

T-cell responses to allergens: epitope-specificity and clinical relevance

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Allergen-specific T cells play an important role in the pathophysiology of atopic allergies. Recently, cDNAs that encode many important allergens have been cloned and their amino acid sequences deduced, thus allowing the elucidation of the epitope-specificity of allergen-specific T cells. Here, Joost van Neerven and colleagues discuss the results of these studies, and the implications for the development of efficient strategies for specific immunotherapy.

In type I allergy there appears to be a breakdown of tolerance to innocuous proteins that is manifest by an immune response that causes a direct hypersensitivity reaction, local tissue damage and even systemic responses. In atopic patients, these symptoms are associated with high serum levels of allergen-specific IgE and eosinophilia, and are induced by a spectrum of type 2 cytokines produced by allergen-specific CD4⁺ T cells. Specific inactivation of these cells, or the induction of T helper 1 (Th1) type cytokines, might directly interfere with the disease process. Therefore, allergen-specific T cells are obvious targets for intervention in atopic disease and a detailed characterization of the epitopes present on major allergens might lead to improved forms of therapy, using either synthetic peptides or recombinant allergens.

T-cell responses to allergens

Many allergen-specific human CD4⁺ T-cell clones have been shown to resemble murine Th2 cells, producing large amounts of interleukin 4 (IL-4) and IL-5, but little or no IL-2 and interferon γ (IFN- γ) upon activation^{1,2}. Th2-like cells have been identified in peripheral blood and lesions of atopic-dermatitis patients, in the nasal mucosa of rhinitis patients, and in the bronchial alveolar lavage (BAL) fluid of asthma patients: observations that highlight the involvement of Th2 cells in atopic diseases^{1,3-5}. Figure 1 gives a schematic representation of the role of T cells in the allergic immune response.

Because activation of allergen-specific Th2-like cells seems to be causally related to the pathophysiology of allergic disease, information about the precise proteins they recognize and their T-cell epitopes is needed before allergen-derived synthetic peptides or recombinant allergens can be considered for immunotherapy.

Major allergens contain multiple T-cell epitopes

A large proportion of allergen-specific T cells are specific for major allergens⁶⁻¹⁹, i.e. proteins that are recognized by serum IgE of more than 50% of allergic patients, and T-cell epitope mapping studies have focused on these molecules. The recent cloning and sequenc-

ing of several cDNAs that encode major allergens has allowed the identification of T-cell epitopes, as well as an estimation of their relative importance in inducing T-cell activation. Epitope mapping studies using long-term T-cell clones and lines, have found that all allergens studied to date, i.e. mite-, grass pollen-, tree pollen-, cat-, bee venom-, and chicken-derived allergens (see Table 1) contain multiple T-cell-activation-inducing epitopes dispersed throughout the molecule^{9,12,14-17,19-33}. These epitopes are recognized by allergen-specific T cells isolated both from atopic patients and from healthy, nonatopic individuals^{12,15,25}. In addition, T-cell clones with distinct epitope specificities for a given allergen can be isolated from a

single atopic donor^{9,10,16}. This suggests that certain epitopes are recognized in the context of different major histocompatibility (MHC) class II molecules^{9,19}, and that certain HLA molecules present multiple allergen-derived epitopes to the immune system. Furthermore, epitopes might exist that can only be presented by a single HLA-DR, DQ or DP molecule.

Polyclonal T-cell responses might give a better representation of the diversity of T-cell responses to allergens than responses measured with T-cell clones because a bias towards certain T-cell clones might be selected during the *in vitro* cloning procedure. As expected, polyclonal allergen-specific T-cell lines have been shown to recognize a broader range of T-cell epitopes, with T-cell lines of some atopic individuals recognizing up to six different epitopes within the same allergen^{10,12}. Interestingly, when peripheral T cells from large panels of patients are tested for reactivity with peptides of major allergens, immunodominant regions can be identified^{11,15,22-24,28,29,31}.

MHC class II restriction and T-cell receptor usage of allergen-specific CD4⁺ T cells

MHC restriction patterns of allergen-specific human T cells appear to be very diverse, as is T-cell epitope recognition. HLA-DRB1, HLA-DRB3, HLA-DP and HLA-DQ restriction has been demonstrated for several allergens^{9,12,15,19,22,34-36}. Such diverse restriction patterns suggest that there is only a weak or no correlation between HLA

alleles and IgE responsiveness. Correlations between HLA and IgE responsiveness have been described (see Table 2) but p-values and relative risks appear to be high only for the smallest allergens, which presumably contain limited sets of T-cell epitopes owing to their size³⁷⁻⁴³. In addition, because allergenic extracts are generally complex mixtures of many allergens, a correlation between HLA and one of these allergens does not strongly affect IgE responsiveness to an allergen extract.

In some immunological diseases there is an oligoclonal expansion of T cells that express a limited number of T-cell receptor (TCR) variable (V) β -gene products^{44,45}. If allergen-specific T cells with a limited use of TCR V-gene products play a role in allergic responses, the possibility exists for immunotherapy specifically targeted at the TCR expressed on these cells. However, as expected from the HLA restriction and epitope diversity, human allergen-specific T-cell clones use a diverse set of T-cell receptor V β - and V α -gene segments^{9,10,30,46-48}. Although only a small number of T-cell clones have been tested in these studies, no biased TCR V-gene product usage could be demonstrated, thus complicating the issue of TCR-directed intervention.

Conversely, the results of Mohapatra *et al.* suggest that the diversity of the TCR V α - and joining (J) α -gene segment usage of Lol p 1-specific T-cell clones appears to be limited⁴⁹, whereas it was shown in another study that T-cell responses to Der p could be inhibited by TCR V β -derived synthetic peptides: indicating that TCR usage by allergen-specific T cells is restricted in some individuals⁵⁰.

A recent study showed that polyclonal populations of T cells, expressing almost the full range of TCR V α - and TCR V β -gene segments, are present in BAL fluid and peripheral blood of allergic-asthma patients⁵¹. However, after exposure to allergens, an oligoclonal T-cell expansion could be observed in BAL fluid, but not in the peripheral blood, suggesting that allergen-specific T cells are expanded or recruited in lung tissue after allergen exposure⁵¹.

TCR usage has also been employed to estimate the longevity of allergen-specific T cells. Wedderburn *et al.* have reported that T-cell clones with identical TCR V and J regions can be isolated from the same patients after an interval of six years⁵². These findings are consistent with data from Ebner *et al.*, who reported that epitope-specificity of Bet v 1-specific T cells from a birch-pollen-allergic patient was unchanged when T cells were isolated from the same patient after a two-year interval¹⁶.

Importance of isoallergenic variation for the design of immunotherapy

It is becoming increasingly clear that many isoallergenic forms of major allergens exist in nature⁵³. These isoallergens differ from one another in one to several amino acids^{18,27,54,55}. Some isoallergens have a very high degree of identity with homologous allergens in related species, which might explain the high degree of cross-reactivity at the IgE level, as well as at the T-cell level.

As a result of structural homology, major-allergen-specific T cells might crossreact with allergens from different species within the same genus, as shown for house dust mite Der f-specific T-cell

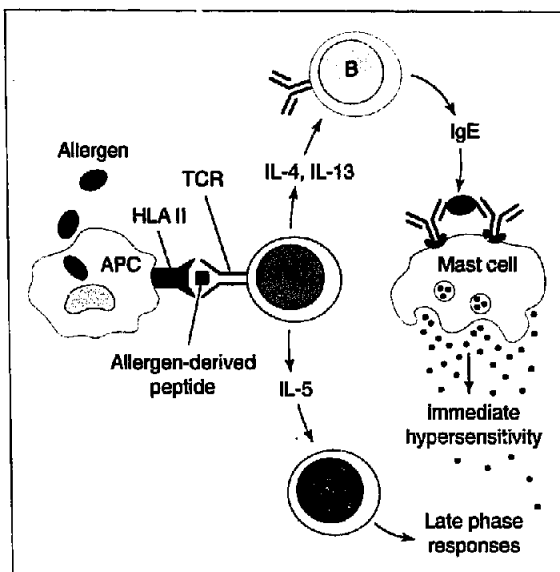


Fig. 1. The role of CD4⁺ T cells in the allergic immune response. Upon entry into the human body, the allergen is taken up and processed by an APC. The presented allergen-derived peptide is recognized by an allergen-specific Th2-like cell that produces IL-4, IL-5 and IL-13. IL-4 and IL-13 induce the isotype switch to IgE in B cells. IgE binds to the high affinity Fc ϵ receptor on mast cells, which degranulate upon Fc ϵ -receptor crosslinking, resulting in the immediate Th1-type response. IL-5 produced by the Th2-like cells plays a role in the differentiation and survival of eosinophilic granulocytes, which are responsible for the late-phase response (especially in allergic asthma). Abbreviations: APC, antigen-presenting cell; EO, eosinophilic granulocytes; IL-4, interleukin 4; TCR, T-cell receptor; Th2, T helper 2 cell.

clones and lines that crossreact with house dust mite Der p (Refs 7, 35). A similar phenomenon can be observed among grass pollen group 1 allergen-specific T cells³⁰ and tree pollen group 1 allergen-specific T cells (S.H. Sparholt *et al.*, unpublished) that crossreact with group 1 allergens from different genera of grasses and trees. At least a part of the latter crossreactivities must result from isoallergenic variation since some natural Bet v 1 or Phl p 1-specific T-cell clones were shown to crossreact with group 1 allergens from other families, but did not react with recombinant Bet v 1 or Phl p 1, representing single isoforms.

The existence of many isoallergens has several implications for possible use of peptides in immunotherapy: T-cell epitopes identified by using T cells that react with recombinant allergens (and their peptides) might represent only a proportion of the repertoire of allergen-specific T cells present in the human body. Studies by Ferreira *et al.*⁵⁶ and by S.H. Sparholt *et al.* (unpublished) clearly show that multiple isoallergens are involved in the sensitization to Bet v 1, the major birch-pollen allergen. Some of the isoforms studied have complete T-cell-activation capacity, but fail to bind IgE *in vitro*, and induce very weak skin prick tests⁵⁶. Such isoforms can be considered for immunotherapy, since they might be safer than natural extracts, owing to decreased IgE binding and the decreased risk

Table 1. Human T-cell epitopes of allergens

Allergen source	Allergen	Size ^a	T-cell epitopes	Individuals tested	T-cell source	Refs
Parental allergens:						
Acarids						
<i>Dermatophagoides</i>	Der p 1	24 kDa, 222 aa	45-67, 94-104, 117-145	2	TCC	9
<i>pteromyzinus</i>	Der p 1		110-119, 110-131	1	TCL and TCC	20
	Der p 1		1-14, 1-56, 15-94, 57-130, 95-208, 188-222, 209-222	18	PBMC	21
	Der p 2	15 kDa, 129 aa	1-15, 11-24, 20-33, 29-42, 38-51, 47-60, 56-69, 92-105, 101-114, 116-129	5	TCL and TCC	10
	Der p 2		1-20, 11-35, 22-50, 36-40, 51-77, 61-86, 78-104, 81-96, 91-105, 87-112, 105-129	18	PBMC and TCC	11
	Der p 2		11-25, 16-31, 21-35, 22-40, 71-86, 81-96, 82-100, 111-129	1	TCL and TCC	22
	Der p 2		20-33	2	TCC	12
	Der p 2		1-15, 11-25, 21-35, 31-47, 41-55, 51-65, 61-75, 71-86, 81-96, 91-105, 101-115, 111-129	24	PBMC	23
Mammals						
<i>Felis domesticus</i>	Fel d 1	17 kDa, 70+92 aa	39-52, 53-66 (chain 1), 9-21, 22-35, 57-70 (chain 2)	4	TCL and TCC	19
	Fel d 1	(dimer)	1-17, 9-25, 18-32, 29-42, 37-55, 44-60, 56-70 (chain 1), 1-22, 12-33, 23-48, 34-59, 49-68, 60-82, 74-92 (chain 2)	53*	TCL	24
Seasonal allergens:						
Trees						
<i>Betula verrucosa</i>	Bet v 1	17 kDa, 159 aa	2-16, 11-22, 61-72, 77-88, 85-96, 113-124, 145-156, 147-158	4	TCC	17
	Bet v 1		1-16, 27-40, 35-46, 75-92, 77-92, 93-110, 141-156	2	TCC	18
	Bet v 1		1-16, 11-26, 61-76, 63-78, 65-80, 75-90, 77-92, 95-110, 97-112, 111-126, 113-128, 127-140, 141-156	9	TCL	25
	Bet v 1		1-15, 8-23, 19-33, 23-43, 46-63, 58-73, 65-79, 73-87, 82-96, 90-104, 117-131, 99-113, 126-140	3	TCL and TCC	26, Sporker et al., unpublished
<i>Cryptomeria japonica</i>	Cry j 1	41-45 kDa, 353 aa	327-346, 337-353	1	TCC	26
Grasses						
<i>Lolium perenne</i>	Lol p 1	34 kDa, 240 aa	191-210	11	TCC	27
	Lol p 1		Several ^b	2	PBMC	28
	Lol p 1		1-20, 11-30, 21-40, 31-50, 41-60, 50-70, 71-90, 91-110, 101-120, 111-130, 121-140, 131-150, 141-160, 151-170, 171-190, 181-200, 191-210, 221-240	8*	TCL and TCC	14
	Lol p 1		Several ^b	6*	PBMC	29
<i>Phleum pratense</i>	Phi p 1	34 kDa, 240 aa	22-36, 25-39, 34-45, 70-84, 73-84, 91-102, 97-111, 91-102, 100-114, 109-123, 121-134, 127-136, 130-141, 142-155, 157-168, 169-183, 211-225, 226-240	9	TCC	30
<i>Poa pratensis</i>	rKBG60	28 kDa, 268 aa	peptide 5, 99-118, 109-128, 149-168, 159-178, 169-188, 199-218, 219-238, 229-248, 239-258, 249-268	13*	PBMC	31
Venom allergens:						
Insects						
<i>Apis mellifera</i>	Api m 1 (PLA ₂)	19 kDa, 134 aa	50-69, 83-97	1	TCL	32
(Honey bee)	Api m 1 (PLA ₂)		45-62, 74-91, 76-93, 81-92, 81-98, 107-124, 111-128, 113-124, 114-131	49*	PBMC and TCC	33
Food allergens:						
Eggs						
Chicken	Ovalbumin	43 kDa, 385 aa	1-33, 198-231, 201-213, 261-277	4	TCC	33

Abbreviations: aa, amino acids; PBMC, peripheral blood mononuclear cells; PLA₂, phospholipase A₂; TCC, T-cell clone; TCL, T-cell line.

* Even though the presence of several T-cell epitopes was described, T-cell epitopes that were recognized by >50% of all individuals tested have been identified in these studies.

^a Sizes are shown as SDS-PAGE mobility of the native protein (in kDa) and as number of amino acids (based on the recombinant sequence).

^b These papers describe reactivity with several peptide pools. Exact amino acid sequences are not clear.

for induction of anaphylactic reactions. However, their potential use might be limited since not all T-cell specificities will be present on these isoforms.

Modulation of allergic responses using synthetic peptides

In order to evaluate the potential of synthetic peptides for immunotherapy, both *in vitro* and *in vivo* experimental systems have been used. Using these models, the ability of allergen-derived synthetic peptides to inhibit cellular responses and humoral responses to allergens has been studied, providing evidence that allergen-specific immune responses can be inhibited.

It has been demonstrated that the incubation of human influenza-specific T-cell clones with supraoptimal concentrations of influenza peptide in the absence of antigen-presenting cells (APCs) resulted in a state of nonresponsiveness (or anergy), during which no proliferative responses were observed – even after subsequent stimulation of the cells with the same peptide in the presence of APCs (Ref. 57).

More recently, using the same experimental conditions, it has been shown that anergy can also be induced in allergen-specific Th2 clones following stimulation with allergen-derived peptides^{58–60}. After initial activation, accompanied by the production of large amounts of cytokines, including IL-4, IL-5, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor α (TNF- α) (S. Fasler and H. Yssel, unpublished), Der p 1-specific Th2 clones become unresponsive to further stimulation with Der p 1-pulsed APCs (Refs 58, 59). Interestingly, stimulation of the anergic T-cell clones with a combination of phorbol ester and calcium ionophore resulted in the production of normal levels of these cytokines^{58,59}, suggesting that peptide-mediated nonresponsiveness might result, in part, from impaired signalling through the TCR/CD3 complex, independent from the expression of this complex on the surface of the cells⁵⁹.

However, information about signalling pathways in human anergic T cells is still limited. It has been reported that the anergic state induced in mouse T-cell clones following stimulation with altered peptides is characterized by a unique pattern of phosphorylation of the TCR ζ chain, as well as a failure of the protein kinase Zap-70 to associate with this chain⁶¹. It has yet to be established whether similar observations can be made in peptide-mediated anergy induced in human T-cell clones. Importantly, in contrast to Der p 1-specific T-cell clones optimally stimulated with antigen-pulsed APCs, anergic Th2 clones failed to give help to B cells for the synthesis of IgE, even in the presence of exogenous IL-4 or IL-13, despite comparable levels of expression of the costimulatory CD40 ligand on both active and anergic T-cell populations⁵⁹.

The activation of allergen-specific T cells and immunoglobulin synthesis in mice can also be inhibited *in vivo* by intra-nasal, oral or

Table 2. Associations between HLA and IgE responsiveness to single allergens

Allergen	Molecular mass (kDa)	HLA-DR	IgE ⁺ (%)	IgE ⁻ (%)	p-value	Relative risk
Amb a 5	5	DR2/Dw2	100	24	<0.0001	65
Lol p 2	11	DR3	47	15	0.007	5.3
Lol p 3	11	DR3	43	18	0.007	3.5
Lol p 3	11	DR3	57	7	0.00001	18
Amb a 6	11.5	DR5	85	14	0.0000007	35
Amb a 6	11.5	DR5	40	6	0.001	23
Alt a 1	14	DR4	26	16	0.006	1.9
Der p 2	15	DR3	19	16	0.034	>1
Bet v 1	17	DRw52a/c	62	33	<0.02	2.5
Bet v 1	17	DRB3*0101	51	30	0.02	2.5
Fel d 1	17	DR1	16	9	0.02	2.0
Der p 1	24	DR3	16	17	0.078	<1
Lol p 1	34	DR3	36	7	0.01	7.3
Lol p 1	34	DR3	33	14	0.01	3.1

subcutaneous administration of peptides^{60,62–64}. Naive mice that were pretreated with the dominant peptide of Fel d 1 or Der p 1 did not develop an immune response when challenged with native Der p 1 or Fel d 1. In addition, ongoing immune responses to native Der p 1 and Fel d 1 could be substantially downregulated by peptide treatment. This could also be achieved using minor epitopes of Der p 1 that are recognized when mice are immunized with these peptides but not when they are immunized with whole protein⁶⁴. It should be noted that administration of peptides results in inhibition of responses to the entire allergen, indicating that not all allergen-derived T-cell epitopes have to be present to obtain *in vivo* tolerance to allergens.

Can synthetic peptides of allergens be used for immunotherapy?

Allergen extracts have been extensively characterized and standardized over the past decades, however, allergen immunotherapy has hardly changed since its introduction by Noon in 1911 (Ref. 65). During immunotherapy, gradually increasing doses of complete allergen extract are injected, resulting in a reduction of clinical symptoms of allergy. T cells are believed to be the target cells that are affected by successful immunotherapy but there is no obvious evidence concerning the mechanism (see Fig. 2).

As a result of the abundance of human T-cell-activation epitopes on allergens (see Table 1), and the problems posed by the occurrence of isoallergenic variation, it is clear that immunotherapy might have an optimal efficacy when natural allergen extracts, and not peptides or recombinant allergens, are used. Cross-epitope inhibition can be demonstrated in experimental models^{62,63}, although as yet, there is no evidence in humans to support the contention that vaccination with a single peptide will downregulate the response to an intact protein.

However, adverse reactions occur occasionally during specific immunotherapy with native allergens as a result of binding of injected allergens to allergen-specific IgE bound to mast cells. This

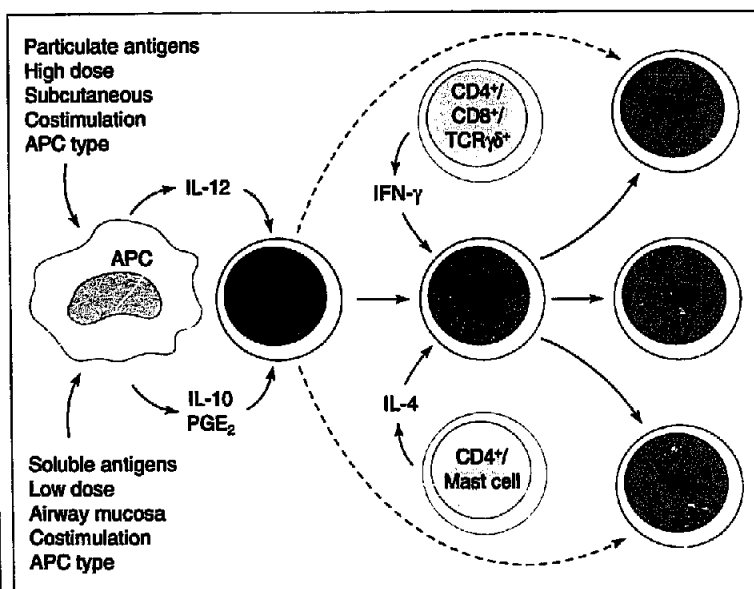


Fig. 2. Factors and cells involved in the generation of Th2, Th0 and Th1 responses. APC-derived factors, T-cell derived cytokines, APC type, and the dose and administration route of allergens can strongly influence the outcome of an allergen-specific T-cell response. During natural sensitization, low doses of allergens are absorbed in the airway mucosa, leading to Th2-type responses in atopic individuals. During specific immunotherapy, high doses of allergens are injected subcutaneously over 3–5 years, resulting in a bias for the production of Th1-type cytokines^{71–73}. Several novel immunotherapy strategies are under development that might specifically interfere with the outcome of allergen-specific T-cell responses. The use of particulate antigens (to select for IL-12-producing professional APCs), naked DNA vaccination (to induce IFN-γ-producing HLA class I-restricted T cells), Th1-biasing adjuvant, and high doses of peptides (high dose without IgE related side-effects) or recombinant allergens (easier to standardize than complex allergen extracts) might result in a bias for the production of Th1-type cytokines. However, oral, nasal, or sublingual delivery of allergens, and high doses of peptides might directly induce tolerance in allergen-specific Th2-like cells. Abbreviations: APC, antigen-presenting cell; IFN-γ, interferon γ; IL-10, interleukin 10; PGE₂, prostaglandin E₂; Th1, T helper 1 cell.

can be avoided if allergen-derived synthetic peptides are used instead of whole allergen extracts. Binding of allergen-specific IgE to allergen-derived peptides is strongly reduced⁶⁶, whereas the desired effects on T cells are unaltered. Therefore, the safety of immunotherapy can increase when peptides or low IgE-binding recombinant allergens are used. The answers to these problems will have to await results of clinical trials with peptides or recombinant allergens. So far, a trial with bee venom phospholipase A₂-derived peptides has shown good clinical efficacy with no adverse reactions⁶⁷, and another trial using Fel d 1-derived peptides is currently under way⁶⁸.

An important question that these clinical studies will have to answer is whether the inhibition of immune responses to major allergens will be sufficient to silence allergic responses to other proteins present in the allergen extract, or whether the specificity of the allergic response will shift to minor allergens that can also be recognized by T cells^{7,19,69}. This might be expected from the work of Gammon *et al.* who showed that T cells with specificities for minor epitopes of antigens can escape tolerance induction⁷⁰. Several studies have indicated that a shift in the production of Th2 to Th1 cyto-

kines takes place in successful immunotherapy^{71–73}; this might result from the activation of IFN-γ-producing, allergen-specific CD8⁺ or TCRγδ⁺ cells that inhibit IgE synthesis, as described in animal models^{74,75}. If this turns out to be the mechanism underlying successful immunotherapy, careful selection and combination of peptides of several major allergens might be the most crucial step in designing peptide therapies. However, the high degree of isoallergenic variation of some allergens, such as tree pollen and grass allergens might favour approaches that are based on the use of natural allergenic extracts that are degraded to peptides⁷⁶, or on the use of recombinant T-cell epitopes that do not bind IgE, as described by Rogers *et al.*¹⁸.

Another strategy for optimizing allergy immunotherapy is directed at finding ways to change the cytokine profiles of allergen-specific CD4⁺ T cells. The crudest method would be to co-inject a protein extract (e.g. purified protein derivative), cytokine (IL-12, IFN-γ), or an IL-12-inducing factor, in combination with allergen extracts in order to shift the T-cell response towards a Th1 spectrum. T cells that mature in this artificially created microenvironment will preferentially become T cells with a Th0- or Th1-type cytokine profile. Alternatively, other approaches might be aimed at inserting allergens in attenuated live, bacterial or viral vectors, that themselves evoke strong Th1-type responses. In addition, studies on the role of APCs in the generation of Th2 vs.

Th1-type responses by the production of soluble mediators such as prostaglandin E₂ or IL-12, respectively, might yield information on the underlying mechanism of the *in vivo* outgrowth of T cells with biased cytokine production profiles⁷⁷.

Concluding remarks

The increasing knowledge of the role of the immune system in the pathophysiology of atopic disease has revealed new possibilities for designing immunotherapeutic approaches. The future course of specific immunotherapy as treatment for allergic diseases will to a large extent be dependent on the results of clinical trials that use synthetic peptides, recombinant allergens, degraded allergenic extracts, or modified allergens that selectively tolerize Th2-type or activate Th0-type or Th1-type responses to allergens.

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Mannose-binding lectin: the pluripotent molecule of the innate immune system

Malcolm W. Turner

Mannose-binding lectin (MBL) is a versatile macromolecule, embodying functional characteristics of IgM,

IgG and C1q. It might be particularly important in the early stages of a primary infection and during the window of vulnerability experienced by all infants following the decay of maternal antibody.

Here, Malcolm Turner reviews recent studies of MBL which suggest the need to reconsider the importance of this protein in the innate immune system.

innate immune system^{3,5–7}. In man the proteins of this family are encoded by a cluster of genes located on the long arm of chromosome 10; there is a single MBL gene (closest to the centromere) and genes for three lung surfactant proteins SP-D, SP-A1 and SP-A2. By contrast, there are two structurally and functionally distinct MBL proteins in rats and mice, and the intron–exon gene organization of these MBL variants has recently been described⁸. The C1q subcomponent of C1 is structurally related to the collectin family but does not possess lectin domains or exhibit sugar-binding activity.

Structure/function correlates in MBL

The exon structure of the human MBL gene^{9,10} can be correlated with distinctive properties in the expressed protein (see Fig. 1). The structure of the carbohydrate recognition domain (CRD) of rat MBL is known in detail^{11,12} and the crystal structure of an entire

Twenty-one years ago a short report describing the affinity chromatography of human liver α -D-mannosidase ended with the prophetic sentence, 'The presence of lectin-like proteins specific for mannose in mammalian cells is a possibility remaining to be investigated'. Three years later such a protein was isolated from a preparation of rabbit liver cytosol¹ and proteins able to bind mannose-terminated glycoproteins were subsequently identified in human, rabbit, bovine, rat and mouse sera (reviewed in Ref. 3). These proteins have been named mannose-binding protein, mannan-binding protein and core-specific lectin but here will be referred to as mannose-binding lectin (MBL) (see Box 1).

MBL is a member of the collectin family of proteins which are characterized by the presence of both a collagenous region and a lectin domain and are now believed to be important constituents of the