

Correlating Low-Similarity Peptide Sequences and Allergenic Epitopes

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Abstract: Although a high number of allergenic peptide epitopes has been experimentally identified and defined, the molecular basis and the precise mechanisms underlying peptide allergenicity are unknown. This issue was analyzed exploring the relationship between peptide allergenicity and sequence similarity to the human proteome. The structured analysis of the data reported in literature put into evidence that the most part of IgE-binding epitopes are (or harbor) pentapeptide unit(s) with no/low similarity to the human proteome, this way suggesting that no or low sequence similarity to the host proteome might represent a minimum common denominator identifying allergenic peptides. The present literature analysis might be of relevance in devising and designing short amino acid modules to be used for blocking pathogenic IgE.

Key Words: IgE-binding peptides; similarity level; sequence uniqueness; proteomic scanning.

INTRODUCTION

A major objective of current work in the allergy field is the identification of the allergenic epitopic sequences by canonical procedures as, for example, epitope mapping [1-3]. Computer-assisted antigenicity predictions have also been developed to select potential antibody binding sites along the sequences of allergenic proteins stored in databases which integrate list of allergenic proteins with various computational tools that can assist structural biology studies related to allergens [4-7]. However, although the ability of certain proteins to induce an allergic response in susceptible individuals is well established, on the other hand the molecular basis underlying allergenicity remains unknown. To date, no common structural characteristics of linear IgE epitopes have been identified. We still ignore the molecular and functional determinants that make a peptide allergenic [8-10].

The current advancement in proteomics and peptidomics is allowing and promoting a new theoretical platform for examining peptide epitopes as defined by the sequence similarity to the host proteome. The underlying scientific rationale is that antigen peptides acquire immunoreactivity in the context of their proteomic similarity level [11]. Sequences uniquely owned by a protein will have high potential to evoke an immune reaction, whereas motifs with high proteomic redundancy should be immunogenically silenced by the tolerance phenomenon. The relationship between sequence redundancy and peptide immunoreactivity has been successfully validated using experimental cancer and autoimmunity models [12-16], so making appealing its validation on allergenic proteins too.

Here, we have browsed through the scientific literature and the available databanks searching for well defined and experimentally validated allergenic epitopes. The epitopic sequences were dissected into sequential pentamers offset by one residue and, then, were analyzed for similarity through PIR proteome database [17]. We used 5-mer sequences as probes to scan allergenic sequences versus host proteomes, since pentapeptides are minimal structural units critically involved in immune recognition [18-22], and found that IgE-binding epitopes of a number of allergens are characterized by being (or harboring) pentapeptide unit(s) with no/low similarity to the human proteome.

IGE-EPITOPIC SEQUENCES: SIMILARITY ANALYSIS TO THE HUMAN PROTEOME

Similarity analysis to the human proteome was conducted on IgE-binding epitopes described in literature and already experimen-

tally defined and validated [23-52]. Sequence similarity analyses of each of the IgE-epitopes to the human proteome was conducted using epitopic 5-mers sequentially overlapped by four residues. Then, each 5-mer probe was analyzed by using PIR non-redundant reference protein database and exact peptide perfect match program (pir.georgetown.edu) [17]. I.e., for each epitopic 5-mer, the entire human proteome (enclosing unidentified and/or hypothetical proteins) was searched for instances of the same identical 5-mer. Any such occurrence was termed a match.

An example is reported in Fig. (1), illustrating the proteomic-based similarity analysis of Cry j 2 IgE-binding epitope (amino acid position 96-116) [23]. The IgE epitopic sequence was dissected into pentamers overlapped by 4 residues, i.e. PGNKK, GNKKF, NKKFV, KKFVV, etc. Then each pentamer was sequentially used as a probe to scan the entire human proteome for identical pentapeptide matches. The similarity level of each pentapeptide is given by the number of times that the pentamer is present in the set of proteins that comprehensively form the human proteome. Pentapeptides having a number of matches ≤ 5 were considered as low-similarity motifs. The histogram of Fig. (1) clearly shows that the density of Cry j 2₉₆₋₁₁₆ PGNKKFVVNNLFFNGPCQPHF 5-mer motif in the human proteome is extremely low. Two out of the pentapeptides forming the IgE-binding epitope, KKFVV and FNGPC, even are absent in the human proteome, this way indicating that the immune system has never encountered them.

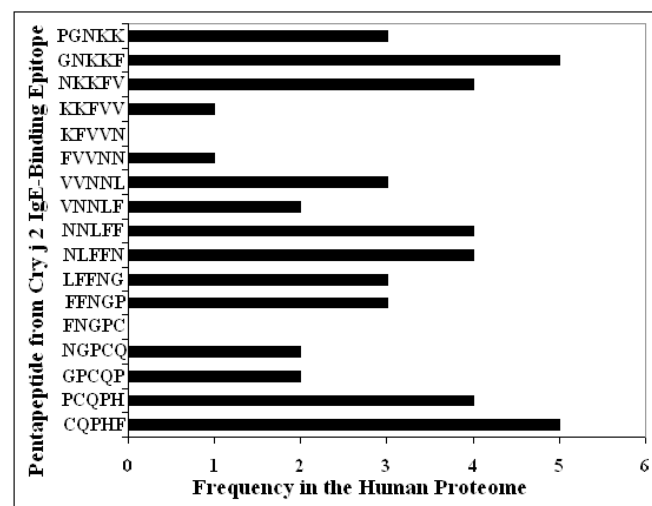


Fig. (1). Cry j 2 IgE-binding epitope sequence: similarity profile to the human proteome.

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Table 1. Allergenic Epitopic Peptides Characterized by Being (or Containing) Pentapeptide Sequences with Low-Similarity to the Human Proteome

Allergen	Species	Aa Pos	Sequence	Matches	Reference
Alt a 1	<i>Alternaria alternata</i>	41	kISEFYgrkp	0	Kurup <i>et al.</i> (2003) [24]
		54	YYNSLgfnik	5	
Ana o 1	<i>Anacardium occidentale</i>	1	aimgpPTKFSfslfl	1	Wang <i>et al.</i> (2002) [25]
		57	keCEKYkYkkggrer	0	
		65	deaeedeNPYVFed	1	
		521	eeffrQGPEWrkeke	2	
Ara h 1	<i>Arachis hypogaea</i>	25	akssPYQKKT	1	Shin <i>et al.</i> (1998) [26]
		65	lEYDPRlvdyd	3	
		97	PGDYDddrrq	4	
		107	prreEGGRWg	4	
		123	rereeDWRQP	1	
		134	edWRRPShqq	2	
		143	qPRKIRpegr	1	
		294	tpgqtEDFFP	1	
		311	sylqeFSRNT	3	
		325	fnaEFNElrr	1	
		344	eqeerGQRRW	3	
		393	diTNPINlre	3	
		409	nnfgkLFEVK	4	
		498	rRYTARlkeg	1	
		525	elhllGFGIN	2	
		539	HRIFLagdkd	2	
		551	IDQIEkqakd	3	
		578	kESHFVsarp	3	
Ara h 2	<i>Arachis hypogaea</i>	15	hasarQQWEL	2	Stanley <i>et al.</i> (1997) [27]
		21	QWELQgdr	2	
		27	DRRCQSQler	2	
		39	IRPCEQHLmq	0	
		49	klQRDEds	4	
Ara h 3	<i>Arachis hypogaea</i>	143	qRCDLDve	2	Xiang <i>et al.</i> (2002) [28]
		245	gfapeflkeAFQVN	1	
		33	ietWNPNNqefecag	0	Rabjohn <i>et al.</i> (1999) [29]
		237	gNIFSGftpefleqa	3	
		276	vTVRGGlrlspdrk	4	
Asp f 1	<i>Aspergillus fumigatus</i>	303	deDEYeydeedrrrg	3	Kurup <i>et al.</i> (1998) [30]
		30	wtCINQQInp	0	
		40	ktNKWEDkrl	0	
		51	YNQAKaesns	1	
		77	WFTNGydgng	0	
		91	grTPIKFgka	1	
		102	cdRPPKHsqn	1	
		114	gkDDHYLlef	0	
		123	fpftpDGHdY	0	
		143	pgparVIYTY	2	
		148	viYTYPNkvf	0	
		159	givaHQRGNq	0	
		167	nQGDLRlesh	5	

(Table 1) contd....

Allergen	Species	Aa Pos	Sequence	Matches	Reference
Asp f 2	<i>Aspergillus fumigatus</i>	58	aTQRRQi	3	Banerjee <i>et al.</i> (1999) [31]
		93	RKYFG	1	
		155	YTTRR	4	
		181	ASDLM	5	
		200	DHFAD	1	
		301	tHEGGQ	2	
Asp f 3	<i>Aspergillus fumigatus</i>	15	vfSYIPWsedk	0	Ramachandran <i>et al.</i> (2002) [32]
		30	acgipinynaskEWADKkvil	0	
		60	vcsarHVPEYi	0	
		85	avlayndayVMSAWgk	0	
		115	pdarfsKSIGW	0	
		130	grtkryalVIDHGkit	1	
		150	epakNHLEFssaetvl	1	
Cra g 1	<i>Crassostrea gigas</i>	92	iqlléeDMERSeer	1	Ishikawa <i>et al.</i> (2001) [33]
Cry j 2	<i>Cryptomeria japonica</i>	96	pgnkkfvnnlFFNGPCQphf	0	Tamura <i>et al.</i> (2003) [23]
		166	GQCKWvngreicndrdpta	0	
		324	SHIIYenveminsenpilingfyct	0	
		346	yctsasACQNQrsavqiqdv	1	
Fag e 1	<i>Fagopyrum esculentum</i>	360	QNVNRpsr	1	Yoshioka <i>et al.</i> (2004) [34]
		384	NNLPlléf	3	
		411	WNLNAh	0	
		434	eGRSVF	5	
		460	kAGNEG	5	
		482	IAGKTsvlra	4	
		526	srdekERERF	4	
Gal d 1	<i>Gallus domesticus</i>	32	tdgvTYTNDCL	0	Mine <i>et al.</i> (2002) [35]
		40	dclleaYSIEF	0	
		56	KEHDGeckev	2	
		71	SSYAN	5	
		80	dgkVMVLCnra	0	
		101	TYDNEssyan	0	
		121	KRHDGgrke	1	
		159	ktygnkCNFCAvves	0	
Gal d 2	<i>Gallus domesticus</i>	38	laMVYLGakdst	2	Mine <i>et al.</i> (2003) [36]
		191	edtQAMPFrv	1	
		251	gleqIESIIN	5	
Gly m G1	<i>Glycine max</i>	217	ggsilsgftleflEHAFSv	2	Beardslee <i>et al.</i> (2000) [37]
		253	gaivtVKGGLsvi	4	
Gly m G2	<i>Glycine max</i>	219	gfapeflkeAFGVN	1	
Hev b 1	<i>Hevea brasiliensis</i>	2	aedeDNQQGq	2	Banerjee <i>et al.</i> (2000) [38]
		16	kYLGfVqdaa	3	
		36	yLFAKDKsgp	3	
		46	lqPGVDlieg	4	
		61	avpLYNRFSY	3	
		65	ynrfSYIPNG	0	
		90	idrsIPPIVK	5	
		99	kDASIQVvsa	2	

(Table 1) contd....

Allergen	Species	Aa Pos	Sequence	Matches	Reference
Hev b 3	<i>Hevea brasiliensis</i>	8	erlkyLDFVR	2	Banerjee <i>et al.</i> (2000) [38]
		29	tlYLYAKdis	1	
		41	lkpgvDTIEN	2	
		60	YYIPLeavkfv	3	
		85	vpPVIKQVsa	3	
		103	APRIVldvas	2	
		118	GVQEGakaly	4	
		138	aVITWRALNk	0	
		159	vptavYFSEK	4	
Hev b 5	<i>Hevea brasiliensis</i>	15	KNETPevt	0	Beezhoid <i>et al.</i> (2001) [39]
		86	DQTTPeekpaepe	0	
		103	eePKHETke	0	
Jug r 1	<i>Juglans regia</i>	35	RGEEM	3	Robotham <i>et al.</i> (2002) [40]
Jun a 1	<i>Juniperus ashei</i>	92	IFSQNmnlikmp	2	Midoro-Horiuti <i>et al.</i> (2003) [41]
		239	afnQFGPNagq	1	
		251	mpRARYGI	3	
		317	WRSTRdafing	2	
Jun a 3	<i>Juniperus ashei</i>	62	aagtasARFWGrtI	2	Soman <i>et al.</i> (2000) [42]
		77	TFDASgksgcqtg	5	
		146	adINAVCpselk	3	
		158	vdGGCNSacnvfkt	1	
		178	NAYVDncpatnysk	2	
Lol p 5	<i>Lolium perenne</i>	49	aanappaDKFKI	0	Suphioglu <i>et al.</i> (1998) [43]
		121	iagalevHAVKPa	2	
		145	gelQIVDKidaa	2	
		161	ataanaaPTNDK	3	
		177	esafNKALNect	2	
		234	amTQAQKagkpa	1	
		265	gaataaAGGYKa	3	
Oct v 1	<i>Octopus vulgaris</i>	77	rvgeeseiaaglNRRIQlleenlerseerIstaqqk	3	Ishikawa <i>et al.</i> (2001) [33]
Par j 1	<i>Parietaria judaica</i>	14	cIPFVQgkekep	1	Asturias <i>et al.</i> (2003) [44]
		68	vseVPKHCGIVd	0	
		114	gpsdPAHKArle	3	
Pen a 1	<i>Penaeus aztecus</i>	43	arslqeeiqQIENDI	0	Jeong <i>et al.</i> (2004) [45]
		86	aINRRIQqlleedle	4	
		133	egladeERMDAlenq	2	
		263	eyeyicddldMTFTEI	0	
Pen ch 13	<i>Penicillium chrysogenum</i>	8	APSWGlsri	4	Lai <i>et al.</i> (2004) [46]
		48	GHADfgr	1	
		112	iaGMDWAvk	1	
		195	sfTNFGSvv	1	
Pen ch 18	<i>Penicillium chrysogenum</i>	175	gvdAYVIDiganvkhvdf	0	Yu <i>et al.</i> (2002) [47]
		180	vidtganvkhvdfGRANW	0	
		201	tipqgdadedgngHGTHCSgtiagk	0	
		358	ilstwVGSDHatntisgtsma	0	
		401	AVADVTPKQL	5	
Per a 1	<i>Periplaneta American</i>	267	irsWEGLP	0	Wu <i>et al.</i> (2002) [48]

(Table 1) contd....

Allergen	Species	Aa Pos	Sequence	Matches	Reference
Per a 3	<i>Periplaneta American</i>	400	tvIRDVPFYq	3	Wu <i>et al.</i> (2003) [49]
		466	NNVDQI	2	
		580	VDKGHnycgypenlli	0	
		595	IPKGKkggqay	2	
Pru p 3	<i>Prunus persica</i>	11	apCIPYVrgg	0	Garcia-Casado <i>et al.</i> (2003) [50]
		31	iRNVNNlart	4	
		36	nlartTPDRQ	3	
		71	gkcgVSIPYk	1	
Ses i 2	<i>Sesamum indicum</i>	44	wesrqcmRHCQMwmsmrg	0	Wolff <i>et al.</i> (2004) [51]
		74	eanqgQFEHFrecnelrdvk	0	
Tri a 19	<i>Triticum aestivum</i>	77	qQIPQQq	5	Stewart <i>et al.</i> (1996) [52]
		65	qQFPQQq	2	
		421	qQYPQQq	4	

Low similarity 5-mers given in capital letters. Low-similarity is numerically defined as ≤ 5 matches. Matches to human proteome calculated as already described in detail [12-16]. Only the lowest similarity pentapeptide is capitalized in each epitope. The similarity level corresponds to the number of times a 5-mer occurs in the set of proteins that comprehensively constitutes the human proteome.

Extending the similarity analysis to the IgE-binding epitopes reported in literature produced the picture delineated in Table 1. It can be seen that what had been found in analysing the Cry J 2 IgE-binding epitope is not an exception, but the rule. Being or having pentamer(s) with zero/low similarity to the human proteome is a common feature of the IgE-binding epitopes analyzed here.

LOW SIMILARITY AS A POSSIBLE MINIMUM COMMON DENOMINATOR OF IGE EPITOPES

In allergology the current challenge is to identify those characteristics that make a protein allergenic. Indeed, although the cascade of cellular and molecular events involved in allergic reactions has been clearly elucidated, nonetheless, the molecular basis of allergy remains unclear. We know that the first step is represented by the contact of a specific allergen with its corresponding IgE antibodies bound to FcεRI receptors on mast cells and basophils. Then, cross-linking of the FcεRI receptors on the surface of mast cells by antigen and IgE causes mast-cell activation and degranulation. Mast cells release histamine, heparin, and other mediators which are the ultimate responsible for the clinical symptoms observed [53]. This picture suggests that the IgE-binding allergen epitopes play an important role in the disease process, and, as a logical consequence, indicates that identification of IgE epitopic sequences on the allergenic proteins is an important step in defining the mechanistic basis of allergy. Actually, much of the research on allergen immunogenicity has focused on the structural properties, such as size, solubility, stability, etc., that contribute to their access to the mucosal-associated immune compartment. Only more recently there has been attention to whether these proteins, or associated molecules, possess innate immunostimulatory properties [54].

Here, IgE-binding epitopes described in literature [23-52] have been explored by computational biology. The data screening indicates that a low level of similarity to the human proteome is a common characteristic of the IgE-binding modules present in allergens. The analyzed experimental models refer to human IgE antibodies so allowing concluding that allergen fragments with a low similarity level to the human proteome are preferred recognized epitopes in allergic subjects. The analysis acquires further value when considering the already demonstrated IgE ability in binding pentapeptide fragments and, more in general, short amino acid fragments [55-57]. Likewise, it also appears of interest to recall the well-known potent modulation that short pentapeptide fragments

may exert in the complex biochemical processes underlying the anaphylactic shock involved in allergic phenomena [58].

Therefore, it seems pertinent to foresee therapeutical applications of the present approach by devising and designing short amino acid modules to be used for blocking pathogenic IgE-induced reactions. In this regard, peptide-based therapeutical approaches would be of special interest in relationship to food hypersensitivity [59], asthma [60] and anaphylaxis [61]. As a matter of fact, attempts to treat peanut allergy using traditional methods of allergen desensitization are accompanied by a high risk of anaphylaxis [62] or side-effects such as osteoporosis [63]. On the contrary, vaccine preparations based on no-similarity segments from allergenic compounds are expected to hit specifically the allergen, without side harmful cross reactions with other proteins, and limit/eliminate corticosteroid regimens. Therefore, from the clinical point of view, the present approach might pave the way to the concrete possibility of safe immunotherapies.

REFERENCES

- [1] Helm RM, Cockrell G, Connaughton C, Sampson HA, Bannon GA, Beilinson V, Nielsen NC, Burks AW. A soybean G2 glycinin allergen. 2. Epitope mapping and three-dimensional modeling. *Int Arch Allergy Immunol* 2000; 123: 213-9.
- [2] Shreffler WG, Lencer DA, Bardina L, Sampson HA. IgE and IgG4 epitope mapping by microarray immunoassay reveals the diversity of immune response to the peanut allergen, Ara h 2. *J Allergy Clin Immunol* 2005; 116: 893-9.
- [3] Reese G, Ayuso R, Leong-Kee SM, Plante MJ, Lehrer SB. Characterization and identification of allergen epitopes: recombinant peptide libraries and synthetic, overlapping peptides. *J Chromatogr B Biomed Sci Appl* 2001; 756: 157-63.
- [4] Stadler MB, Stadler BM. Allergenicity prediction by protein sequence. *FASEB J* 2003; 17: 1141-3.
- [5] Ivanciu O, Schein CH, Braun W. SDAP: database and computational tools for allergenic proteins. *Nucleic Acids Res* 2003; 31: 359-62.
- [6] Fiers MW, Kleter GA, Nijland H, Peijnenburg AA, Nap JP, van Ham RC. Allermatch, a webtool for the prediction of potential allergenicity according to current FAO/WHO Codex alimentarius guidelines. *BMC Bioinformatics* 2004; 5: 133.
- [7] Saha S, Raghava GP. AlgPred: prediction of allergenic proteins and mapping of IgE epitopes. *Nucleic Acids Res* 2006; 34: W202-9.
- [8] Bredehorst R, David K. What establishes a protein as an allergen? *J Chromatogr B Biomed Sci Appl* 2001; 756: 33-40.

- [9] Huby RD, Dearman RJ, Kimber I. Why are some proteins allergens? *Toxicol Sci* 2000; 55: 235-46.
- [10] Lehrer SB, Horner WE, Reese G. Why are some proteins allergenic? Implications for biotechnology. *Crit Rev Food Sci Nutr* 1996; 36: 553-64.
- [11] Kanduc D. Peptidomimetic immunogenic peptides and sequence redundancy. *Curr Drug Discov Technol* 2005; 2: 239-44.
- [12] Natale C, Giannini T, Lucchese A, Kanduc D. Computer-assisted analysis of molecular mimicry between HPV16 E7 oncoprotein and human protein sequences. *Immunol Cell Biol* 2000; 78: 580-5.
- [13] Lucchese A, Mittelman A, Tessitore L, Serpico R, Sinha AA, Kanduc D. Proteomic definition of a desmoglein linear determinant common to *Pemphigus vulgaris* and *Pemphigus foliaceus*. *J Transl Med* 2006; 4: 37.
- [14] Dummer R, Mittelman A, Fanizzi FP, Lucchese G, Willers J, Kanduc D. Non-self-discrimination as a driving concept in the identification of an immunodominant HMW-MAA epitopic peptide sequence by autoantibodies from melanoma cancer patients. *Int J Cancer* 2004; 111: 720-6.
- [15] Lucchese A, Willers J, Mittelman A, Kanduc D, Dummer R. Proteomic scan for tyrosinase peptide antigenic pattern in vitiligo and melanoma: role of sequence similarity and HLA-DR1 affinity. *J Immunol* 2005; 175: 7009-20.
- [16] Angelini G, Bonamonte D, Lucchese A, Favia G, Serpico R, Mittelman A, Simone S, Sinha AA, Kanduc D. Preliminary data on *Pemphigus vulgaris* treatment by a proteomics-defined peptide: a case report. *J Transl Med* 2006; 4: 43.
- [17] Wu CH, Huang H, Arminski L, Castro-Alvare J, Chen Y, Hu ZZ, *et al.* The Protein Information Resource: an integrated public resource of functional annotation of proteins. *Nucleic Acids Res* 2002; 30: 35-7.
- [18] Niman HL, Houghten RA, Walker LE, Reisfeld RA, Wilson IA, Hogle JM, Lerner RA. Generation of protein-reactive antibodies by short peptides is an event of high frequency: implications for the structural basis of immune recognition. *Proc Natl Acad Sci USA* 1983; 80: 4949-53.
- [19] Reddehase MJ, Rothbard JB, Koszinowski UH. A pentapeptide as minimal antigenic determinant for MHC class I-restricted T lymphocytes. *Nature* 1989; 337: 651-3.
- [20] Hemmer B, Kondo T, Gran B, Pinilla C, Cortese I, Pascal J, Tzou A, McFarland HF, Houghten R, Martin R. Minimal peptide length requirements for CD4(+) T cell clones-implications for molecular mimicry and T cell survival. *Int Immunol* 2000; 12: 375-83.
- [21] Gautam AM, Pearson CI, Smilek DE, Steinman L, McDevitt HO. A polyalanine peptide with only five native myelin basic protein residues induces autoimmune encephalomyelitis. *J Exp Med* 1992; 176: 605-9.
- [22] Lucchese G, Stufano A, Trost B, Kuslik A, Kanduc D. Peptidology: short amino acid modules in cell biology and immunology. *Amino Acids* 2006; DOI 10.1007/s00726-006-0458-z
- [23] Tamura Y, Kawaguchi J, N. Serizawa, K. Hirahara, A. Shiraishi, H. Nigi, Y. Taniguchi, M. Toda, S. Inouye, T. Takemori, M. Sakaguchi, Analysis of sequential immunoglobulin E-binding epitope of Japanese cedar pollen allergen (Cry j 2) in humans, monkeys and mice. *Clin Exp Allergy* 2003; 33: 211-7.
- [24] Kurup VP, Vijay HM, Kumar V, Castillo L, Elms N. IgE binding synthetic peptides of Alt a 1, a major allergen of *Alternaria alternata*. *Peptides* 2003; 24: 179-85.
- [25] Wang F, Robotham JM, Teuber SS, Tawde P, Sathe SK, Roux KH. Ana o 1, a cashew (*Anacardium occidentale*) allergen of the vicilin seed storage protein family. *J Allergy Clin Immunol* 2002; 110: 160-6.
- [26] Shin DS, Compadre CM, Maleki SJ, Kopper RA, Sampson H, Huang SK, Burks AW, Bannan GA. Biochemical and structural analysis of the IgE binding sites on Ara h 1, an abundant and highly allergenic peanut protein. *J Biol Chem* 1998; 273: 13753-9.
- [27] Stanley JS, King N, Burks AW, Huang SK, Sampson H, Cockrell G, Helm RM, West CM, Bannan GA. Identification and mutational analysis of the immunodominant IgE binding epitopes of the major peanut allergen Ara h 2. *Arch Biochem Biophys* 1997; 342: 244-53.
- [28] Xiang P, Beardslee TA, Zeece MG, Markwell J, Sarath G. Identification and analysis of a conserved immunoglobulin E-binding epitope in soybean G1a and G2a and peanut Ara h 3 glycinins. *Arch Biochem Biophys* 2002; 408: 51-7.
- [29] Rabinjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, Bannan GA. Molecular cloning and epitope analysis of the peanut allergen Ara h 3. *J Clin Invest* 1999; 103: 535-42.
- [30] Kurup VP, Banerjee B, Murali PS, Greenberger PA, Krishnan M, Hari V, Fink JN. Immunodominant peptide epitopes of allergen, Asp f 1 from the fungus *Aspergillus fumigatus*. *Peptides* 1998; 19: 1469-77.
- [31] Banerjee B, Greenberger P.A, Fink JN, Kurup VP. Conformational and linear B-cell epitopes of Asp f 2, a major allergen of *Aspergillus fumigatus*, bind differently to immunoglobulin E antibody in the sera of allergic bronchopulmonary aspergillosis patients. *Infect. Immun.* 1999; 67: 2284-91.
- [32] Ramachandran H, Jayaraman V, Banerjee B, Greenberger PA, Kelly KJ, Fink JN, Kurup VP. IgE binding conformational epitopes of Asp f 3, a major allergen of *Aspergillus fumigatus*. *Clin Immun* 2002; 103: 324-33.
- [33] Ishikawa M, Suzuki F, Ishida M, Nagashima Y, Shiomi K. Identification of tropomyosin as a major allergen in the octopus *Octopus vulgaris* and elucidation of its IgE-binding epitopes. *Fisheries Sci* 2001; 67: 934-42.
- [34] Yoshioka H, Ohmoto T, Urisu A, Mine Y, Adachi T. Expression and epitope analysis of the major allergenic protein Fag e 1 from buckwheat. *J Plant Physiol* 2004; 161: 761-7.
- [35] Mine Y, Zhang JW. Identification and Fine Mapping of IgG and IgE Epitopes in Ovomucoid. *Biochem Biophys Res Commun* 2002; 292: 1070-4.
- [36] Mine Y, Rupa P. Fine mapping and structural analysis of immunodominant IgE allergenic epitopes in chicken egg ovalbumin. *Protein Eng* 2003; 16: 747-52.
- [37] Beardslee TA, Zeece MG, Sarath G, Markwell JP. Soybean glycinin G1 acidic chain shares IgE epitopes with peanut allergen Ara h3. *Int Arch Allergy Immunol* 2000; 123: 299-307.
- [38] Banerjee B, Kanitpong K, Fink JN, Zussman M, Sussman GL, Kelly KJ, Kurup VP. Unique and shared IgE epitopes of Hev b 1 and Hev b 3 in latex allergy. *Mol Immunol* 2000; 37: 789-98.
- [39] Beezhold DH, Hickey VL, Sussman GL. Mutational analysis of the IgE epitopes in the latex allergen Hev b 5. *J Allergy Clin Immunol* 2001; 107: 1069-76.
- [40] Robotham JM, Teuber SS, Sathe SK, Roux KH. Linear IgE epitope mapping of the English walnut (*Juglans regia*) major food allergen, Jug r 1. *J Allergy Clin Immunol* 2002; 109: 143-9.
- [41] Midoro-Horiuti T, Mathura V, Schein CH, Braun W, Yu S, Watanabe M, Lee JC, Brooks EG, Goldblum RM. Major linear IgE epitopes of mountain cedar pollen allergen Jun a 1 map to the pectate lyase catalytic site. *Mol Immunol* 2003; 40: 555-62.
- [42] Soman KV, Midoro-Horiuti T, Ferreon JC, Goldblum RM, Brooks EG, Kurosky A, Braun W, Schein CH. Homology modeling and characterization of IgE binding epitopes of mountain cedar allergen Jun a 3. *Biophys J* 2000; 79: 1601-9.
- [43] Suphioglu C, Blaher B, Rolland JM, McCluskey J, Schappi G, Kenrick J, Singh MB, Knox RB. Molecular basis of IgE-recognition of Lol p 5, a major allergen of rye-grass pollen. *Mol Immunol* 1998; 35: 293-305.
- [44] Asturias JA, Gomez-Bayon N, Eserverri JL, Martinez A. Par j 1 and Par j 2, the major allergens from *Parietaria judaica* pollen, have similar immunoglobulin E epitopes. *Clin Exp Allergy* 2003; 33: 518-24.
- [45] Jeong KY, Lee J, Lee IY, Ree HI, Hong CS, Yong TS. Analysis of amino acid sequence variations and immunoglobulin E-binding epitopes of German cockroach tropomyosin. *Clin Diagn Lab Immunol* 2004; 11: 874-8.
- [46] Lai HY, Tam MF, Chou H, Lee SS, Tai HY, Shen HD. Molecular and structural analysis of immunoglobulin E-binding epitopes of Pen ch 13, an alkaline serine protease major allergen from *Penicillium chrysogenum*. *Clin Exp Allergy* 2004; 34: 1926-33.
- [47] Yu CJ, Chen YM, Su SN, Forouhar F, Lee SH, Chow LP. Molecular and immunological characterization and IgE epitope mapping of Pen ch18 a major allergen of *Penicillium chrysogenum*. *Biochem J* 2002; 363: 707-15.
- [48] Wu CH, Lee MF, Yang JS, Tseng CY. IgE-binding epitopes of the American cockroach Per a 1 allergen. *Mol Immunol* 2002; 39: 459-64.

- [49] Wu CH, Lee MF, Tseng CY. IgE-binding epitopes of the American cockroach *Per a 3* allergen. *Allergy* 2003; 58: 986-92.
- [50] Garcia-Casado G, Pacios LF, Diaz-Perales A, Sanchez-Monge R, Lombardero M, Garcia-Selles FJ, Polo F, Barber D, Salcedo G. Identification of IgE-binding epitopes of the major peach allergen Pru p 3. *J Allergy Clin Immunol* 2003; 112: 599-605.
- [51] Wolff N, Yannai S, Karin N, Levy Y, Reifen R, Dalal I, Cogan U. Identification and characterization of linear B-cell epitopes of beta-globulin, a major allergen of sesame seeds. *J Allergy Clin Immunol* 2004; 114: 1151-8.
- [52] Matsuo H, Kohno K, Niihara H, Morita E. Specific IgE determination to epitope peptides of omega-5 gliadin and high molecular weight glutenin subunit is a useful tool for diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Immunol* 2005; 175: 8116-22.
- [53] Stewart GA, Thompson PJ. The biochemistry of common aeroallergens. *Clin Exp Allergy* 1996; 26: 1020-44.
- [54] Shreffler WG, Castro RR, Kucuk ZY, Charlop-Powers Z, Grishina G, Yoo S, Burks AW, Sampson HA. The major glycoprotein allergen from *Arachis hypogaea*, Ara h 1, is a ligand of dendritic cell-specific ICAM-grabbing nonintegrin and acts as a Th2 adjuvant *in vitro*. *J Immunol* 2006; 177: 3677-85.
- [55] Tanabe S. IgE-binding abilities of pentapeptides, QQPF and PQQPF, in wheat gliadin. *J Nutr Sci Vitaminol (Tokyo)*. 2004; 50: 367-70.
- [56] Iwasaki A, Doi T, Umetani M, Watanabe M, Suda M, Hattori Y, Nagoya T. Affinity improvement of the high-affinity immunoglobulin E receptor by phage display. *Biochem Biophys Res Commun*. 2002; 293: 542-8.
- [57] Mikol DD, Ditlow C, Usatin D, Biswas P, Kalbfleisch J, Milner A, Calenoff E. Serum IgE reactive against small myelin protein-derived peptides is increased in multiple sclerosis patients. *J Neuroimmunol*. 2006; 180: 40-9.
- [58] Jankovic BD, Maric D. Enkephalins and anaphylactic shock: modulation and prevention of shock in the rat. *Immunol Lett*. 1987; 15: 153-60.
- [59] Puglisi G, Frieri M. Update on Hidden Food Allergens and Food Labeling. *Allergy Asthma Proc* In Press, 2007.
- [60] Huang YC, Leyko BT, Frieri M. Effects of omalizumab and budesonide on markers of inflammation in human bronchial epithelial cells. *Ann Allergy Asthma Immunol* 2005; 95: 443-51.
- [61] Frieri M. Anaphylaxis. In: Expert Guide to Critical Care, American College of Physicians, Chapter 65, Philadelphia, Pa. In press, 2007.
- [62] King N, Helm R, Stanley JS, Vieths S, Luttkopf D, Hatahet L, Sampson H, Pons L, Burks W, Bannon GA. Allergenic characteristics of a modified peanut allergen. *Mol Nutr Food Res* 2005; 49: 963-71.
- [63] Ledford D, Apter A, Brenner AM, Rubin K, Prestwood K, Frieri M, Lukert B. Osteoporosis in the corticosteroid-treated patient with asthma. *J Allergy Clin Immunol* 1998; 102: 353-62.