

ALLERGIES IN THE WORKPLACE

CROSS-REACTIVITY OF FOOD ALLERGENS WITH LATEX – DIAGNOSTIC AND CLINICAL IMPLICATIONS

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ABSTRACT

Considerable efforts have been undertaken to characterise the molecular features of *Hevea brasiliensis* latex allergens as a result of the high prevalence of latex allergy in well-defined risk groups such as health-care workers (HCW) and children with spina bifida (SB). Most of the latex allergens have been purified to homogeneity by conventional purification methods or by molecular cloning techniques. The clear advantage of recombinant proteins in contrast to native proteins is that it is possible to produce large-scale quantities at high reproducible quality. Several latex allergens have sequence homology to other allergens (like chitinases, enolase, profilin, patatin-like protein) while others are unique and do not share any similarity. Some of these allergens are responsible for the so called 'latex-fruit syndrome'. With the knowledge and use of the single allergens it is possible to improve the *in vivo* and *in vitro* diagnosis and establish a component-resolved diagnostic approach as prerequisite for specific immunotherapy strategies.

INTRODUCTION

Natural rubber latex (NRL) allergy is well known as an important allergic disease, especially among health-care workers (HCW) and patients needing multiple operations, e.g. spina bifida (SB) patients. Several proteins from the *Hevea brasiliensis* tree, which remain in latex products such as gloves and other medical equipment, and items used in daily living, are involved in the allergic reactions. In the last few years many efforts have been made to identify the major latex allergens and also to produce them in recombinant form. Currently 13 allergens (Hev b 1-13) have been included in the latest nomenclature list of the International Nomenclature Committee of Allergens (IUIS) and assigned official numbers.¹⁻³ Approximately 30-50% of individuals who are allergic to NRL show an associated hypersensitivity to some plant-derived foods, especially freshly consumed fruits (the so-called 'latex-fruit syndrome').⁴ By using recombinant and native single allergens to determine individual NRL-sensitisation patterns, it is feasible to analyse the possible cross-reactivity or co-sensitisation between different fruits and NRL.

Diagnosis of latex allergy

The diagnosis of latex allergy should be based on both a positive clinical history and a positive *in vivo* test result. The determination and quantification of NRL-specific IgE antibodies determined by use of *in vitro* tests are not always associated with clinical NRL-protein sensitivity. Based on the specific symptoms (urticaria, acute erythema, respiratory symptoms from allergic rhinitis to asthma) of the patient, a challenge test may also be performed. As prerequisites for correct *in vivo* and *in vitro* testing, standardised skin-test extracts and well characterised allergen mixtures for IgE-determination are necessary tools. Studies have demonstrated cases of disagreement between results of latex-specific IgE analysis and skin-prick test with latex extract. This phenomenon may be explained by non-specific skin reactivity to the allergen extract, failure of the *in vitro* test to detect certain latex-specific IgE-antibodies or a combination of both. False-negative IgE test results may be due to the absence or low stability of some allergen components in the allergen extract used for antibody capture.

In our studies on this topic⁵ 8 of 16 subjects with clear latex allergy but negative IgE test results showed IgE-reactivity to Hev b 5. This finding suggests that the latex allergen Hev b 5 might play a special role in the diagnostic test showing false-negative IgE results. In consequence of these results a latex ImmunoCAP with rHev b 5 added to the latex extract was developed and used to retest a panel of sera of confirmed latex-allergic individuals. With the Hev b 5-complemented test a significantly higher IgE-antibody level was obtained for a proportion of these sera and a small number of sera converted from negative to positive test results. These results display a new approach to improve *in vitro* allergy diagnostics: if a relevant allergen component is present only in suboptimal amounts in a natural allergen extract, that component can be added as a stable recombinant protein to the extract preparation during production. The new latex allergen ImmunoCAP spiked



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with rHev b 5 has been shown to be an improvement on the *in vitro* test for an IgE-related sensitisation.^{5,6}

Important NRL allergens, such as Hev b 2 and Hev b 13, are glycosylated proteins. Hev b 2, for example, has beta-1,3 glucanase activity and the heterogeneous glycosylation of the amino acid residues could be a source of the multiple allergenicity of natural Hev b 2. Previously we demonstrated that the recombinant form of Hev b 2 produced in *Escherichia coli* was not able to bind specific IgE,⁷ implying that the glycan chains seem to be important for the IgE reactivity. However, the IgE reactivity of the glycosylated latex allergens seems not to be restricted only to their glycan chains. Furthermore, our data have also demonstrated that in only a minority of patients with clinically relevant latex allergy were cross-reactive carbohydrate determinants (CCDs) recognised. In the case of these glycosylated allergens a combined binding is conceivable, comprising a peptide and a carbohydrate epitope on the same allergen molecule. In contrast to our patients with clear latex-induced latex sensitisation, in patients who are not *de novo* sensitised to the allergen tested, the carbohydrate epitopes recognised by the patients' IgE are highly cross-reactive, and the clinical relevance of the positive test results have to be considered. Proteins with CCDs such as horseradish peroxidase (HRP) and bromelain could be used as an *in vitro* screening tool for differentiating true latex allergy from clinically insignificant elevated IgE to NRL.^{8,9}

Based on the analysis of the sensitisation profiles, Hev b 2, 5, 6.01 and 13 are major allergens for HCW and SB patients and together with Hev b 1, the major allergen for SB, this allergen panel should be included in sufficient amounts in a standardised latex diagnostic extract. Furthermore, allergens such as Hev b 7, 8, 9, 10, 11 and 12 have to be considered for testing cross-reactivity in individual cases. CCDs are only of minor relevance in patients with clinically relevant latex allergy. Component-resolved diagnostics for latex allergy have set the stage for specific immunotherapy strategies.

Cross-reactivity between latex and fruits

Several types of proteins have been identified as being involved in the latex-fruit syndrome: class I chitinases^{10,11} from avocado and banana containing an N-terminal hevein-like domain cross-react with hevein (Hev b 6.02), a major IgE allergen for patients allergic to NRL. Other important NRL-allergens are Hev b 2 (which shows cross-reactivity with proteins of bell pepper), Hev b 7, a patatin-like protein (cross-reactivity with its homologous protein in potato)¹² and the Hev b 12 (lipid transfer protein showing cross-reactivity with its counterpart in peach).¹³ Furthermore, patients with allergy to plant-derived foods and associated pollinosis show a high frequency of IgE reactivity to the pan-allergen profilin (Hev b 8 in NRL), which may cause elevated serum IgE determination to NRL.¹⁴ Allergens like the enolase Hev b 9 and the manganese superoxide dismutase Hev b 10¹⁵ may be the reason for cross-reactivity between moulds and latex. On the other hand, allergens like Hev b 1 and Hev b 3 are typical for latex; they do not show any cross-reactivity with other plants and therefore they are specific (Fig. 1).

By using recombinant and native single allergens to determine individual NRL-sensitisation patterns, it is feasible to analyse the possible cross-reactivity or co-sensitisation between different fruits and NRL. Concerning specific IgE reactivity to chestnut and NRL, with this approach we were able to detect that in patients' sera recognising rHev b 5 and/or rHev b 6.01 the concomitant sensitisation to chestnut seemed to

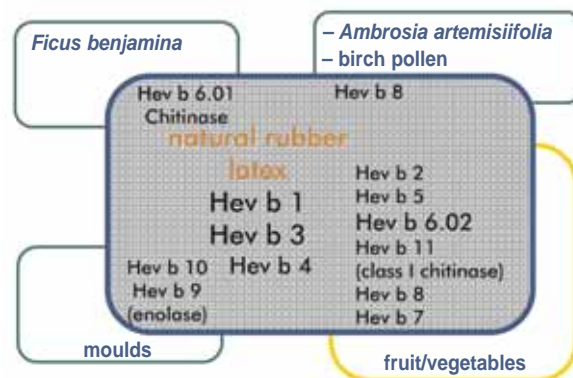


Fig. 1. Molecular background of cross-reactivity.

be independent of NRL. In contrast, patients' sera with IgE predominantly reactive to rHev b 8 displayed cross-inhibition between chestnut and NRL, indicating that Hev b 8 could be involved in the cross-reactivity between chestnut and NRL.¹⁶ By means of inhibition experiments we detected that Hev b 6.01/Hev b 6.02 were the relevant allergens for the cross-reactivity between NRL and acerola (*Malpighia glabra* L., Barbados cherry) in a patient with severe anaphylactic symptoms after consuming apple-juice containing traces of acerola.¹⁷ Knowing the responsible latex allergens which can elucidate more or less severe allergic reactions after ingestion of special fruits will make it possible to protect latex-sensitised patients from these effects.

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Declaration of conflict of interest

The authors declare no conflict of interest.

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PRODUCT NEWS

PIMECROLIMUS CREAM 1% IN ATOPIC DERMATITIS: A 6-MONTH, OPEN-LABEL TRIAL IN PAEDIATRIC PATIENTS

Pimecrolimus, a new, non-steroid, inflammatory-cytokine inhibitor, has been shown to prevent progression to flare in atopic dermatitis (AD) and to improve long-term disease control when applied as a 1% cream. In this 6-month, open-label, multinational study, 177 infants aged 3-23 months and 489 children aged 2-17 years, with mild to severe AD, were included. The study was designed to evaluate the efficacy and safety of pimecrolimus cream 1% used as a first-line treatment. Treatment consisted of an initial bid regimen, for as long as signs and symptoms of disease persisted; this was followed by treatment as required at the first signs and symptoms of AD. Emollients were allowed as per the physician's normal practice, and topical corticosteroids could be used to treat severe flares at the discretion of the physician. Efficacy was assessed by evaluations of pruritus, and total-body and facial Investigators' Global Assessment (IGA). Results from the first return visit (day 7) showed an improvement from baseline of ≥ 1 in total-body and facial IGA for infants (59.1% and 72.8% of patients, respectively) and children (59.3% and 62.2%, respectively). Pruritus was absent or mild in 67.8% and 65.4% of infants and children, respec-

tively. This level of improvement in the patient population was maintained throughout the 6-month study. Adverse events occurred in 75.7% of infants and 71.1% of children. Most adverse events were common childhood illnesses that would be expected in this population (e.g. nasopharyngitis (infants 22.0%, children 12.8%), upper respiratory tract infection (infants 18.6%, children 11.9%) and cough (infants 8.5%, children 10.1%)). Concerning pimecrolimus's local tolerability, application-site burning occurred in 2.3% of infants and 7.0% of children, and local pruritus occurred in 0.6% infants and 1.0% children. Application-site reactions were most frequently reported during the first 6 weeks of treatment and were mild to moderate in intensity. In conclusion, pimecrolimus cream 1% was effective in the treatment of the early signs and symptoms of AD (including pruritus) in infants and children, and demonstrated a good safety profile.

Reference available on request. Contact Thoko Nzama, 011-929-9111

