

STATE OF THE ART REVIEW

Latex allergy: a model for therapy

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Clinical and
Experimental
Allergy

Summary

Allergy to natural rubber latex products emerged as an important clinical condition following an increase in the use of latex gloves for barrier protection in the early 1980s. In addition to latex glove users, other high-risk groups with different latex exposure include spina bifida patients and others with multiple surgical procedures. Subjects with fruit and vegetable allergy are also at risk due to cross-reactive allergens. Following the significant advances in the identification and characterization of common aeroallergens, latex allergy was well placed to become an excellent model of therapy. Awareness of latex allergy and modes of sensitization enabled epidemiological studies to inform allergen avoidance initiatives, substantially reducing inadvertent exposure in major hospitals in Western countries. Spina bifida is often identified *in utero* or soon after birth, allowing vigorous latex allergen avoidance with enhanced efficacy of primary prevention. However, changing demographics of latex allergy and technological revolution in countries such as China and India are predicted to unleash a second wave of latex allergy reemphasizing the incentive for improved manufacturing procedures for latex products. The desirable high tensile strength and elasticity of natural rubber latex have made the commercial identification of good alternatives very difficult but this would also be attractive for primary prevention. In addition, an effective specific immunotherapy regimen would be valuable for selected high-risk atopic individuals. Current subcutaneous and sublingual immunotherapy schedules have been tested for treatment of latex allergy with evidence of efficacy but the risks of adverse events are high. For such potent allergens as latex, hypoallergenic but T cell-reactive preparations are required for clinical use. Identification of allergenic components of latex products, with generation of monoclonal antibodies and recombinant allergens, allowed sequence determination and mapping of T cell and B cell epitopes. Together, these reagents and data facilitated improved diagnostics and investigation of novel-specific therapeutics. Potential hypoallergenic latex preparations identified include modified non-IgE-reactive allergen molecules and short T cell epitope peptides. The co-administration of adjunct therapies such as anti-IgE or corticosteroids and of appropriate adjuvants for induction of regulatory T cell response offers promise for clinically effective, safe latex-specific vaccines.

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Introduction

Latex allergy emerged relatively recently as an important medical condition, causing significant morbidity due to rhinoconjunctivitis, urticaria and food allergy, asthma and anaphylaxis. The condition was poorly recognized until there was a dramatic increase in reported cases associated with the burgeoning use of latex gloves for barrier protection against human immunodeficiency virus (HIV) and hepatitis infection among healthcare workers (HCW) in the 1980s. The clinical importance of latex

allergy was flagged by cases of intraoperative anaphylaxis and several high-risk groups were identified. With a pressing need to identify the allergenic components of natural rubber latex products to minimize allergen exposure and to develop specific diagnostics and treatments, latex allergy became a model for therapy. Compared with the relatively slow evolution of knowledge on common aeroallergens such as grass pollens and dust mites over several decades, the progress in latex allergen identification and characterization of immunoreactivity was rapid due to the existing sophisticated technology and

Table 1. Latex allergy risk factors

Risk factor	Detail	References
Occupation	Healthcare workers, dentists, rubber plantation workers, food handlers, security personnel, greenhouse workers, construction workers, hairdressers, domestic workers	[8–10]
Multiple surgical operations		[12, 16–19]
Spina bifida		[11, 12, 15]
Atopy		[13, 20, 21]
Eczema		[14, 22]
Fruit and vegetable allergy	Banana, avocado, chestnut, kiwi fruit, papaya, mango, bell pepper, fig, tomato, celery, potato	[23, 24]
Genetic	IL-13 and IL-18 promoter polymorphisms; HLA-DQ8-DR4 (with Hev b 6.02-specific IgE)	[25, 26]

knowledge base. Nevertheless, latex allergy presented some unusual features and effective management remains challenging.

Latex allergy – evolution of an epidemic and beyond

Early isolated case reports of latex allergy were of contact urticaria due to exposure to a rubber dental prosthesis [1] and household latex gloves [2]. Following the introduction of universal precautions for minimization of HIV and hepatitis infection and an influx of high-protein, powdered latex gloves in the early 1980s to meet this demand, the number of reported cases of contact urticaria increased dramatically [3–5]. The reported clinical spectrum and severity of latex allergy widened with numerous reports of rhinoconjunctivitis, asthma and intraoperative anaphylaxis [6, 7]. Latex became recognized as a major cause of occupational asthma [8–10], and in addition to occupation, spina bifida, multiple surgical procedures, atopy and eczema were established as risk factors for developing latex allergy [11–15] (Table 1). Patients with primary fruit and vegetable allergy were also observed to be at a higher risk of developing latex allergy [23, 24], now understood as being due to structural homologies between latex and food allergens. To date, evidence for genetic risk factors for latex allergy is sparse, with one study showing an association between IL-13 and IL-18 promoter polymorphisms and latex allergy [25] and another showing an association between HLA-DQ8 and the HLA-DQ8-DR4 haplotype and Hev b 6.02-specific IgE response [26].

Interestingly, the increased prevalence of latex allergy was accompanied by an increase in atopy, but undoubtedly the major factors influencing the dramatic increase in cases of latex allergy were the utilization of high-protein latex products, especially by the HCW population, and greater clinical awareness. Estimates of the prevalence of latex allergy have been confounded by substantial changes in latex exposure over the last few decades coupled with variation in the diagnostic approach. Methods to detect latex-specific IgE included *in vitro* assays and skin prick testing (SPT), and latex allergen target preparations for these tests ranged from latex glove eluates to standardized reagents [27]. Some studies used challenge testing, which usually involves the blind application of a latex glove on a wetted finger and then hand, with a non-latex glove as a control [28]. The high anaphylactic potential of latex allergens means that a specific inhalation challenge is not commonly used in clinical practice but may be used safely in specialized challenge laboratories for research studies or for the diagnosis of occupational asthma due to latex allergy [29, 30]. Again, standardization of wear and challenge tests has been problematic due to variability of allergen content in test materials. Bousquet et al. performed a meta-analysis to determine the prevalence of latex allergy in HCW, restricting their analyses to studies performed up to 2003 and excluding studies where subjects used powder-free gloves and/or low-allergen gloves [31]. Overall, 4.3% of HCW had latex allergy and 6.9–7.8% had positive latex SPTs. In the general population, the prevalence of clinical latex allergy was found to be 1.37% and that of latex sensitization was 2.08% [31].

With the realization that powdered latex gloves were particularly potent sensitizers, there was pressure from the market for powder-free gloves. Glove donning powder was shown to adsorb proteins leached from the latex gloves during manufacture and use [32]. This, coupled with progress in identification of allergenic proteins of natural rubber latex, led to a revolution in latex glove manufacture and usage. Several studies in healthcare institutions demonstrated a decline in the prevalence of latex allergy over a relatively short period following the advent of powder-free and low-protein gloves (e.g. [33]), pointing to the importance of occupational health and safety intervention strategies.

Despite success in reducing the incidence of latex allergy among HCW latex glove users, other population groups remain at risk. Children with spina bifida have a particularly high rate of latex sensitization, with a prevalence of 37% reported in Australia [34], 40% in Europe [35] and 60% in the United States [36]. The experience of multiple surgical procedures exposes these children to a range of rubber products from an early age [37] and is a risk factor for latex allergy [11, 12, 15] (Table 1). Although efforts to reduce latex exposure during surgery have

Table 2. Defined latex allergens

Latex allergen	Protein name	Function	Size (kDa)	Allergen importance*	
				Latex glove users	Spina bifida
Hev b 1	Rubber elongation factor	Rubber biosynthesis	14.6 (forms a tetramer of 58 kDa)	Minor	Major
Hev b 2	β -1,3-glucanase	Anti-fungal	34–36	Minor	Minor
Hev b 3	Small rubber particle protein	Rubber biosynthesis	24	Minor	Major
Hev b 4	Component of the lutoid microhelix complex	Lecithinase and cyanogenic glucosidase	100–115 (53–55 and 57)	Minor	Minor
Hev b 5	Acidic protein	Unknown	16	Major	Major/minor
Hev b 6.01	Prohevein	Hevein precursor	20	Major	Major
Hev b 6.02	Hevein	Anti-fungal	4.7	Major	Major
Hev b 6.03	C-terminal fragment	Unknown	16	Minor	Minor
Hev b 7.01	Patatin homologue from B-serum	Esterase, rubber biosynthesis inhibitor	42	Minor	Minor
Hev b 7.02	Patatin homologue from C-serum	Esterase, rubber biosynthesis inhibitor	42	Minor	Minor
Hev b 8	Profilin	Cytoskeletal, actin inhibitor	14	Minor	Minor
Hev b 9	Enolase	Housekeeping enzyme	47.6	Minor	None
Hev b 10	Mn superoxide dismutase	Housekeeping enzyme	26	Minor	Minor
Hev b 11	Class I chitinase	Anti-fungal	33	Minor	No data
Hev b 12	Lipid transfer protein	Housekeeping enzyme	9.3	Minor	None
Hev b 13	Early nodule-specific protein homologue	Lipolytic esterase	43	Minor	Minor

*Major allergen is defined as having $\geq 50\%$ frequency of serum IgE reactivity for relevant latex-allergic subject group; major/minor indicates conflicting data.

reduced sensitization, especially to proteins of dipped latex products [38, 16], the frequent use of in-dwelling catheters may continue to expose these children to the latex proteins of solid rubber products.

Recently, there has been a paradigm shift of latex allergy from HCW to a range of other occupations including food handlers, security personnel, greenhouse workers, construction workers, hairdressers as well as domestic users [39–41]. The prevalence of latex allergy is increasing in Taiwan [42], Portugal [43] and Poland [44] and another epidemic of latex allergy is predicted in other such countries undergoing technological revolutions such as China and India.

Clearly, there is a need for accurate diagnosis and effective therapy for latex allergy. Position statements were developed by Australian, European and American allergy associations and international working parties defining criteria for clinical and laboratory diagnosis and management of latex-allergic diseases (e.g. BSACI [27]). Although education programmes and occupational and health safety guidelines have been introduced to minimize latex allergen exposure, it is estimated that approximately 40 000 medical and consumer products contain natural rubber latex. Barrier properties, elasticity and tensile strength of latex gloves remain superior to most synthetic alternatives. The challenge of improving latex allergen avoidance strategies and developing specific treatments requires detailed knowledge

of the allergenic components of latex products and of key factors that influence the development of adverse immune reactions to latex allergens.

The nature of latex allergens

As the latex allergy epidemic of the 1980s unfolded, there was pressure to develop reliable diagnostic methods and to define the clinically important allergenic components of latex precisely. Two-dimensional gel electrophoresis and microsequencing revealed over 200 polypeptides in natural rubber latex, of which 50–60 are immunoreactive [45, 46]. Over a period of only about 8 years, immunoassays using latex-allergic donor sera and SPT narrowed the important allergenic components of latex to a limited set and 13 latex proteins, designated Hev b 1 to Hev b 13, were officially registered by the International Union of Immunological Societies as latex allergens (Table 2; www.allergen.org; see reviews [47, 48]). Isoforms of some latex allergens have been identified (e.g. Hev b 7.01 and Hev b 7.02 [49]), and it is likely that further cloning studies will reveal additional complexity at this level. It is not clear why latex allergens can elicit such severe reactions, but the close proximity of IgE epitopes topographically may be one such factor. For example, repetitive linear IgE-binding epitopes have been demonstrated in Hev b 5, which has a relatively linear molecular

Table 3. Fruit and vegetable proteins with sequence homology to latex allergens

Latex allergen	Fruit/vegetable	Molecular entity	IgE cross-reactivity demonstrated	Clinically relevant cross-reactivity	References
Hev b 2	Bell pepper	l-Ascorbate peroxidase	Yes; predominant IgE reactivity with carbohydrate moiety	Unknown	[52]
	Olive	1,3- β -Glucanase (Ole e 9)			[53]
	Olive	Undefined (Ole e 10)			[54]
Hev b 5	Kiwi fruit	pKIWI501	No	Unknown	[55]
	Potato	Acidic protein			
	Sugar beet	Undefined			[56]
Hev b 6.02	Banana	Class I chitinases	Yes	Yes	[57, 58]
	Avocado				[59]
	Chestnut				[60, 61]
	Sweet pepper				[62]
Hev b 7	Potato	Patatin	Yes	Unclear	[49, 63–65]
	Tomato	Undefined			[66]
Hev b 8	Celery tuber	Profilins	Yes	Probable	[67]
	Banana				[68]
	Pineapple				
	Bell pepper				[52]
Hev b 12	Peach	Lipid transfer protein	Yes	No	[69]
	Cherry				
Hev b 13	Potato tuber	Patatin (carbohydrate moiety)	Yes	Unknown	[70]

conformation [50]. Intrinsic pro-inflammatory properties of latex allergens may also play a role [51]. The biological function of some but not all latex allergens has been determined. Hev b 2, Hev b 4, Hev b 6 and Hev b 10 are plant defence proteins and many latex allergens have enzymatic activity (Table 2), shown for other allergens to potentially promote allergenicity. Of potential significance for the latex-fruit syndrome, several latex allergens show sequence homology with fruit and vegetable proteins and serum IgE cross-reactivity has been demonstrated (Table 3). However, the clinical significance of all these cross-reactivities is not clear.

Despite the rapidity of latex allergen identification, consensus definition of the allergens of greatest clinical importance has been more problematic. Studies used different assay techniques and a variety of allergen preparations, both natural and recombinant. The ability to draw firm conclusions from many studies was compromised by small sample sizes and poor clinical characterization of subjects. However, patterns of immunoreactivity of latex allergens are emerging [47, 48]. For latex-allergic HCW, several studies have shown that Hev b 5 and Hev b 6.01/Hev b 6.02 are recognized at a high frequency [71–76], although more recent data from Finland show a lower frequency of IgE reactivity with Hev b 5 compared with Hev b 6 [51]. Earlier studies suggested that Hev b 2, Hev b 7 and Hev b 13 were also important allergens for latex glove users [71, 77, 78], but recent testing using highly purified allergen preparations refutes these findings [72, 70, 79]. In most studies, Hev b 1 and Hev b 3 are found to be major allergens for spina bifida

patients, consistent with frequent exposure to solid rubber products, but others report a high frequency of reactivity also with Hev b 5 and Hev b 6.01 [72, 77, 78].

The identification and molecular characterization of latex allergens (Table 2) and determination of their localization to different components of natural rubber latex (Fig. 1) suggest rational strategies for reduction of allergens during the manufacture of latex products and for specific treatments.

Therapy for latex allergy through allergen avoidance

The development of hypoallergenic latex products requires knowledge of the chemistry of latex manufacture and effects of processing steps on residual allergenicity. Rubber latex is obtained from the commercial rubber tree *Hevea brasiliensis* by making a half spiral cut into the bark of the tree. The yield of latex is improved by collection in the morning following an overnight build-up of pressure in the lactifers, and further strategies for improving latex productivity include selective breeding and hormone treatment [27]. The latter approaches, together with the frequent wounding of the tree during latex collection, are likely to increase the content of pathogenicity-related proteins such as hevein, chitinase and β -1,3-glucanase [82, 80]. Several of these proteins are important latex allergens (Table 2), pointing to measures that might be implemented in this first step of manufacture to reduce the allergenicity of latex products.

A source of variation in the allergenicity of latex products was found to be the time and temperature of

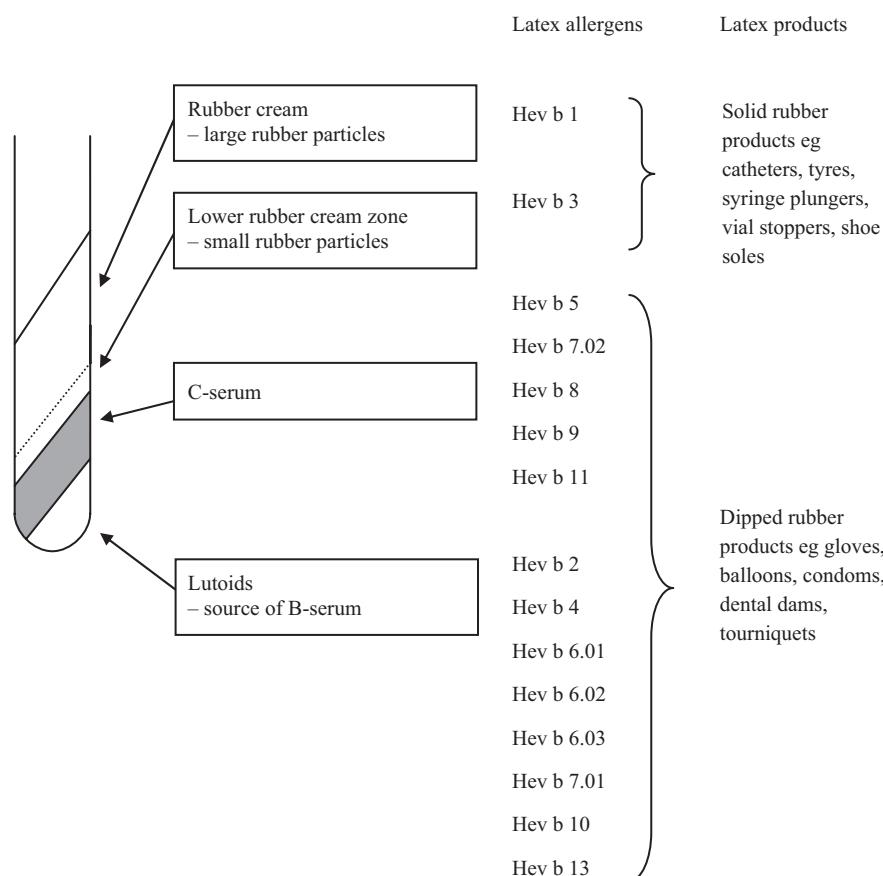


Fig. 1. Localization of latex allergens to natural rubber latex fractions. After centrifugation at $44\,000 \times g$ at 4°C for 1 h, natural rubber latex separates into three main fractions: upper – rubber particles; intermediate – aqueous phase (C-serum); and bottom – lutoids (release B-serum on rupture by repeated freeze-thawing, storage or 0.7% ammoniation). The latex allergens associated with each of these fractions are shown. The upper, rubber particle layer is used to make solid rubber products while dipped latex products are made from the lower fractions [80, 81].

latex storage before use in product manufacture. Latex collected in southeast Asia and west Africa and exported to Europe or the United States for latex product manufacture can take up to 6 weeks, with temperatures exceeding 40°C during sea transport. This results in increased protein degradation and thus lower allergenicity of products compared with those produced locally [83].

The tapped latex is either coagulated, washed, rolled and dried for manufacture of dry rubber products such as catheters, tyres, syringe plungers, vial stoppers and shoe soles, or stabilized by addition of 0.25% ammonia, aged and centrifuged to produce a concentrate for manufacture of dipped latex products such as gloves, balloons, condoms, dental dams and tourniquets [27]. Both processes may also involve treatment with a variety of chemicals depending on the product end use, and with vulcanizing agents and accelerators before vulcanization. Accelerators such as thiurams, carbamates and benzothiazoles may cause contact allergy [27, 84, 85] as can added phenols and cresols [86], but IgE-mediated latex allergy results from sensitization to latex proteins. The two manufacturing processes result in products with very different aller-

genicity and differential expression of allergenic proteins. Compared with dipped latex products, solid rubber products contain very low levels of latex proteins [87] and have relatively higher contents of Hev b 1 and Hev b 3, as these proteins are bound to rubber particles (Fig. 1). Allergenicity of dry rubber products is also reduced by the more prolonged high temperatures during their preparation [88]. In contrast, dipped latex products contain higher protein levels including the allergens Hev b 5, Hev b 6 and Hev b 13 [32, 89–91]. In the case of Hev b 5, the levels may even be enriched through processing [89].

An integral step in the production of latex products is leaching with water to remove proteins and salts. This may occur at different stages of manufacture. Following concerns about the high allergenicity of latex gloves, washing was increased in the manufacturing process with subsequent reduced protein content and allergenicity [80]. Assays to measure residual levels of latex allergens in manufactured products are necessary to inform good manufacturing practice (e.g. inhibition ELISA for detection of residual Hev b 5 in latex products [89]). Using such an assay, domestic latex gloves were shown to contain

higher allergen levels than surgical gloves [89]. A recent report showed that the sum value of four clinically relevant allergens (Hev b 1, Hev b 3, Hev b 5 and Hev b 6.02) showed a strong correlation with SPT-validated human serum IgE inhibition ELISA values and threshold levels could be set for assigning low, moderate or high allergenicity of medical gloves [92].

In addition to recognition of measures for reducing the allergenicity of latex products during manufacture, an important key to early intervention strategies emerged from the recognition that exposure and sensitization to latex followed breaching of mucosal surfaces and aerosol transmission. With the reduction of latex proteins in gloves by the measures described earlier in the text and the use of powder-free gloves, measured latex allergen levels in HCW environments declined dramatically [93–95]. Initially, talc was used to facilitate glove donning, but this was found to cause granulomata and adhesions and so was replaced with cornstarch particles. The high-molecular-weight polysaccharides of these particles adsorb latex proteins from the internal surface of the glove. Protein levels are particularly high at this surface, as this surface is initially on the outside of the latex on the glove mould during vulcanization when large amounts of water move to the surface and evaporate [96]. As a result of adsorption of latex proteins to the starch particles, when powdered gloves are removed, a latex allergen-loaded aerosol is generated. Different-sized particles are used, with those in powdered examination gloves being of a more respirable size range than those of surgical gloves [97].

In the western world, the use of powder-free gloves is now standard practice in many healthcare settings. Combined with education programmes, this strategy reduced the incidence of latex allergy markedly over a period of 2 years [95, 98]. Latex-free operating theatres enable latex-allergic patients to undergo surgery safely [99]. Spina bifida is often identified *in utero* or soon after birth, and so allows vigorous latex allergen avoidance, enhancing the efficacy of primary prevention [38, 16]. However, these measures present considerable challenges and cost to the healthcare industry and exposure to other forms of natural rubber latex and cross-reactive foods can induce allergic reactions [100]. With the large range of latex products in common use in the community, latex sensitization continues. Many domestic latex gloves still contain high protein levels and readily detectable latex allergens [100]. Individuals with latex-fruit syndrome present another management challenge. Severely affected latex-allergic individuals are recommended to wear medic-alert bracelets and to have anaphylaxis management kits. Some may be compelled to change occupation [101]. The current mainstay management for latex allergy is allergen avoidance and symptomatic medication. Currently, specific immunotherapy (SIT) is associated with a high risk of

adverse events and is not available in routine clinical practice. Refined allergen preparations and administration regimens must be developed to allow widespread use.

Specific immunotherapy for latex allergy – current status

SIT is the only therapy for allergy known to influence the natural history of allergic diseases. The clinical efficacy of SIT is established for treatment of hymenoptera venom allergy and for aeroallergen-induced rhinoconjunctivitis and asthma [102, 103]. SIT for grass pollen allergy has been shown to be long lasting [104] and, in children, is able to prevent the progression of allergic rhinitis to asthma [105] and development of new sensitizations [106]. The mechanisms proposed for SIT-induced down-regulation of adverse immune reactions to allergens include immune deviation from a more T-helper type 2 (Th2)-polarized allergen-induced cytokine response to a Th1-polarized, increased production of the immunoregulatory cytokines IL-10 and TGF- β with the potential for enhancing regulatory T cell activity and specific antibody isotype switching from IgE to IgA, IgG1 and IgG4 (see reviews [107, 108]). Despite advances in the standardization of allergen preparations and regimens for SIT [102], conventional SIT remains contraindicated for moderate to severe asthmatics and application to treatment of latex allergy is at present limited due to the high potency of latex allergens.

Isolated reports of successful latex-specific therapy using subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) have been published (see review [109]). A landmark report in 2000 described a multi-centre, randomized, placebo-controlled trial using the Stallergenes (S. Antony, France) standardized, low-ammoniated latex preparation [110]. Seventeen HCW with latex allergy were randomized to SCIT or placebo, receiving a 2-day rush immunotherapy regimen comprising up-dosing to a maximum tolerated dose with the 10 IR (index of reactivity) or 100 IR vial of the extract, depending on the sensitivity. The value 100 IR/mL is defined as the concentration of extract that elicits a SPT weal geometric mean diameter of 7 mm in 30 subjects sensitive to the corresponding allergen [111]. A 12-month maintenance phase of injections followed at the maximum tolerated dose, initially fortnightly and then monthly. A statistically significant decrease in symptoms of rhinoconjunctivitis and urticaria but not asthma was observed in the active treatment group. Notably, the placebo group had an increased asthma incidence at study commencement compared with the active group. Although treatment was efficacious, significant sideeffects were noted, including a local reaction rate of over 40% in the group on active treatment compared with 15% in the placebo group. In the active group, 15% of injections induced rhinitis flares, 2.7% asthma, 0.6% angioedema and 0.3% systemic

anaphylaxis. Of most concern, adverse effects occurred just as frequently during maintenance injections as in the induction phase. Subsequently, a second study of SCIT in latex allergy was reported in 2003 [112]. A randomized-controlled trial was performed in 24 subjects with occupational latex allergy including respiratory sensitization, using a standardized extract from ALK-Abello (Madrid, Spain). Subjects tolerated a mean of 11.1 µg of latex protein. However, as in Leynadier's study, systemic reactions were very common, accompanying 8% of the total injections in 68.7% of the patients. As in the first study, despite the high rate of adverse reactions, efficacy was demonstrated with a significant reduction in cutaneous sensitivity and specific airway hyper-reactivity to latex [112].

However, in contrast to these two studies, a subsequent controlled trial of 12 months of latex-specific SCIT in 23 patients with latex rhinoconjunctivitis failed to show a significant difference in either symptom or medication scores between active and control groups [113]. It was suggested that this discrepancy may reflect lower symptom levels at baseline and a low maintenance dose of therapy. Nevertheless, a high frequency of systemic reactions was reported. Of concern in another study was the development of new sensitizations to additional latex allergens after 6 months of latex immunotherapy in three of 16 patients on active treatment, although specific IgE levels were low and failed to translate to clinical symptoms at that time [114].

In view of the high frequency of adverse events with SCIT for latex allergy, the sublingual route may be more attractive. In general, reports of SLIT for allergic disease suggest fewer adverse events despite the need for much higher doses for efficacy compared with SCIT [115, 116]. A recent Cochrane Collaborative meta-analysis showed that SLIT is an effective, safe alternative to SCIT for asthma treatment [117] and analysis of immunological mechanisms of SLIT reveal both common and unique features compared with SCIT [118, 119]. SLIT for latex allergy has been reported in both major studies and case reports. Early studies were non-randomized and open label. In the first trial, 24 latex-allergic subjects were studied, half of whom received a rush immunotherapy protocol with a sublingual latex extract (ALK-Abello) to a maximum of 50 µg/mL [120]. Impressively, no sideeffects were reported and, after 3 months of latex SLIT, subjects tolerated wearing latex gloves for 6 h and could undergo medical procedures without latex-related allergic symptoms, whereas control subjects retained their latex allergy symptoms. Subsequently, two large double-blind placebo-controlled studies of SLIT for latex allergy were performed. In one of these studies, 18 adult patients with latex-induced urticaria received SLIT using the ALK-Abello latex extract and 17 control patients received placebo [121]. After 12 months of SLIT, symptom scores were improved and medication scores reduced in all subjects, with no reports

of severe adverse events. Paediatric patients with cutaneous and/or respiratory symptoms of latex allergy including oral allergy syndrome were included in the second randomized, double-blind placebo-controlled study of latex SLIT [122], also demonstrating safe and efficacious treatment. Interestingly, the number of foods triggering oral allergy symptoms increased in control but not active subjects over the 12-month study period. A smaller, open study of SLIT in 10 latex-allergic children with a history of multiple surgical procedures using a rush protocol resulted in decreased symptom scores after 1 year, with no adverse reactions during the induction phase and only mild local symptoms occurring in two patients during maintenance treatment [123].

Despite these encouraging reports on the efficacy and safety of SLIT for latex allergy, other studies report higher frequencies of adverse events. For example, in a study of 26 latex-allergic subjects treated successfully by SLIT, 25% of doses elicited side-effects, although mainly local, and treatment was needed in 10% of the cases [124]. Of more concern is a recent report of anaphylaxis in a 36-year-old latex-allergic woman with urticaria and asthma [125]. This occurred 20 min after the maximum scheduled dose of a rush SLIT protocol was given and required treatment in the emergency room. The authors recommended that rush SLIT should always be performed in a protected setting with resuscitation equipment available.

These studies highlight some of the inherent complexities of SIT in latex allergy. Paradoxically, the most latex-sensitive patients who have the greatest potential benefit from desensitization are the ones at most risk of suffering adverse effects from therapy. Allergen avoidance strategies alone may be sufficient for patients with mild or moderate latex allergy [126], but for those with severe allergy, exposure to even minute quantities of latex protein may induce symptoms. In our modern-day environment, natural rubber latex is a ubiquitous material and severely affected individuals are at risk of anaphylaxis from everyday activities, whereas mildly affected individuals have no difficulty [127]. Clinical trials to date indicate a significant risk of adverse events ranging from anaphylaxis to severe local sideeffects with SCIT using crude latex extracts. A negative correlation was reported between baseline Hev b 6.01-specific serum IgE level and maximum tolerated dose of latex extract during SCIT [114]. SLIT perhaps offers decreased side-effects, but additional controlled studies are needed before wide acceptance as a therapeutic option. Currently, SIT using crude extracts is experimental and should be overseen by an experienced allergist in a hospital setting where intensive care backup is readily available. The complexities of current SIT studies using latex extracts support a need for the development of novel approaches such as using recombinant hypoallergenic mutants, DNA vaccines or T cell epitope peptides (Fig. 2). Experimental models of

latex allergy allow investigation of allergen forms, routes of sensitization, mechanisms of down-regulating the adverse immune response to allergens and evaluation of novel specific treatments [129–134].

Recombinant allergens for specific immunotherapy

Recombinant DNA technology allows expression of latex allergens for improved immunological characterization and structural modification via genetic engineering as a prelude to safer latex immunotherapy. In principle, the simple expression of deglycosylated latex allergens using bacterial systems should generate preparations with reduced or ablated IgE reactivity in cases of allergens where the predominant IgE-reactive sites of the native molecule are the carbohydrate moieties, i.e. Hev b 2, Hev b 4 and Hev b 13. The use of such recombinant forms for hypoallergenic latex preparations for immunomodulation has not yet been evaluated. Conservation of T cell epitopes of recombinant allergens with disruption of B cell epitopes offers another approach of abrogated IgE reactivity with maintained efficacy through T cell activation [128, 135]. 'Proof of concept' of this approach was demonstrated in a double-blind placebo-controlled clinical trial of recombinant fragments of the major birch pollen allergen, Bet v 1, where immunization with recombinant proteins safely decreased symptoms in birch pollen-allergic individuals [136].

A latex vaccine for use in latex glove-allergic patients would need inclusion of Hev b 5 and Hev b 6. The highly conserved tertiary structure, major allergen status and pivotal role in the latex-fruit syndrome of Hev b 6 make it a particularly attractive candidate for this approach. Hev b 6.02 is the only latex allergen for which the crystal structure has been determined [137]. Six single-point mutations of Hev b 6.02, disrupting the tertiary structure, abrogated skin test reactivity *in vivo* and decreased binding to Hev b 6.02-specific IgE *in vitro* [138]. A separate study of site-directed mutagenesis of four cysteine residues in the Hev b 6.02 molecule to change conformation through disruption of the disulphide bonds that anchor the tertiary structure resulted in markedly decreased IgE binding but maintenance of T cell reactivity [139], necessary qualities for a candidate vaccine. In the case of Hev b 5, the molecular structure is more linear and linear IgE-binding epitopes have been identified [140]. Modification by alanine substitution of amino acids in eight of 11 of these epitopes resulted in a 4500-fold reduction in IgE binding. Thus, recombinant strategies are available for each of the major allergens of relevance for developing a vaccine for latex glove-allergic patients. The potential for enhancing the efficacy of recombinant allergen preparations for immunotherapy by incorporating immunostimulatory DNA is suggested by studies using recombinant

ragweed allergen [141], but this option has not been trialled for latex allergy.

Peptide immunotherapy

Another approach showing promise for the treatment of allergic diseases is peptide immunotherapy using short synthetic peptides based on dominant T cell epitopes of allergens [142, 143]. The use of short linear peptides allows retention of T cell activation without the ability to cross-link effector cell-bound IgE, which could trigger anaphylaxis. Although several algorithms have been devised for predicting MHC class II binding peptides, reliable identification of dominant T cell-reactive sites on allergen molecules requires *in vitro* testing of proliferative and cytokine responses to peptides by peripheral blood T cell cultures of a panel of allergic donors. Based on the known protein sequence of major allergens, synthetic overlapping peptides, usually 15–20-mers, are screened for allergic donor T cell reactivity and then core epitopes are determined using additional truncated peptide series (e.g. [144, 145]).

To date, clinical experience with peptide immunotherapy for allergy is restricted largely to the treatment of cat and venom allergy (see review [146]). While IgE-mediated immediate adverse events were avoided using these short peptides, early studies using high-dose Fel d 1 peptide treatment reported isolated late asthmatic reactions in some subjects, likely due to mediator release by activated allergen-specific T cells. Inhalation studies demonstrated increased numbers of CD4⁺ T cells in the airways of cat-allergic subjects 6 h after Fel d 1 peptide challenge, correlating with increased airway hyper-responsiveness [147]. Marked up-regulation of the potent vasodilator, calcitonin gene-related peptide in CD4⁺ T cells and CD68⁺ submucosal inflammatory cells was observed [148]. In later clinical trials, careful up dosing of peptides was found to avoid late reactions and further studies are underway to determine the optimal dose, dose interval and route of administration of peptides for clinical efficacy [142].

Peptide immunotherapy has not yet been tested clinically for latex allergy, but dominant T cell-reactive sites have been mapped for Hev b 1 [149], Hev b 3 [150], Hev b 5 [151], Hev b 6.01 and Hev b 6.03 [152, 153]. Using latex glove users' blood samples, the T cell-reactive regions of Hev b 6.01 mapped predominantly within the Hev b 6.02 domain [152], consistent with the high content of Hev b 6.02 in latex gloves [91]. An alternative approach to designing a hypoallergenic allergen peptide for Hev b 6.02 was to synthesize the Hev b 6.02 43-mer peptide with alanine substitutions for four cysteine residues to disrupt potential IgE-binding activity [139]. This peptide variant was shown to maintain T cell reactivity but no basophil-activating activity.

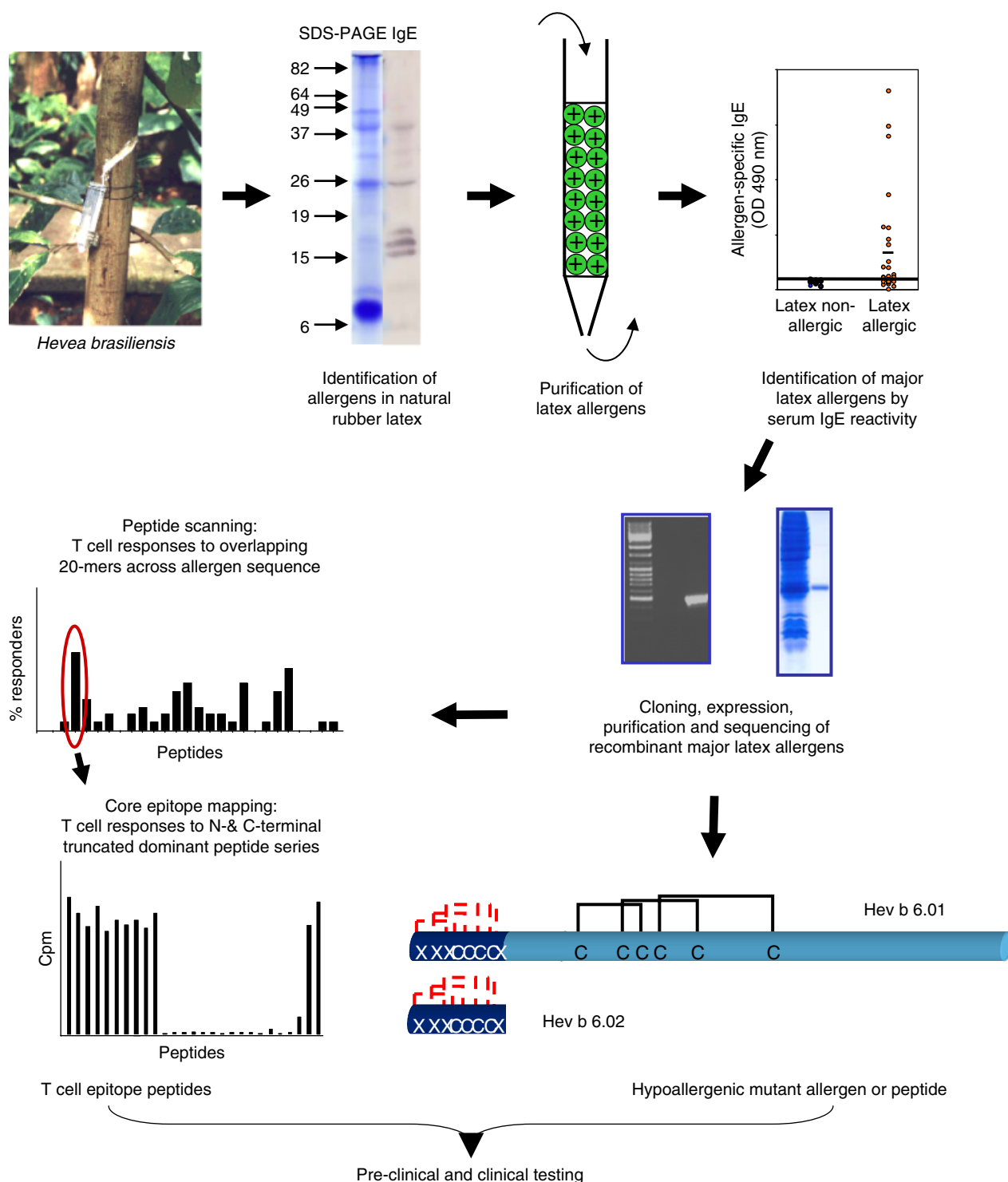


Fig. 2. Path to development of hypoallergenic latex preparations for specific immunotherapy. Allergenic components of natural rubber latex are identified by SDS-PAGE analysis and immunoblotting with patient serum IgE. Allergens are purified, for example by ion exchange chromatography, and used in defined ELISA to determine the frequency of serum IgE reactivity. Cloning and expression of major allergens enable sequencing and generation of hypoallergenic preparations either by recombinant techniques or mapping of dominant T cell epitopes. Hypoallergenicity but T cell reactivity of preparations is confirmed by T cell proliferation and basophil activation assays, respectively. Finally, the candidate vaccine comprising an appropriate set of molecules and/or peptides to target all relevant major allergens is tested in pre-clinical and clinical trials, and the optimal dose, dose interval, route and adjuvant for immunotherapy efficacy are established [128].

As for other allergens, T cell-reactive sites reported for latex allergens are spread over the whole molecule, but sites of immunodominance exist. The high frequency of reactivity, often greater than 50%, is consistent with the promiscuity of MHC class II binding of these peptides and few studies have identified HLA-restricted motifs [149]. Thus, appropriate selection of a combination of peptides based on the dominant epitopes of relevant major allergens is a promising approach for latex allergy immunotherapy [128, 142].

Concluding comments

Knowledge of latex allergy from a clinical and immunological perspective has evolved rapidly over the last two decades. High-risk groups are identified and important allergenic components of dry rubber and dipped latex products are characterized. Considerable advances have been made in management of latex allergy through latex allergen avoidance, especially for HCW and individuals requiring frequent surgical procedures. Nevertheless, some individuals remain at risk of serious adverse reactions to latex and cross-reacting food allergens and another epidemic of latex allergy in newly industrialized countries is predicted. The goal of SIT for latex allergy requires novel approaches to avoid the risk of serious adverse reactions due to the high allergenic potency of latex allergens. Recombinant hypoallergenic preparations and T cell epitope-based peptides are readily standardized and have been identified as potentially safe but effective formulations for specific treatment of latex allergy, but the optimal route of delivery, vehicle and adjuvant for clinical use have not been determined. This development should capitalize on advances in knowledge of factors that influence the shape of an immune response to other allergens and antigens. The importance of dendritic cell subtype and activity in determining the outcome of allergen encounter is relevant when choosing a route and possible adjuvant for SIT [154]. Selected adjuvants, either conjugated or co-administered with the allergen vaccine, may promote induction of tolerogenic dendritic cells by targeting particular pattern recognition receptors (PRR) [155] or costimulatory molecules [156]. Prospects of safer but effective treatment using SLIT should continue to be explored and optimal mechanisms for inducing oral tolerance and effective targeting of mucosal dendritic cells should be determined [157, 158]. The ability to promote regulatory T cell function by particular adjuvant-PRR interactions should enhance down-regulation of both Th1- and Th2-type adverse responses to allergen [159, 160]. Finally, the advantages of adjunct therapies such as anti-IgE antibody (see review [161]) and corticosteroids [162] to increase safety of treatment and driving regulatory T cell responses are attractive.

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