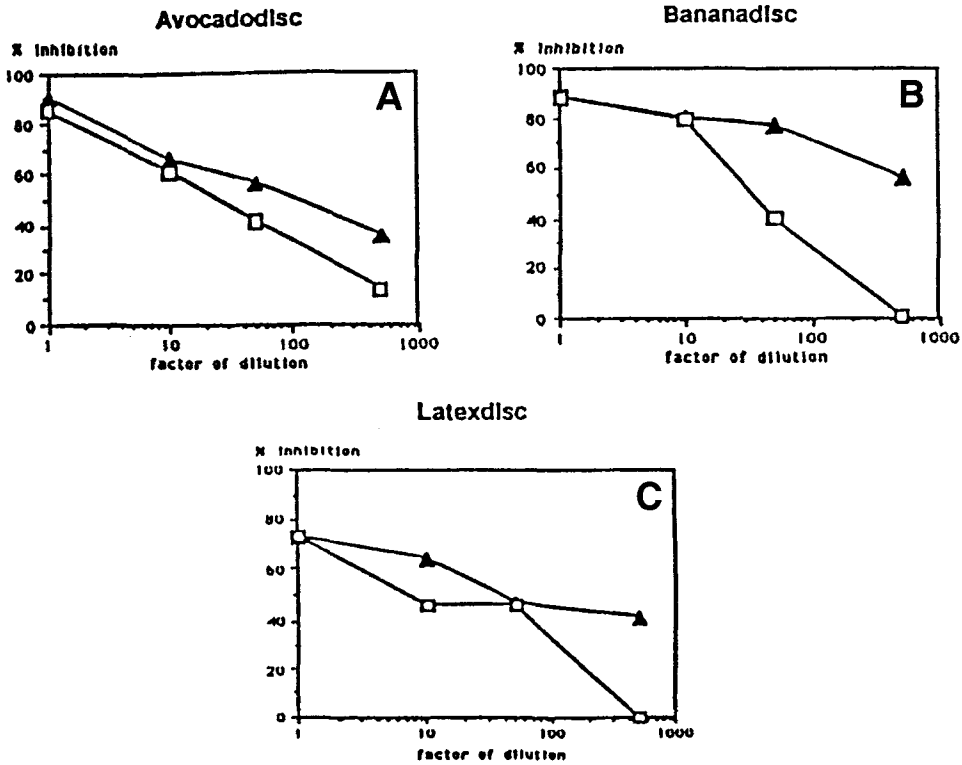


Fig. 1. RAST inhibition among avocado, banana, and natural rubber latex. Results are indicated in percentage of inhibition against the RAST disk after preincubation with avocado (▲) or banana (□) extracts. Avocado and banana extracts inhibited the respective fruit disk of each other from 60–80% (dilution 1/10) to 90% (dilution 1/1) and the latex disk from 46–64% (dilution 1/10) to 73% (dilution 1/1). (Reproduced from ref. 29 with permission.)

Crossreactivity Studied by Serologic Inhibition Methods

Significant crossreactivity between NRL and banana allergens in RAST inhibition studies was first reported by M'Raihi et al. (26), then by Ross et al. (65). We reported (29) that banana and avocado extracts could inhibit the reciprocal RAST nearly completely, whereas both of them were capable of partial inhibition of latex RAST (Fig. 1). Blanco et al. (30) reported that latex inhibited the avocado RAST by up to 74%, with a pool of sera from 17 patients allergic to avocado. In the chestnut RAST, maximum inhibition by latex was 44%; in the banana RAST, it was 28%. Ahlroth et al. (32) found that NRL inhibited binding to an avocado disk, and avocado extract inhibited binding to a latex disk, both in a dose-dependent manner. Similar studies reported by Mäkinen-Kiljunen (14) revealed maximal inhibition of 60% reciprocally between latex and banana. Rodriguez et al. (37) and DeCorres et al. (36) reported

similar results with latex and chestnut, although in the latter report, chestnut extract did not inhibit the binding of latex to the latex disk. We have recently shown by immunoblot inhibition that crossreacting antigens are present in latex, banana, and avocado extracts (13). This observation was confirmed for latex and banana by Alenius et al. (23), with evidence of 14 IgE-binding banana allergens of different molecular sizes. They found evidence that these allergens bound IgE in sera from 10 out of 22 latex-sensitive patients. Finally, it was reported that latex proteins completely blocked the binding of papain-specific IgE to disks with papain, whereas papain inhibited the binding of latex-specific IgE to latex disks by only 31% (50).

Crossreactivity Studied by Other Methods

Kurup et al. (64) coupled food and latex allergen extracts to Affigel beads, passed sera from latex-sensitive patients over the resulting columns, eluted the antibodies that were bound to the columns, then assayed the eluates for IgE activity. The results demonstrated that there was partial crossreactivity of the eluted antibodies with wheat, oat, banana, and potato allergens, with considerable differences that depend on the allergen and the patient's serum. By immunospot inhibition, Mäkinen-Kiljunen (14) demonstrated crossantigenicity between latex and banana, with fairly good inhibition with NRL. Using rocket immunoelectrophoresis, rocket radioimmuno-electrophoresis, crossed-line immunoelectrophoresis, and crossed-line radioimmuno-electrophoresis, several groups have shown that rabbit antilatelatex antibodies can precipitate banana antigens (14,27,66).

Identification of Allergens that Crossreact

Many proteins of similar structure and function—in particular their antigenic epitopes—are known to be widely distributed in the plant kingdom. This explains why, even though the plants concerned belong to very distinct families (Table 1), we find cross-sensitivities and crossallergies between NRL and plant-derived foods with no apparent similarity.

Latex Allergens

Natural rubber latex is a suspension of rubber particles in a complex liquid mixture of proteins and other organic substances (2,67). On centrifugation, it separates into several fractions: an upper fraction containing mostly rubber particles, a middle liquid fraction (the C serum), and the bottom lutoid fraction containing particles and organelles coming from the lutoidic tonoplast (67,68). The protein content of fresh latex is on the order of 16 mg/mL. On electrophoresis, at least 16 polypeptides—from 10 to 100 kDa—can be identified. The most abundant are

Table 1
Hevea Species and Other Plants with Known Crossreactivity and their Botanical Relationship

Subclass	Order	Family	Genus	Species ^a	Vernacular name
Rosidae	Euphorbiales	Euphorbiaceae	<i>Hevea</i>	<i>brasiliensis</i>	Natural rubber
Rosidae	Fabales	Papilionaceae	<i>Arachis</i>	<i>hypogaea</i>	Peanut
		(leguminosae)			
Magnolidae	Laurales	Lauraceae	<i>Phaeolus</i>	<i>vulgaris</i>	Kidney bean
Hamamelidae	Fagales	Fagaceae	<i>Persea</i>	<i>gratissima</i>	Avocado
Caryophyllidae	Urticales	Moraceae	<i>Castanea</i>	<i>sativa</i>	Chestnut
Dilleniidae	Dilleniales	Dilleniaceae	<i>Ficus</i>	<i>benjamina</i>	Weeping fig
Dilleniidae	Violales	Passifloraceae	<i>Actinidia</i>	<i>sinensis</i>	Kiwi
		Caricaceae	<i>Passiflora</i>	<i>edulis</i>	Passion fruit
		Cucurbitaceae	<i>Carica</i>	<i>papaya</i>	Papaya
Asteridae	Gentianales	Asclepiadaceae	<i>Cucumis</i>	<i>melo</i>	Melon
	Polemoniales	Solanaceae	<i>Marsdenia</i>	<i>condurango</i>	Condurango bark
			<i>Solanum</i>	<i>tuberosum</i>	Potato
			<i>Lycopersicon</i>	<i>hypersicum</i>	Tomato
			<i>Nicotiana</i>	<i>tabacum</i>	Tobacco
	Asterales	Compositae	<i>Ambrosia</i>	<i>elator</i>	Ragweed
Monocotyledons					
Commelinidae	Poales	Graminaceae	<i>Poa</i>	<i>pratensis</i>	Blue grass
			<i>Triticum</i>	<i>sativum</i>	Wheat
			<i>Oryza</i>	<i>sativa</i>	Rice
	Bromeliales	Bromeliaceae	<i>Ananas</i>	<i>comosus</i>	Pineapple
	Zingiberales	Musaceae	<i>Musa</i>	<i>acuminata</i>	Banana

^aThe more frequent.

Table 2
Characterization of Natural Rubber Latex Proteins Sharing Epitopes
and Crossreacting with Allergens of Other Plants

Molecular weight, kDa	Identification	Crossreaction With
14.6	Rubber elongation factor	Papain
15	Profilin	Ragweed
20	Prohevein	Ragweed <i>N</i> -acetyl glucosamine (cereals, barley root) Win 1, Win 2 (solanaceae) CBP 20 and PR4 (tobacco)
30	Hevamine	Lysozyme (fig, papaya, avocado, banana)
36	?	1,3 b glucosidases (tomato, kidney bean)
46	?	Patatin (Solanaceae)
110	?	Patatin (Solanaceae)

those at 10, 14, 20, 30, and 100 kDa (13,69–77). They have a typical basic charge and migrate in the pH range from 4.0 to 6.5 (2,71). On two-dimensional electrophoresis, 240 individual polypeptides, of which 57 are IgE-binding, have been identified in fresh NRL (25). Latex allergens are present not only in fresh latex, but they have also been identified in ammoniated latex and in aqueous extracts of a broad range of rubber products, especially in medical-use gloves. Table 2 lists those NRL proteins that have been shown to share epitopes with proteins from other plant sources.

Prohevein

Prohevein, a chitin-binding protein with a mol wt of 20 kDa, is perhaps the most important NRL allergen (24). It is the most abundant protein in latex, especially in the lutoid fraction. Prohevein appears to be the 20-kDa polypeptide that was previously identified in a number of studies as an important latex allergen. It is spontaneously cleaved into two fragments, one of which is hevein (mol wt 4.7 kDa). The other is one of the 14- to 14.5-kDa IgE-binding polypeptides that was identified as a latex allergen by many investigators earlier on. The hevein domain of the prohevein molecule probably plays a major role in the IgE-binding activity of prohevein (78). Structural homologies between prohevein and ragweed allergens and between prohevein and some cereal lectins (the *N*-acetylglucosamine of cereal agglutinins [56,64,79]

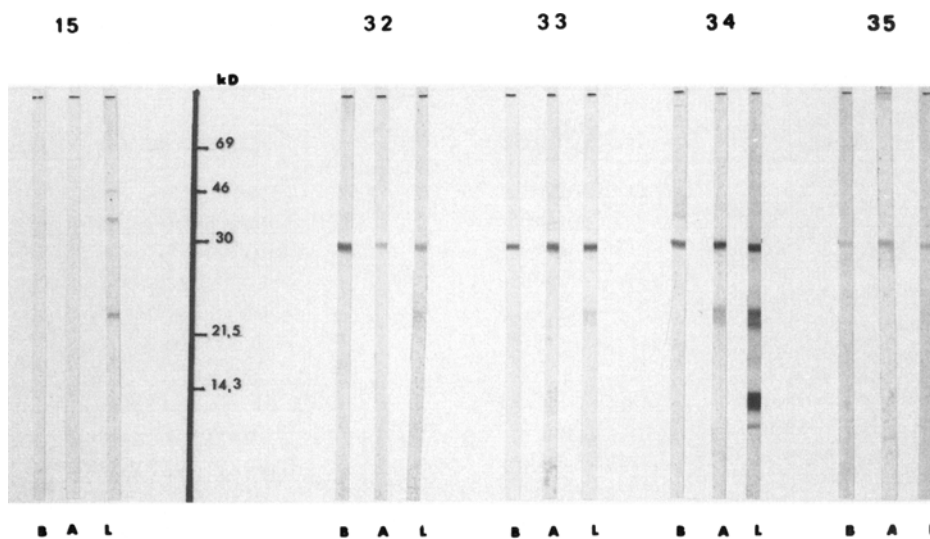


Fig. 2. Selected immunoblotting results with sera from latex allergic patients without ($n^{\circ}15$) or with an associated fruit allergy ($n^{\circ}32$ to 35). B, banana; A, avocado; L, fresh natural latex; KD, Kilodalton. (Reproduced from ref. 13 with permission.)

and barley root-specific lectin [80]) provide a basis for crossreactivity with latex-specific IgE. For example, prohevein (500 ng/mL) completely inhibits the binding of wheat agglutinin to its homologous IgE antibody on immunoblots (81). Significant structural homology was also demonstrated between prohevein and other plant lectins and chitin-binding proteins. The latter is presented as defense-related proteins that exist widely in plants—for example, WIN 1 and WIN 2 and the CBP 20 and PR4 proteins from plants of the Solanaceae family (79,80,82).

Lysozyme

Allergens with a mol wt of about 30 kDa have been described in a number of reports (12–14,24,32). These may be hevine (83), a plant chitinase/lysozyme that is detectable in the bottom fraction of centrifuged NRL associated with the lutoid particles (67). Alenius et al. (24) demonstrated 100% sequence homology between a 30-kDa NRL allergen and hevine. NRL is known to contain a 30-kDa protein with lysozyme activity, pH optimum 4.0 (84). Recently, Yagami et al. (85,86) isolated and characterized a lysozyme from NRL by cation exchange and gel filtration chromatography.

Thirty kilodalton allergens that crossreact with NRL have been isolated from several fruits (Fig. 2). On immunoblots, we found that a

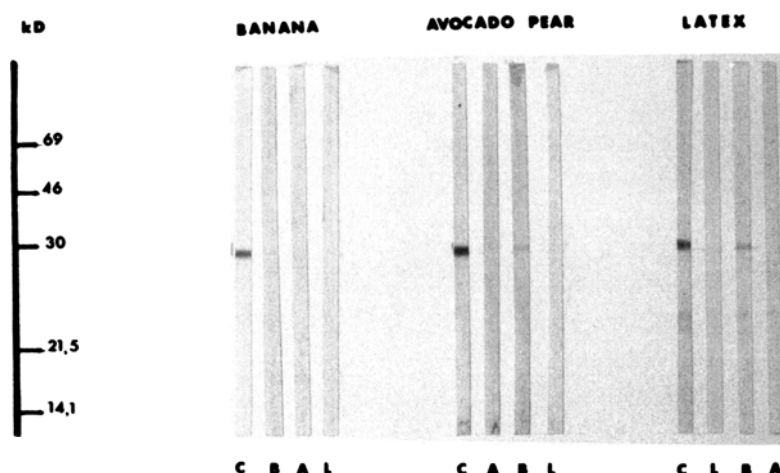


Fig. 3. Representative immunoblot patterns of reactivity observed in inhibition studies. Serum from a patient allergic to latex, banana, and avocado was incubated with 50 μ g of banana extract (first panel), avocado extract (second panel), and latex extract (third panel), then tested in immunoblot vs banana (lane B), avocado (lane A), and natural rubber latex (lane L). Lane C shows the initial pattern without preincubation. After preincubation of this serum with either a banana or an avocado extract, complete inhibition was seen in both cases. After preincubation of the same serum with latex extract, partial inhibition was seen on the banana immunoblot, whereas complete inhibition was seen on the avocado immunoblot. (Reproduced from ref. 13 with permission.)

30-kDa allergen was recognized by 9 out of 10 sera from patients sensitive to both latex and food (banana and/or avocado) (13). In contrast, sera from only two out of seven patients who were clinically allergic to latex, but not to either of these two foods, contained detectable IgE to one or both of these foods, including IgE that reacted with this 30-kDa polypeptide. On immunoblots, binding of IgE to this polypeptide was completely blocked by preincubation of the sera with extracts of these two foods. Preincubation with NRL totally blocked blotting on avocado extract, but only partially blocked blotting on banana extract (Fig. 3). Similar crossreactivity was shown by Guilloux et al. (12,87), and they found that binding to two banana allergens (mol wt 33 and 37 kDa) could be inhibited by preincubation of the sera with NRL. Of the several polypeptides recognized on avocado immunoblots by the sera from NRL allergic patients, Ahlroth et al. (32) found the most intense reactions occurred on the 27- and 52-kDa polypeptide bands. Binding to the 27-kDa avocado polypeptide was partially inhibited by preincubation of the sera with NRL.

It should be noted that latex lysozyme is very similar in composition to the lysozyme of fig and papaya (67,88) as well as to the lysozyme

of a number of other plants (79,89–93). Lysozyme activity has also been found in avocado (20), and a 30-kDa avocado protein that crossreacts with a latex protein has recently been identified as a chitinase with lysozyme activity (94). It is also possible that the 28- to 29-kDa allergen that was identified on SDS-PAGE and on immunoblots in the latex of the weeping fig is a lysozyme (57).

Rubber Elongation Factor

Rubber elongation factor (REF), which is a 58-kDa protein with an isoelectric point of 8.45, is localized on the surface of rubber particles. It is an enzyme involved in the biosynthesis of the polyisoprene chain, which is the building block of the rubber molecule. REF also acts as a carrier for the *cis*-isoprene units that are added to the growing rubber molecule (95). This protein, purified from raw latex and from latex gloves by Czuppon et al. (96), is a noncovalent homotetramer molecule, in which the 14.6-kDa monomer was identified by amino acid composition and sequence homologies of tryptic peptides to be REF. It is reported to completely block binding to IgE antibodies in the serum of latex-sensitive patients. The purified allergen—which these authors named Hev b 1—induced allergic reactions in the nanogram range in latex-sensitive patients. Czuppon et al. recognize REF as a major NRL allergen, but its classification as such has been questioned by others (97). The same group of investigators (50) also found that latex-specific IgE would bind purified REF and papain, and they explain this observation on the basis of structural homologies between the two substances: they share five sequence-identical trimers and two identical tetramers. However, this finding has not yet been substantiated by other investigators, and homologies between REF and other latex-associated food allergens have not been reported.

Other Allergens

A 36-kDa protein isolated from the lutoid organelles of NRL binds latex-specific IgE (24). Three peptides obtained from this protein were sequenced and found to have from 67–83% homology with 1–3 glucosidases from several different plants. Latex glucosidases remain to be characterized, but they might be significant crossreacting allergens.

Beezhold et al. (98) have isolated 46- and 110-kDa proteins from NRL that react with latex-specific IgE. The N-terminal sequence of the 46-kDa protein has partial homology with the potato protein patatin (16). Patatin is a storage protein found in plants in the Solanaceae family, including potato and tomato (99), but the above two NRL proteins have not yet been further characterized as patatin-related. Moreover, binding of NRL proteins with mol wt of 28, 31, 38,

70, and 80 kDa to latex-specific IgE in immunoblots could be blocked by a potato extract; paradoxically, the 46-kDa band was only partially blocked by this extract.

Profilin

Profilin is a 15-kDa IgE-binding protein that is present in NRL but it is not detectable in latex glove extracts (100). It has been designated as a "panallergen," being present in a number of plant species and identified as a crossreacting allergen in birch and mugwort pollens and celery (101). Vallier et al. (100) reported that only 2 out of 19 sera from latex- and banana-sensitive patients reacted with profilin, leading them to suggest that it was probably not a major latex allergen. They consider that the presence of IgE antibodies to profilin in patients allergic to latex may be a consequence of sensitization to profilins in plants other than *H. brasiliensis* (100). Their finding could also explain the apparent cross-sensitization between NRL and ragweed since purified ragweed profilin inhibits the latex CAP RAST by 80%.

Conclusion

Polypeptides with allergenic properties have been found to be present in both NRL and a growing number of plants, particularly those consumed as food. This provides an explanation for the numerous crossreactions that have been reported. To date, however, only a few of these allergens have been well characterized.

It has been suggested that some of these crossreacting allergens may be "defense-related proteins" (1,85,86). One of the main roles of such proteins is to protect the plant from attack by pathogens, and some stress proteins have been found to have antifungal, antibacterial, and/or insecticidal activities (102). In this way, lysozymes are considered to be "defense-related proteins" in higher order plants.

When the rubber tree is tapped, the cytoplasmic contents of the laticiferous cells, including rubber particles and lutoid organelles, are expelled to the exterior and collected as latex (67). It is now known that repeated tapping—that is, wounding, of *H. brasiliensis*, which is necessary for the collection of latex—increases the amount of defense-related proteins, including lysozyme but also hevein, and prohevein (79) and perhaps also a 46-kDa protein, in the tree's laticiferous cells (98). Defense-related proteins can also be induced by stimulating plants, including the rubber tree, with growth regulators such as ethylene (66,103), auxin, gibberelin, cytokinin (86), or phytohormones. Biotic and abiotic stresses also enhance their production (67,79).

This suggested to us the idea, in agreement with Yagami et al. (86), that the latex obtained in huge quantities from genetically selected,

phytohormone-treated, and heavily wounded trees might contain large amounts of defense-related proteins. We further suggest that the same results may occur in plants that are the source of fruits and vegetable foods. Because of the universality of plant responses, this might explain some of the apparent increase in the number of different crossreactions reported in latex- and/or food-sensitive patients.

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