
Review article

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Latex antigens: identification and use in clinical and experimental studies, including crossreactivity with food and pollen allergens

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Learning Objectives: The purpose of this review is to introduce the reader to the range of latex allergens that have been identified by polypeptide sequencing. This knowledge is important for the assessment of clinical latex hypersensitivity, including crossreactivity with food and aeroallergens.

Data Sources: Medline search and relevant publications and reviews from the English medical literature since 1989.

Results: Of the more than 150 polypeptides in natural latex rubber, 35 or more can act as allergens and are recognized by IgE antibodies in the sera of latex-sensitive subjects. Complete or partial amino acid sequence data have now been obtained for 20 or more allergens, and have facilitated cloning of genes and development of allergen-specific antibodies. In latex-sensitive adults, hevein (Hev b6), rubber elongation factor (Hev b1) and Hev b5 are reported as major allergens, while in children with spina bifida, latex particle proteins are important allergens. Although incomplete, the data for finished latex products indicate that the number as well as diversity of latex antigens are limited compared with the allergen profile of natural rubber latex. Latex allergen sequence data allows epitope mapping, which establishes the molecular basis for understanding crossreactivity between latex, food, and aeroallergens.

Conclusion: The identification of latex allergens is paving the way for studying the molecular basis of immunoreactivity to these proteins, including crossreactivity with food and other allergens. The development of reagents to detect and measure antigen-specific responses will increase diagnostic specificity of allergic reactions to latex products.

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INTRODUCTION

Immediate hypersensitivity to natural rubber latex (NRL) or latex products is an IgE-mediated reaction to the polypeptides contained in NRL.^{1–3} Several latex allergens have now been identified, and this identification has paved the way for understanding pro-

cessing of these proteins in the immune system and generation of immediate hypersensitivity reactions.³ This information is helpful in the diagnosis and treatment of latex allergy, as well as for the screening of the allergenicity of finished latex products. From a diagnostic perspective, it is important to differentiate between primary latex sensitivity and crossreactive interactions with food and aeroallergens. We still lack a clear understanding about the molecular basis of this crossreactivity between these antigens, but from the available latex antigen sequence

data it is now possible to perform epitope mapping. Distinguishing between latex, food, or aeroallergen sensitivity is important in atopic people, since it is reported that the prevalence of latex allergy is higher in an atopic than in a non-atopic population.^{4–6} This raises the question as to whether latex, food, or pollen allergens are the primary sensitizing antigen.⁶ In this communication we will review what is currently known about identified latex allergens, including identification of major epitopes, and their crossreactivity with food and aeroallergen determinants.

NATURAL RUBBER LATEX (NRL) CONTAINS A COMPLEX COLLECTION OF PROTEINS DERIVED FROM THE CYTOPLASM OF *H. BRASILIENSIS* LACTIFERS

Most of the natural rubber in the world is obtained from the latex of the rubber tree, *Hevea brasiliensis*.⁷ Latex is the cytoplasm of specialized tube-like cells, known as lactifers, and functions to seal damaged sites.⁷ The cytoplasm contains cytosol, rubber particles, and subcellular organelles, all of which participate in the sealing process. Sealing is a coagulation process involving aggregation of rubber particles by a protein, hevein, which is released from organelles known as lutoids.^{8,9} Lutoids contain B-serum which is enriched for prohevein and divalent cations. Hevein interacts with a glycosylated 22-kD receptor protein in the lipoprotein envelope around rubber particles, leading to

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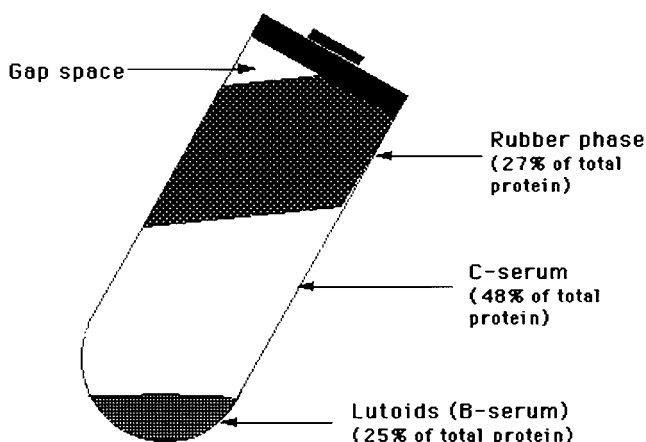


Figure 1. Fresh hevea latex centrifuged at 59,000 *g*.

their aggregation. In addition to the glycosylated receptor protein on the surface of rubber particles, these particles also contain the enzyme rubber elongation factor (REF). Rubber elongation factor is a 14-kD protein which allows another enzyme, prenyltransferase, to link short isoprene units into cis-1,4-polyisoprene chains, which are responsible for the structural integrity of latex.⁷⁻⁹

In addition to the proteins named above, NRL contains a vast number of polypeptides which are potential allergens. These proteins are localized in 3 major fractions that are obtained during ultracentrifugation of fresh Hevea latex,¹⁰ namely: (1) a white creamy layer at the top which contains virtually all the rubber particles; (2) a translucent fluid called C-serum, which corresponds to latex cytosol; and (3) a bottom fraction containing organelles, including the lutoids (Fig 1). The rubber phase, C-serum and B-serum contain 27%, 48%, and 25%, respectively, of the total NRL protein content. The complexity of NRL polypeptides is best demonstrated by two dimensional (2D) gel electrophoresis, which demonstrates a wide range of molecular weights (MW) and isoelectric points (pI).¹¹⁻¹⁵ Briefly, C-serum exhibits between 150 to 240 individual polypeptides on 2D gels, while rubber particles have a much simpler protein profile,

namely two clusters of lower MW polypeptides. While the MW of C-serum proteins range from 4 to 110 kD, rubber particle proteins are usually less than 30 kD.¹¹⁻¹⁵ Immunoblot analysis of these 2D gels with the sera of latex-sensitive people (LSP), show that many but not all NRL polypeptides bind to IgE antibodies.¹¹⁻¹⁴ The number of IgE binding polypeptides in C-serum was estimated as 35 to 40, 57, and 60, respectively, by 3 independent investigators.¹¹⁻¹⁴ It is important to point out that each individual spot on the 2D immunoblot does not necessarily represent a distinct protein, since some spots of similar MW may represent isoelectric variants of the same protein. Similarly, spots of different MW may represent fragments or aggregates of single allergens. Protein degradation is a well-recognized phenomenon that occurs in latex extracts, and is enhanced by ammonification, heating, and storage. In contrast to C-serum, IgE-binding polypeptides in rubber particles are limited in number and appear on 2D immunoblots as a series of lower MW spots in the 8 to 14-kD and 23-kD ranges.^{11,12} Most of these spots represent REF (Hev b1), REF fragments, or related peptides. Where one dimensional (1D) electrophoresis of NRL allergens was used prior to immunoblotting, fewer IgE reactive polypeptides were identified due

to the limited resolving power of this technique.¹⁶⁻¹⁹ Nonetheless, 1D approaches have been helpful in characterizing a number of "major" latex allergens (see section on major antigens), and showing the wide range of latex response profiles in sera from LSP.¹⁶⁻¹⁹ This variability may reflect the roles of immune response genes as well as the source of the primary sensitizing antigen (see section on HLA alleles).

Taken together, 2D electrophoresis and immunoblotting have resolved a large number of possible allergens in NRL, and have demonstrated that the allergen profile of C-serum differs from the allergen profile of latex particles. Although the Baur group has now sequenced more than 20 of the 60 IgE-binding polypeptides on their 2D gels,^{11,12} it is not possible yet to define the exact number of latex allergens. In spite of the apparent complexity of IgE-binding NRL polypeptides, the number of IgE-binding polypeptides in finished latex products, such as gloves, are limited in number and may simplify the number of clinically relevant allergens that play a role in latex sensitivity in HCW (see section on finished latex products). Further, a number of so-called "major latex allergens" have been identified in health care workers (HCW) and spinal bifida patients (SBP), which implies that some antigens may be more allergenic than others (see section on major antigens).

SEVERAL LATEX ANTIGENS HAVE NOW BEEN PURIFIED, SEQUENCED AND THEIR GENES CLONED

Using glove extracts, the first major latex antigen which was identified by Czuppon et al, was REF.²⁰ Rubber elongation factor, also known as Hev b1 by the international latex allergen nomenclature, is a rubber particle protein which migrates on 2D gels at 14.6 kD along with a cluster of 8 to 14-kD degradation products (Table 1).^{11,12} The REF gene has been cloned.²¹ Aleenius et al¹⁷ used chromatographic purification to identify 3 NRL proteins, namely prohevein, hevamine, and

β -1,3-glucanase (Table 1). Prohevein is a 20-kD, two-domain protein that is post-translationally processed into a 4.7-kD, N-terminal fragment, hevein, and a 14-kD, C-terminal domain.²²⁻²⁴ A homologue of the 43 amino acid N-terminal hevein domain also appears in several plant proteins such as wheat germ agglutinin, endochitinases, and potato wound inducing proteins, while the C-terminal fragment is related to barley seed proteins which play a role in plant defense.^{11,12} Hevein and prohevein, but not the C-terminal fragment of prohevein, are major allergens in adult HCW.^{17,24} β -1,3-Glucanase (Hev b2) is a 36-kD, IgE binding protein that exists as several isozymes and is not a major allergen.¹⁷ Hevamine is a 29.5-kD, bifunctional enzyme with both lysozyme and chitinase activity. Hevamine is known to exist as two isoforms.¹⁷ This protein does not have an official allergen designation because it is infrequently recognized by the sera of LSP.¹⁷ Beezhold et al¹⁶ purified a 46-kD allergen, also known as Hev b7, from natural latex and found significant sequence homology to patatin, a potato protein. Hev b7 is recognized by IgE antibodies in 25% of sera from HCW.^{16,25} A 27-kD polypeptide, which is recognized by IgE antibodies in the sera of latex-sensitized SBP, was partially sequenced by Alenius et al and exhibits REF homology (Table 1).^{26,27} Lu et al and Alenius et al described a 23-kD latex allergen with REF homology as a major latex antigen in latex-sensitive SBP (Table 1).^{26,28,29} Vallier et al³⁰ demonstrated the presence of profilin (Hev b12) in NRL. Profilins is a family of functional plant pan-allergens, which play an important role in crossreactivity between food and pollen allergens.^{31,32} Profilin, however, does not appear to be a major allergen in latex sensitivity.³⁰ All of the above identifications were achieved by conventional protein chemistry and biochemical procedures. Recently, Akasawa et al³³ isolated and sequenced the cDNA coding for Hev b5 from a *H. brasiliensis* cDNA library. This protein has 50% homology to an acidic kiwi fruit allergen, termed

Table 1. Complete or Partially Sequenced Latex Antigens

Name/Homology	Nomenclature	Molecular Weight, kD	Cell Local*	Ref.
REF	Hev b1	14.5	P	20,21
β -1,3 glucanase	Hev b2	36	B	11,12,17
REF-like particle prot	Hev b3	23	P	35
Microhelix prot. complex	Hev b4	50-57 R* 100-110 NR*	B	33,34
	Hev b5	16	C	33,34
Prohevein	Hev b6.01	21	B	17,22,23
Hevein	Hev b6.02	4.7	B, C	22,23
Prohevein C-domain	Hev b6.03	14	B	22,23
Patatin-like	Hev b7	46	C	16,25
Profilin	Hev b12	15.7	C, P	30
REF homol		27	P	26,27
Endochitinase precursor		29	C	11,12
Proteosome component		26	C	11,12
Triosephosphate isomerase		29	C	11,12
Triosephosphate isomerase		35	C	11,12
Superoxide dismutase homol		24.5	C	11,12
Enolase homol		51	C	11,12

P = particle, B = B-serum, C = C-serum, R = reduced, and NR = non-reduced.

pk1W1505.³³ Similar results were obtained by Slater et al,³⁴ who also demonstrated that Hev b5 is a major allergen in HCW. Above approaches have now also been supplemented by 2D separation and microsequencing of the individual polypeptide spots.^{11,12} Posch et al^{11,12} have identified several new antigens in C-serum and latex particles with this approach (Table 1). Altogether, the above methods have now yielded complete or partial amino acid sequence for more than 20 different latex antigens (Table 1). The localization of these antigens in latex particles, C-serum, and lutoids are listed in Table 1.

Due to the availability of amino acid sequence, genes for a number of latex antigens have been cloned, and have been used to construct recombinant latex antigens.^{9,17,34} One approach has been to link the cDNA sequence of the latex gene to the cDNA of a fusion protein, eg, maltose binding protein (MBP). Maltose binding protein can be used to purify those fusion proteins by affinity chromatography. This approach allows the production of latex antigens in large quantities, as has been demonstrated for the production of recombinant REF, Hev b5, the N-

terminal domain of hevein (4.7 kD), the C-terminal domain of hevein (14 kD) and prohevein (20 kD).^{9,17,34}

The availability of purified and recombinant antigens has facilitated the study of IgE-mediated immune reactivity to individual antigens in the sera of LSP. This has led to the identification of a number of "major" latex antigens (see section on major allergens). Recombinant proteins were also used to raise polyvalent antisera in rabbits and to produce monoclonal antibodies (mAb) in mice.^{11,28,29,35-38} The availability of monoclonal antibodies has allowed the identification of individual antigens in latex glove extracts, and has facilitated studies on the effect of ammonification, heating, and storage on the degradation of those antigens during manufacturing.^{28,29} These antibodies are also useful in following large scale purification of NRL or glove antigens. In the future, we expect that many mAb will be employed in immunoassays to measure the content of specific latex allergens on finished latex products. This will be especially helpful for identifying "major latex antigens" on finished products, eg, gloves.

MAJOR LATEX ALLERGENS HAVE BEEN IDENTIFIED, AND HAVE DELINEATED RESPONSE DIFFERENCES IN LATEX-SENSITIVE ADULTS VERSUS CHILDREN

Rubber elongation factor or Hev b1, the first identified latex antigen, was reported to act as a "major antigen" by Czuppon et al.²⁰ For the purpose of this communication a major antigen is defined as a peptide to which >50% of people in a latex-sensitive population respond by producing IgE antibodies. Later studies using immunoblotting instead of ELISA, called Czuppon's data into question,¹⁴ and the study was repeated in a larger cohort.³⁹ It was demonstrated that the prevalences of anti-Hev b1 antibodies were 52.3% and 81%, respectively, in HCW and children with SB.³⁹ This confirms that Hev b1 is indeed a major allergen.³⁹ Further, enzyme allergosorbent inhibition suggests that Hev b1 may be the unique sensitizer in 45% of latex-sensitive SB patients.³⁹

In addition to REF, hevein and prohevein appear to act as major allergens in >75% of HCW or LSP (Table 2).^{17,24,40} Hevein represents the 4.7 kD N-terminal domain of its 20-kD precursor, prohevein, which is derived from B-serum.^{17,22} The major allergenic epitopes in prohevein are localized in its N-terminal domain, and it is

therefore not surprising that the C-terminal domain of prohevein infrequently acts as an allergen in LSP.¹⁷ Hev b5 has recently been identified as a major allergen.³⁴ Slater et al have identified a response in 95% of adult HCW,³⁴ while Akasawa et al have identified a response to Hev b5 in 52% of LSP.³³ Lu et al²⁸ identified a 23-kD, REF homologue as an IgE-binding allergen which is recognized by the sera of 76% to 80% of SBP. In contrast, only 20% of HCW responded to this antigen.²⁸ Akasawa et al¹⁴ identified 18 and 25.6-kD, C-serum proteins that reacted with the sera of >50% of LSP in immunoblots, but called into question the concept of major allergens due to the high degree of variability in the allergen recognition profile from individual to individual. Similarly, Tomazic et al⁴¹ found variability in the allergen recognition profile when a panel of human sera were evaluated against protein extracts from non-ammoniated latex. The concept of major latex allergens appears to be generally accepted, and it is possible that additional major allergens will be identified in future.

In contrast to major allergens, a number of latex allergens have been defined which are less frequently recognized by latex-sensitive sera. For instance, hevamine is not a major allergen¹⁷ while β -1,3-glucanase¹⁷ and an incompletely characterized 46-kD pro-

tein only reacts with 20% of LSP sera.^{16,17}

A critical question is whether reactivity to a particular latex allergen or group of latex allergens can distinguish clinically recognizable latex allergic subsets? Some evidence exist for differences in the response pattern of SBP and adult HCW to latex particle proteins. Yeang et al³⁷ found that two latex particle proteins, REF (Hev b1) and Hev b3, reacted with IgE from latex-sensitive SBP but not adult patients. These data need to be compared, however, to that of Chen et al²⁴ who found that although there is a high response rate (80%) to Hev b1 in SBP, 52.3% of HCW actually do mount an IgE response. Alenius et al²⁷ found a high rate of reactivity to 14 and 27-kD, NRL proteins in children with SB.²⁷ Further, the presence of IgE antibodies to these allergens may indicate a more severe clinical response to latex. The 14-kD protein may be identical to Hev b1 but was not characterized as such by these authors.²⁷ In later studies, the 27-kD protein was partially sequenced and shown to have REF homology.²⁶ In yet another study, the same group found that this 27-kD protein, which presents as three isoelectric variants, is included in a cluster of 11 latex antigens that may define a more severe clinical SB subset, including children with anaphylactic reactions to latex.¹³ These data need to be independently confirmed, however, since the occurrence of anaphylaxis was documented in the US but not in Scandinavian children.²⁷ None of seven HCW tested reacted to this antigen cluster.¹³ Lu et al²⁸ identified a 23-kD glove allergen that was recognized by sera by the majority of latex-sensitive SB patients, compared with only one of five HCW tested.²⁸ This antigen is apparently generated by NRL ammonification, and is found in glove extracts as well as in the glove substance. These authors postulated that ammonia leads to the precipitation of the 23-kD protein, leading to its incorporation into the glove substance along with rubber particles.²⁹ Taken together, these results are suggestive but not conclusive for a high

Table 2. Major Latex Allergens

Antigen	Studied by	Rate*	Reference
Hevein/prohevein	Palosio et al Baur et al	78% LSP	40
		75% HCW	24
		27% SBP	24
		81% LSP	24
	Alenius et al	83% LSP	17
		75% LSP	17
REF (Hev b1)	Czuppon et al	100% SBP	20
	Akasawa et al	22% LSP	14
	Alenius et al	92% SBP	27
	Chen et al	51% SBP	39
		52% HCW	39
REF-like 23 kD particle prot	Lu et al	76% SBP	28
Hev b5	Slater et al	95% HCW	34
	Akasawa et al	52% LSP	33

* HCW = health care worker, SBP = spina bifida patient, and LSP = latex sensitive people.

rate of reactivity to latex particle antigens in SB compared with adult subjects. This does not exclude, however, that SB patients react to C-serum or lutoid allergens. While the exact reasons for the differences in the allergen recognition profile of adults and SB are not known, it has been postulated that age, frequency of surgical intervention, genetic predisposition, atopic status, and route of exposure may play a role in the putative high rate of reactivity to latex in SB patients.⁴² Yeang et al³⁷ have postulated that since rubber particles are water insoluble, they do not transfer from the glove to the skin in HCW, but could be transferred to body cavity mucosal membranes of SB patients which comes into direct contact with catheter or surgeons gloves. This hypothesis needs to be proven.

A key question is whether among a group of latex-sensitive individuals, antigen-specific responses can depict those who are more likely to develop an illness or a more severe clinical response. As discussed above, SBP who react with REF and the 27-kD antigen appear to be at an increased risk for anaphylactic reactions during latex exposure.^{13,26,27} The number of cases on which this assumption is based are small and this work needs to be independently confirmed.²⁷ Utilizing ammoniated latex and an immunoblotting protocol for IgE reactivity, Beezhold et al¹⁶ have described a correlation between heterogeneous diffuse reactivity with ammoniated latex polypeptides and clinically severe responses. Again, the number of subjects in that study are limited and requires independent confirmation. Clearly more work is required to determine the clinical importance of reactions to individual latex allergens.

NUMBER OF IgE-BINDING POLYPEPTIDES IN FINISHED LATEX PRODUCTS ARE LIMITED COMPARED WITH THE NRL ANTIGEN PROFILE

Some of the NRL allergens have been shown to be present on finished latex products such as gloves. Lu et al²⁰ have identified REF on latex gloves and in

glove powder. Lu et al^{28,29} have used mAb reagents to the 23-kD antigen to examine finished latex products. They found reactivity with 12 of 16 products tested, including all gloves used in that study.²⁹ Alenius et al²² purified 6 hydrophilic polypeptides with sequence identity to hevein from surgical gloves. Further, purified hevein inhibited 72% of the IgE reactivity to the immobilized glove allergen, indicating that hevein is likely an important allergen on latex gloves.²²

In contrast to NRL, which contains >35 IgE-binding polypeptides, finished latex products and gloves appear to contain a limited number of allergenic peptides.^{15,24,41,43-47} Most studies using immunoblotting to look at the number and size of IgE-binding peptides on finished products, report limited allergen profiles.^{41,44,45,47} While the number of allergenic peptides varied from 0 to 10 in different studies, one study demonstrated an average of 2 to 4 allergenic peptides per glove type.⁴¹ Most of these polypeptides electrophoresed in the 6.5 to 50 kD range, which is compatible with the idea that degradation of NRL peptides during the manufacturing process yields smaller proteins. A significant exception to these studies, is a study in which aerolized glove powder was collected onto filters placed in work sites or on the body of HCW.⁴⁵ When these filters were analyzed by immunoblotting, the allergens varied from 70 to 100 kD in size.⁴⁵ The reasons for differences in size of latex allergens from aqueous extracts versus aeroallergens are unclear, and requires further work.

As for NRL antigens, there was heterogeneity in the ability of individual sera to recognize allergen extracts made from gloves.⁴¹ There was also a considerable variation in the total protein and allergen content of different latex glove brands.⁴⁶ Further, the amounts of protein eluting from the gloves did not always correlate with the number or abundance of IgE-binding peptides on gloves, indicating that total protein content is a poor parameter for allergenicity. While antibodies to specific polypeptides should theo-

retically be useful for determining specific allergen content, the allergen make-up of most commercial latex products is still unknown.

A crucial question is whether the antigenic determinants on finished products are different or similar to NRL determinants. Since epitope mapping for latex allergens has only commenced fairly recently, this question cannot be fully answered at this stage. Arguments for the generation of neo-antigens on finished latex products have been made by Tomazic et al⁴¹ who showed the appearance of new immunoblotting bands in glove extracts compared with NRL. Similarly, immunoblotting inhibition studies by Akasawa et al⁴⁴ demonstrated that NRL incompletely inhibited IgE reactivity to ammoniated latex or glove antigens. This suggests the existence of new epitopes on ammoniated latex and glove antigens.

IMPORTANCE OF SPECIFIC LATEX ALLERGENS IN THE STUDY OF CROSSREACTIVITY WITH FOOD AND AEROALLERGENS

It is well recognized that rubber latex allergy is associated with clinical or serologic crossreactivity to food allergens.¹⁻³ Well known crossreactive fruits include avocado, banana, chestnut, kiwi, papaya, potato, and peaches. There is also serologic crossreactivity between latex and aeroallergens, eg, grass and weed pollen.⁴⁷ The issue of latex crossreactivity raises several important questions, namely: (1) What is the molecular basis for crossreactivity, eg, sharing of epitopes?; (2) What is the primary sensitizing antigen?; and (3) What is the relative contribution of latex or crossreactive antigens in causing symptoms?

While answers to the above questions are still pending, it is clear that the identification of latex epitopes will pave the way towards providing some of these answers. The potential value of epitope mapping is illustrated by studies of crossreactivity between REF (Hev b1) and papain.⁴⁸ Baur et al⁴⁸ looked at crossreactivity of IgE sera

which recognize potentially homologous epitopes in latex and papain allergens. This study was performed with the sera of 36 latex-exposed subjects and 22 papain workers.⁴⁸ Briefly, 50% of papain-sensitized individuals reacted with latex in a CAP immunoassay.⁴⁸ Using sera from individual patients sensitized to both antigens, reciprocal inhibition experiments showed that papain incompletely (<31%) inhibited IgE binding to immobilized latex antigen, while latex protein inhibited IgE binding to papain by 91%.⁴⁸ This shows that although papain epitopes are present in latex proteins, the major latex-specific epitopes differ from papain epitopes. It is interesting that while Hev b1 and papain contain 5 identical trimers and 2 identical tetramers in their primary sequences,³⁶ the major IgE-binding epitopes in Hev

b1 are actually composed of 13 to 16 amino acid domains. One of these epitopes at amino acids position 31 to 64 contains two homologous tetramers and one homologous trimer, while the other major Hev b1 epitope at amino acids 121 to 137 is devoid of these sequences.³⁶ It is possible, therefore, that while the major Hev b1 epitope at 31 to 64 cross-reacts with papain, the epitope at position 121 to 137 is latex-specific, and not sensitive to papain inhibition. If this hypothesis is correct, it should theoretically be possible to use short polypeptide sequences, representative of each Hev b1 epitope to test IgE reactivity in latex-sensitive and papain-sensitive people. One possible scenario is that people who are primarily papain sensitive will interact with one but not the other epitope, while latex-sensitive people may rec-

ognize both epitopes. An extrapolation of this approach to other allergens, may help to differentiate between food allergic and latex-allergic individuals.

A brief summary of crossreactivities between specific latex antigens and food allergens appear in Table 3. It is noteworthy that latex antigens are often homologous to plant enzymes or plant proteins which play a defense role, eg, protecting against insects (eg, chitinase), bacteria or fungi (eg, lysozyme). The hevein sequence also reveals 4 microdomains that are homologous to domains in the type IV pathogenesis-related plant protein family.²³ These include proteins found in tobacco, soybean, and potato. Latex allergens with enzymatic potential include a 29-kD chitinase homologue, a 26-kD proteosome-like protein, a 24.5-kD homologue of superoxide dismutase, 29 and 35 kD homologues of triose-phosphate isomerase, a 51-kD homologue of enolase, and a 36-kD β -1,3-glucanase (Hev b2) (Table 3).¹¹ The importance of the homology between latex proteins and plant enzymes are that these enzymes are widely distributed throughout the plant kingdom and may form the basis for crossreactivity between latex and a variety of food substances.

In addition to sharing of epitopes at the amino acid level, crossreactivity between latex and other plant allergens may also involve carbohydrate determinants. In this regard, it is well known that N-linked carbohydrate groups on food and grass pollen can induce crossreactive IgE antibodies.^{52,53} For instance, up to a third of grass pollen-sensitive subjects exhibit significant levels of peanut IgE antibodies in the RAST, without clinical or prick skin test reactivity to peanut antigen.⁵³ Further, NRL, grass pollen and weed pollen share periodate-sensitive IgE epitopes, indicating that carbohydrate determinants play a role in serologic and possibly also clinical cross-reactivity between these allergens.⁴⁷ In particular, weed and timothy grass pollen extracts strongly inhibited IgE binding to NRL antigens in immunoblotting and immunoassays.⁴⁷ In con-

Table 3. Crossreactivity of Specific Latex Allergens With Foods

1. Hev b5 ³⁴ :	46% homology to Kiwi fruit pK1W1501, protein 38% homology to a stolon tip protein (potato) contains 5 identical trimers and 2 identical tetramers as papain
2. Hev b1 ⁴⁸ :	
3. Hevamine:	
a. Jekel et al ⁴⁹	Hevamine shows 60% homology to cucumber chitinase and 95% homology to chitinase/lysozyme of <i>Parthenocissus quinoquofolia</i> .
b. Delbourg et al ⁵⁰	Hevamine and banana proteins of 33 and 37-kD share common epitopes (immunoblot inhibition)
c. Lavaud et al ⁵¹	Hevamine share common epitopes with 30-kD banana and avocado antigens (immunoblot inhibition)
4. Hevein epitope mapping ²³ :	4 of 6 IgE binding epitopes had homology to type IV pathogenesis-related plant protein family, eg: WIN 1/WIN 2 potato CBP 20 tobacco PRP 4A tobacco GLY M soybean
5. Series of plant enzymes in latex sap revealed by 2DE and microsequencing. Potential allergens ¹¹ :	
29 kD	chitinase/lysozyme
26 kD	proteosome
29.35 kD	triose phosphate isomerases
24.5 kD	superoxide dismutase
51 kD	enolase
6. Profilin ⁵⁰ :	IgE-binding component in cytosolic fraction of NRL reacted with 35/36 sera containing IgE to ragweed-profilin. Profilin present in banana extract

trast, latex extracts did not substantially interfere in IgE binding to timothy grass pollen extracts.⁴⁷ These findings suggest that there may be two classes of latex-allergic individuals: One group may be preferentially sensitized to pollen and other plant products, and will only respond to latex on an incidental basis, while the second group may be originally sensitized to latex and may be primarily latex responsive.⁴⁷ If this hypothesis is correct, it will have important implications for diagnosing latex allergy. Further, if the serologic crossreactivity between latex, food, and aeroallergens is as extensive as the serologic crossreactivity between peanut and grass pollen antigens,⁵³ it is possible that immunoassays may be overestimating the true prevalence of clinical latex reactivity. While it does not exclude the use of serologic assays for determining the epidemiology of sensitization, a sensitive and specific skin test is superior for diagnosing clinical latex reactivity.⁵⁴ Until such a skin test reagent is FDA approved and available for testing, it may be prudent to reserve judgment about the primary source of sensitization in people with crossreactive antibodies to latex, foods, and aeroallergens. The mere fact that the prevalence of latex sensitivity is increased in atopic people, suggests that a significant number of so-called latex allergic people may in fact be food allergic individuals, or people who suffer from pollen allergy.^{4,5}

IgE EPITOPE MAPPING OF PURIFIED LATEX ANTIGENS

Epitope mapping is a technique in which a series of overlapping peptides representative of the entire primary sequence is synthesized and then individually tested for reactivity with antibodies to that antigen. The ultimate goal is to define the epitopes to which the antibodies react. Knowledge about the epitope distribution in an allergen is helpful in studies of crossreactivity, understanding the complexity of the immune response to that allergen, understanding the genetics of the immune response to that allergen and vaccine

development. To date, the IgE-binding epitopes of the Hev b1 and hevein have been mapped.^{23,36,55} There are, however, differences in the Hev b1 epitopes recognized by individual latex-sensitive sera. These differences may represent variations in allergen presentation, eg, the role of the MHC, or the role of other immune response genes.

HLA CLASS II ALLELES PLAY A ROLE IN THE IgE RESPONSE TO HEVEIN, AND SIGNIFIES THE ROLE OF ANTIGEN PRESENTING CELLS AND T CELLS IN THE IMMEDIATE HYPERSENSITIVITY RESPONSE TO LATEX ANTIGENS

It is well known that for a number of aeroallergens there is an association of select MHC-II genes.⁵⁶ In ragweed hypersensitivity, for instance, Amb a5 and Amb t5 responsiveness are strongly associated with HLA-DR2, while Amb a6 responsiveness is associated with HLA-DR5.⁵⁵ Rihs et al⁵⁷ have investigated the relationship between HLA class II alleles and the IgE-specific immune response to the 4.7 kD hevein polypeptide. They compared 51 latex-sensitized individuals, with positive or negative hevein responses, to 90 healthy controls. Their approach was a polymerase chain reaction (PCR)-based technique which amplifies the second exon in the HLA-DRB1 and HLA-DQB1 genes. Briefly, there was a statistically significant increase in DR4 and DQ8 expression in hevein-positive compared with hevein-negative, latex-sensitive individuals. There was also increased expression of a combination of both MHC-II markers in hevein-positive compared with control subjects. Another interesting finding was that in the latex-sensitive, hevein-negative group there was a statistically significant increase of DR7 versus a control group.⁵⁷ This suggests that DR7 may be involved in protection against hevein allergy. In contrast, the frequency of DR7, but not other class II determinants, was increased in SBP with latex as well as Hev b1-IgE responsiveness.⁵⁸

While immediate hypersensitivity reactions to latex is dependent on IgE, it needs to be considered that these antibodies are produced in B-lymphocytes with the cooperation of antigen-presenting cells and T-lymphocytes. Antigen-presenting cells such as macrophages process the allergen and display epitopes on the cell surface in association with MHC-II molecules. T-cells, which recognize the presented antigen, induce B-cell activation by direct interaction as well as through the secretion of cytokines (eg, IL-4); these activation signals play a role in IgE isotype switching and B-cell differentiation. Epitope analysis for determining MHC-II interactive sites on Hev b1 has revealed the presence of a HLA-DR4Dwx4 binding motif.⁵⁹ In addition, T-cells may mediate a delayed type hypersensitivity response (DTH) to latex antigens independent of B-cell involvement. In fact, delayed type hypersensitivity responses to rubber products were at one stage considered more prevalent than IgE-mediated reactions, but that situation has changed with improvements in the manufacturing process. Delayed type hypersensitivity responses are directed towards preservatives and chemicals used in the manufacturing process.

Two groups have studied cellular immune responses to purified latex allergens using lymphocyte proliferation assays.^{28,60} Only latex-exposed subjects responded to latex antigens in these assays. There was no correlation between latex-specific IgE levels and latex-induced lymphocyte proliferation responses in the studies using Hev b1 as antigen.⁶⁰ Lu et al,²⁸ however, found that the cellular response to the 23-kD, REF-like protein correlates with IgE production in SBP, suggesting that in this setting, there may be a correlation between IgE and cellular responsiveness.²⁸ Only small numbers of patients were studied, however.

CONCLUSION

Natural rubber latex contains a number of allergens localized in C-serum, B-serum and rubber particles. More than 20 of these allergens have now been

sequenced, and those data have been used to define epitopes and to develop recombinant antigens and mAb. Although there is considerable variation in the allergen recognition profile of individual patients, a limited number of major allergens have been identified. These antigens and their epitopes may help to develop more specific diagnostic tests which can distinguish between primary and crossreactive latex allergy. Recombinant antigens and mAb may also help in development of allergen-specific assays which can be used to quantitate specific antigens on finished products and in the environment. Highly purified allergens may also be helpful in development of a vaccine which can be used to desensitize latex-sensitive individuals.

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CME Examination

Identification No 008-011

Questions 1–20, Nel A and Gjujuluva C. 1998;81:388–398.

CME Test Questions (mark all correct answers for each question)

1. IgE inducing latex allergens may consist of:
 - a. Polypeptides
 - b. Complex carbohydrates
 - c. Glycoproteins
 - d. Plant enzymes
 - e. Manufacturing chemicals
2. Natural rubber latex represents:
 - a. The sap from *H. brasiliensis*
 - b. The gum from *H. brasiliensis*
 - c. The cytosol from specialized *H. brasiliensis* cells
 - d. The bark from the *H. brasiliensis* tree
 - e. An extract from *H. brasiliensis*
3. Latex proteins are derived from
 - a. C-serum
 - b. Mitochondria
 - c. Cytosol
 - d. Nucleoplasm
 - e. Luteoids
4. The number of individual polypeptides detectable in natural rubber latex by 2D electrophoresis and silver staining amount to:
 - a. >100,000
 - b. >10,000
 - c. >1,000
 - d. >100
 - e. >10
5. The biological function(s) of natural rubber latex from *H. brasiliensis* include:
 - a. Role as a sealant
 - b. Protection against insects
 - c. A growth medium
 - d. Bark formation
 - e. A foliage agent
6. Major latex allergens include:
 - a. Hevamine
 - b. Hev b2 (β -1, 3 glucanase)
 - c. Prohevein N-terminal domain
 - d. Prohevein C-terminal domain
 - e. Hev b5
7. Differences in the immunoreactivity to latex in sensitized spina bifida (SB) vs adult patients is/are:
 - a. A higher overall propensity of SBP to react to latex particle antigens
 - b. Reaction with a cluster of 11 allergens, including 14 and 27 kD proteins, in SBP
 - c. Reaction with a cluster of 11 allergens, including 14 and 27 kD proteins, in adults
 - d. Absence of a response to C-serum and luteoid antigens in SBP
 - e. Lack of a response to latex particle proteins in adults
8. Latex antigens on finished latex products:
 - a. Are derived from NRL polypeptides which may be modified to include new antigenic determinants
 - b. Are only found in the cornstarch powder on the glove
 - c. Have been well characterized on most finished products and include an expanded profile of allergens
 - d. Are limited in diversity for most latex gloves tested to date
 - e. Include hevein, REF and a 23-kD REF-like protein
9. IgE response profiles to latex allergens in a randomly selected latex-sensitive population:
 - a. Are relatively homogenous with little variation from individual to individual because these responses are mostly directed towards major latex antigens
 - b. Are quite heterogeneous in spite of the existence of major latex antigens
 - c. Clearly segregate primary latex sensitive people from people with crossreactive antibodies, eg, to food
 - d. Partially depends on the involvement of immune response genes such as HLA class II antigens
 - e. May depend on the route of sensitization, e.g. spina bifida patients vs adult HCW
10. Serologic crossreactivity with latex antigens:
 - a. Papain
 - b. Potato
 - c. Tobacco proteins
 - d. Oranges
 - e. Timothy grass
11. The molecular basis for cross-reactivity between latex, food and aeroallergens is likely premised on:
 - a. Sharing of epitopes along the primary amino acid sequence
 - b. Sharing of related carbohydrate groups, such as are found on glycoproteins
 - c. Sharing of evolutionary conserved biologic functions, eg, participation in plant defenses or enzymatic activity
 - d. Sharing of epitopes which interact with the T-cell antigen receptor
 - e. The atopic potential of the individual
12. IgE epitope mapping has been completed for the following latex antigens:
 - a. Hev b1 (REF)
 - b. Hevein
 - c. Patatin
 - d. Profilin
 - e. Enolase

13. Regarding hevein and its precursor:
 - a. It is derived from B-serum
 - b. It is not present in C-serum
 - c. Hevein represents the N-terminal 15-kD domain of its 20-kD precursor, pro-hevein
 - d. Most of the antigenicity of prohevein is concentrated in its N-terminal domain
 - e. It is a major latex antigen
14. Regarding REF (rubber elongation factor):
 - a. It is a rubber particle protein
 - b. MW 36 kD
 - c. Plays an active role in agglutination of rubber particles
 - d. It is a major allergen in children with spina bifida but not in adults
 - e. Antigen nomenclature = Hev b6
15. Regarding Hev b5
 - a. It's alternative name is endochitinase
 - b. Rubber particle protein
 - c. Acts as a major allergen
 - d. Gene has been cloned and used to generate a MBP fusion protein
 - e. MW 16 kD
16. Factors which may be involved in sensitization to latex allergens in spina bifida patients:
 - a. Age of exposure
 - b. Atopic status
 - c. Number and frequency of surgical intervention
 - d. Exposure to household products
 - e. Exposure to surgical gloves and indwelling catheters
17. Protein content of surgical gloves:
 - a. Is a poor predictor of allergenicity
 - b. Correlates with the number and amounts of allergens present
 - c. Is largely representative of NRL proteins
 - d. Is largely confined to the glove powder
 - e. Is a parameter that can be used to distinguish between allergenic and hypoallergenic gloves
18. Exploration of MHC class II associations in people with latex allergy:
 - a. Is wasteful since MHC-II is not important in humoral (IgE) responses
 - b. Has been proven for most major allergens
 - c. Is a logical extension of the concept that there is T-cell help for B-cell mediated IgE production
 - d. Has yielded a positive association for IgE mediated reactions to hevein
19. Cellular immune responses to latex allergens
 - a. Are clinically non-relevant
 - b. Have not been shown to occur to date
 - c. Have been shown for Hev b1, in which case it has excellent correlation with IgE levels to latex allergens
 - d. Requires processing of latex allergens by antigen presenting cells
 - e. Involves T-helper lymphocyte responses, which require MHC II/T-cell antigen receptor/peptide interactions
20. Clinical importance of obtaining latex allergen sequence data:
 - a. Development of recombinant peptides which can be used to discriminate between latex-specific and crossreactive IgE
 - b. Devising more specific and sensitive serological tests for latex sensitization
 - c. Development of a latex vaccine
 - d. Determining presence of specific allergens on finished latex products
 - e. Determine the exact number of latex allergens

Answers to CME examination—Annals of Allergy, Asthma & Immunology (Identification No 008-009) Spach DH and D Black: Antibiotic resistance in community-acquired respiratory tract infections: current issues. *Ann Allergy Asthma Immunol* 1998;81:293–303.

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| 2. d | 7. a | 12. d | 17. a |
| 3. d | 8. b | 13. a | 18. d |
| 4. a | 9. c | 14. d | 19. b |
| 5. c | 10. c | 15. a | 20. b |

Answers to CME examination—Annals of Allergy, Asthma & Immunology (Identification No 008-010) Scharf MB and Cohen AP: Diagnostic and treatment implications of nasal obstruction in snoring and obstructive sleep apnea. *Ann Allergy Asthma Immunol* 1998;81:279–290.

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| 1. c | 7. e | 13. e | 19. e | 25. e |
| 2. d | 8. e | 14. c | 20. c | 26. c |
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| 4. a | 10. c | 16. b | 22. e | |
| 5. d | 11. d | 17. c | 23. a | |
| 6. c | 12. d | 18. c | 24. c | |