Title:

Delayed-Type hypersensitivity to latex: Computational prediction of MHC class II epitopes on latex allergens

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Abstract

Delayed type hypersensitivity to natural rubber latex is rare compared to IgE mediated immediate reactions. Binding of allergens to MHC Class II is a crucial step in the presentation of antigens to CD4+ T Cells responsible for delayed reactions. Computational prediction of MHC class II epitopes on thirteen known latex allergens using SMM-align method revealed strong binding with several alleles. This shows that latex allergens are capable of initiating delayed type hypersensitivity in susceptible individuals.

Background

Natural rubber latex (NRL) derived from the rubber tree (Hevea brasiliensis) is an important allergen causing mostly IgE mediated immediate reactions like urticaria, angioedema and asthma. [1] The existence of a true NRL induced delayed type hypersensitivity (type IV) is still debated. Delayed type hypersensitivity reactions are attributed to additives like thiurams and carbamates. [2] The coexistence of the type I and type IV patterns and entities like protein contact dermatitis [3] further complicate the issue. However incidence of true type IV hypersensitivities ranging from 1.2 to 6% has been reported following the introduction of an NRL containing patch test series. [4]

During the sensitization phase of contact hypersensitivity, epidermal Langerhans' cells internalise the allergen, migrate to the regional lymph node and present the processed allergen bound to MHC Class II molecules to CD4 T cells. MHC Class II binding site consists of a groove open at both ends and several pockets binding peptides with 13 to 25 residues. [5] MHC molecules exhibit high degree of genetic variation which enables them to bind variety of peptides.

As IgE from latex-sensitive patients bind to several proteins, there is still no consensus on which latex proteins are antigenic. However information on thirteen officially accepted latex allergens designated serially from Hev b 1 to 13 is available from the online repository www.allergen.org and are summarized in Table 1. [6,[7]

We tried to computationally predict the MHC class II epitopes on these antigens using SMM-align method. SMM-align is a novel stabilization matrix alignment method based

on scoring matrices that evaluate the contribution to binding of different residues in a peptide. [8] T cells are likely to recognize MHC binding peptides and initiate a cellular response. [9]

Methodology

The protein sequences of all thirteen allergens were downloaded from www.allergen.org and were added to a single file. This file was used for MHC Class II epitope prediction with the publicly available SMM-align server using default parameters. The server returns IC50 prediction scores (concentration of competing ligand which displaces 50% of the specific ligand) covering fourteen HLA DR alleles for each nanomer within the query peptide. Allergens with at least one nanomer with IC50 value less than fifty were considered as binders.

Results

Strong binding to one or more alleles was shown by all allergens except Hev b 5. Hev b 2 was the most promiscuous allergen binding several alleles. DRB1*0101 was the most commonly bound allele. Results are summarized in Table 1.

Discussion

NRL is an allergen causing mostly IgE mediated immediate type hypersensitivity. Though there have been significant advances in molecular biology of latex allergens, their ability to initiate delayed-type hypersensitivity has been subject to debate. Computational prediction of MHC class II binding regions on latex allergens adds credence to reports of type IV contact hypersensitivity to NRL. [4]

Prediction of MHC binding peptides is a commonly employed step in the identification of T cell epitopes. [9] MHC epitope related data is available from several databases like SYFPEITHI, [10] MHCBN [11] and IEDB [12]. Several algorithms like ARB [13] and SMM-align [8] are available for prediction of MHC class II binding peptides. Algorithms for scanning promiscuous peptides that can bind multiple MHC class II molecules are also available. [14] Promiscuous peptides are important for vaccine development and immunotherapy. [5] In our study Hev b 2 bound to six out of fourteen tested HLA DR alleles.

Conclusion

Most of the characterized latex allergens contain segments which can strongly bind MHC class II alleles and are capable of initiating delayed type hypersensitivity without a hapten in susceptible individuals. Certain promiscuous allergens like Hev b 2 bind to several MHC alleles making them ideal candidates for immunotherapy. [15] However computational prediction of MHC binding has limited accuracy and clinical validation is essential.

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Table 1: Latex allergens and binding MHC Class II alleles

Allergen	**Biochemical Name**	**Alleles showing strong binding predicted by SMM-Align**
Heb b 1	Rubber Elongation Factor	DRB1*0101 DRB1*1302
Hev b 2	Beta-1,3-glucanase	DRB1*0101 DRB1*0701 DRB1*0901 DRB1*1302 DRB1*1501 DRB4*0101
Hev b 3	Small rubber particle protein	DRB1*0101 DRB1*1302
Hev b 4	Lecithinase homologue	DRB1*0101 DRB1*0401 DRB1*1302
Hev b 5	Acidic protein	-
Hev b 6	Hevein precursor	DRB1*0101 DRB1*0404 DRB1*0701 DRB1*1302
Hev b 7	Patatin-like protein	DRB1*0101 DRB1*1302 DRB1*1501

Hev b 8	Profilin	DRB1*0101
Hev b 9	Enolase	DRB1*0101 DRB1*1302
Hev b 10	Superoxide dismutase (Mn)	DRB1*0101 DRB1*1302
Hev b 11	Class I Chitinase	DRB1*0101 DRB1*0404
Hev b 12	Lipid transfer protein	DRB1*0101 DRB1*0404
Hev b 13	Esterase	DRB1*0101