

Biochemical properties of aeroallergens: contributory factors in allergic sensitization?

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Recent studies indicate that the majority of clinically important aeroallergens are biochemically active. A diverse range of properties have been demonstrated but most possess either enzymatic activity (principally hydrolytic), enzyme inhibitory activity, low molecular weight ligand transporting or regulatory properties. In addition, some allergens are glycosylated and/or are structurally similar to proteins which have evolved to function in the respiratory system *per se*. Little attention has been given to the possibility that the biochemical activity of an allergen or any post-translational modifications contribute to sensitization. In this review, mechanisms with the potential to influence immunogenicity are discussed including interaction with respiratory secretions, epithelial disruption, interactions with immunocompetent cells and receptor mediated endocytosis. Given that many aeroallergens are structurally and functionally similar to a variety of endogenous (e.g. lysosomal enzymes) and exogenous proteins (e.g. microbial enzymes and glycoproteins), particular attention has been directed to the latter. This process represents an important non-adaptive defence mechanism which has evolved to recognize and process such proteins and it is feasible that it plays a similar role in the processing of some allergens entering the respiratory system.

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The general features of many of the clinically important aeroallergens have been known for some time (reviewed 1–4) and the data indicate that, structurally, allergens are indistinguishable from conventional antigens. As such, physicochemical properties such as size, solubility, foreignness, dose and exposure frequency, together with genetic factors, relating to both allergen non-specific (i.e. total IgE) and allergen specific IgE production, are all likely to be important factors influencing the immunogenicity of proteins entering the respiratory tract (reviewed 1, 2, 5, 6). In recent years, however, more detailed knowledge of allergen structure has emerged due to the application of sophisticated molecular biological and protein chemistry techniques (reviewed 7–9). The amino acid sequences of more than 40 allergens are now known, and the number of clinically significant allergens remaining to be sequenced is rapidly diminishing. As these allergens have been studied, information regarding both their biochemical activities and normal biological roles has emerged (reviewed 4, 9).

These findings have given rise to the possibility that such activities influence immunogenicity but little formal attention has been given to this hypothesis. However, a number of observations are consistent with the proposal. For example, airborne bacterial serine protease concentration has been correlated with allergic sensitization in the detergent industry and threshold limit exposure values have been established (10–11). In addition, studies from our own laboratory have shown that many domestically important aeroallergens are similar to enzymatically active allergens encountered in occupational settings (Table 1). In this regard, it was demonstrated that the dust mite allergens (Groups I–IV) were biochemically similar (12–15) to cysteine proteases, lysozyme, serine proteases and amylase from plants, hen egg white, bacteria and fungi respectively (16–19).

On the basis of these similarities, the possibility that the biochemical activity associated with mite allergens may be significant has stimulated experiments to investigate possible contributory mechanisms (20). It is, of course, possible that such ob-

Table 1. Similarity between hydrolytic occupational allergens and dust mite allergens

Mite allergen	Occupational allergen	Industry
Mite group I	Plant cysteine proteases, e.g. bromelain, papain, chymopapain	Blood banking, Food processing, Chemonucleolysis
Mite group II	Lysozyme	Egg processing
Mite group III	Bacterial serine proteases, e.g. subtilisin, mammalian pancreatic extracts	Detergent, Pharmaceutical
Mite group IV	Fungal amylase, Bacterial amylase	Baking, Detergent

servations are purely coincidental and have little relevance to immunogenicity. However, data continue to accumulate suggesting that most allergens possess features capable of influencing sensitization in genetically susceptible individuals. In this review, we describe several ways in which the various activities associated with aeroallergens could influence host immune responses.

Biochemical properties of allergens

An examination of allergens known or thought to be biochemically active reveals that they possess an array of properties, although no one particular activity appears to link them together. However, it is possible to arbitrarily divide the majority into several broad groups, based either on demonstrable activity or significant homology with proteins of known function (4). These groups include the hydrolytic enzymes, enzyme inhibitors, transport proteins, and regulatory proteins (Table 2). Of these groupings, the most significant clinical allergens characterised so far appear to possess either enzymatic or enzyme inhibitory properties.

Despite these groupings, the biochemical properties of many of the major aeroallergens remain to be elucidated but with further study it is likely that many will fall within the above groups. However, there are sufficient data to provide clues as to the possible biochemical role of some of the remaining allergens. This is particularly so for the

major pollen allergens where extensive amino acid sequence data indicate significant homologies between allergens and enzymes involved in pectin degradation (4, 21, 22), and between allergens and protease inhibitors (23).

Allergen biochemistry and immunogenicity

Of central importance to immunogenicity is the recognition of foreign proteins by appropriate antigen presenting cells. A number of cell types have been described with the potential to present antigen in the context of the respiratory system and include MHC Class II positive dendritic cells, alveolar macrophages, monocytes and epithelial cells (reviewed 24, 25). Of these, current evidence suggests that the former may be particularly important with regard to the initiation and development of immune responses since they are possibly the only cells capable of presenting antigen to naive T cells (24). In contrast, lung macrophages do not appear to be good antigen presenting cells under steady-state conditions, and monocytes are usually absent. However, once activated or recruited into the lung, such cells are also likely to be able to efficiently present antigen *in vivo* (25).

Dendritic cells form a contiguous network within the epithelium and are found in both the upper and lower respiratory tree where they interdigitate with epithelial cells (26, 27) in a manner analogous to that described for Langerhans cells in

Table 2. A summary of the major groups of biochemically active allergens

Biochemical activity	Allergens
<i>Hydrolytic enzymes</i>	
Serine Proteases	Group III mite trypsins, group VI mite chymotrypsins, mammalian trypsin, mammalian chymotrypsin, bacterial subtilisins
Cysteine protease	Group I mite allergens, papain, bromelain
Carbohydrases	Group II mite allergens, egg white lysozyme, mite group IV amylase, fungal amylase, bacterial amylase, cellulase, xylanase, mammalian amylase, <i>Amb a I</i> and <i>II</i> (?), <i>Cry j I</i> (?)
Enzyme inhibitors	<i>Ric c I</i> (?), wheat CM16, barley CMB, ragweed cystatin, <i>Ole e I</i> (?), <i>Gal d I</i> , <i>Gal d II</i> (?)
Transport proteins	Group X grass pollen cytochrome c, <i>Amb a III</i> (?), <i>Amb a VI</i> (?), <i>Amb a VII</i> (?), <i>Mus m I</i> , <i>Rat n II</i> , <i>Fel d I</i> (?), <i>Gal d III</i> , <i>Chi t I</i> , β -lactoglobulin
Regulatory proteins	Grass, weed and tree pollen profilin, tree pollen calmodulin, <i>Gad c I</i>

The (?) indicates that allergens shows homology to proteins known to possess appropriate activity. Refer to (1-4, 9) for individual allergen references

Table 3. N-Terminal sequences of mammalian pro-inflammatory serine proteases and mite proteases

Protease	Sequence																			
	1																			20
<i>Der f III</i>	I	V	G	G	V	K	A	Q	A	G	D	*	P	Y	Q	I	S	L	Q	S
<i>Der f III</i>	I	V	G	G	V	K	A	L	A	G	D	*	P	Y	E	I	S	L	E	V
Df protease	I	V	G	G	V	K	A	Q	A	G	D	*	P	Y	Q	I	S	L	Q	S
Df trypsin	I	V	G	G	V	K	A	Q	A	G	D	*	P	Y	Q	I	S	L	Q	S
<i>Der p III</i>	I	V	G	G	E	K	A	L	A	G	E	*	P	Y	Q	I	S	L		
Human kallikrein	I	V	G	G	T	N	S	S	W	G	E	W	P	W	Q	V	S	L	Q	V
Dog trypsin	I	V	G	G	R	E	A	P	G	S	K	W	P	W	Q	V	S	L	R	L
Human trypsin	I	V	G	G	Q	E	A	P	R	S	K	W	P	W	Q	V	S	L	R	V
Df chymotrypsin	(A)	(V)	G	G	Q	D	A	D	L	A	E	A	P	F	Q	I	S	L	L	K
Dp chymotrypsin	(A)	I	G	X	Q	(P)	A	A	E	(A)	(E)	A	P	F	Q	I	(S)	L	M	K
Rat chymase	I	I	G	G	V	E	S	R	P	H	S	R	P	Y	M	A	H	L	E	I
Rat chymase	I	I	G	G	R	E	S	R	P	H	S	R	P	Y	M	A	Y	L	Q	I

One letter code used throughout. Letters in parentheses indicate uncertainty. Residues showing identity with any of the trypsin-like or chymotrypsin-like mite allergens are indicated by bold type whereas those residues considered to be chemically similar (A, S, T; D, E; N, Q; I, L, M, V; F, Y, W) are underlined. Sequences were obtained from (40, 65, 66, 98–104)

the skin. Their dendritic processes do not appear to protrude through the epithelium but are limited by the tight junctions connecting each cell. Therefore, to fulfill their antigen presenting role, allergen must cross the mucous layer and penetrate the tight junctions between epithelial cells to contact immunocompetent cells. The precise mechanisms are unclear but given that the junctions are relatively impermeable to proteins (reviewed 28, 29), it is feasible that events leading to epithelial disruption could have marked influence on the recognition of inspired antigens.

Allergens and mucosal permeability

Direct effects on permeability – It is clear that epithelial integrity can be modified by many factors and studies so far indicate that tobacco smoke, viral infection, ozone, nitric oxide, sulphur dioxide (reviewed 30) and proteases (31) are all capable of altering mucosal permeability. It, therefore, seems reasonable to suggest that allergens with intrinsic proteolytic activity may directly breach mucosal barriers, facilitating access to the underlying immune system. Supporting this, recent collaborative studies from our laboratory have shown that the Group I cysteine protease allergen, *Der p I*, from *Dermatophagoides pteronyssinus* can affect mucosal integrity (20). These studies showed that exposure of the apical surface of bovine bronchial mucosa to either proteolytically active *Der p I* or faecally enriched growth medium at concentrations within the anticipated physiological range (< 10 mg/ml 32) significantly increased the apical-basolateral flux of a high molecular weight protein marker. The mechanism underlying these observations is unclear at present but it did not appear to be cytopathic in origin, a finding confirmed in fur-

ther studies performed using a variety of epithelial cells including canine tracheal epithelium in tissue culture (33). We also showed that the concentration of antioxidants such as reduced glutathione known to be present in respiratory pericellular fluid was sufficient to activate the purified mite allergen.

Indirect effects on permeability – Proteases are also capable of degranulating mast cells in a non-IgE dependent manner and it is possible that the release of histamine and other mediators by this mechanism could alter epithelial permeability. Degranulation has been observed with both endogenous mast cell derived proteases such as chymase together with the exogenous mammalian serine proteases, α -chymotrypsin and trypsin (34–36). We have recently shown that an elastase-like protease from the dust mite is also capable of degranulating rat peritoneal mast cells, and the ability of other mite proteases to induce histamine release is currently under investigation. We were able to show that the potency of the mite enzyme was similar to those of bovine trypsin and chymotrypsin (37). Together, these data suggest that local histamine release may occur on deposition of faecal particles in the vicinity of luminal mast cells, and hence have a significant effect on epithelial permeability.

It is also feasible that the deposition of proteolytically active allergens could stimulate the release of other proteases which could influence epithelial permeability or immunogenicity. For example, it has been shown that exposure of polymorphonuclear leucocytes to kallikrein results in the release of a variety of lysosomal enzymes such as collagenase and lysozyme (38). This observation is particularly significant since it has been shown that the

Table 4. Protease binding receptors on cells

Receptor	Ligand	Cell type distribution
Cystatin receptor	Cysteine proteases	Macrophages
α_2 -Macroglobulin receptor (Low density lipoprotein receptor related protein)	Cysteine and serine proteases, bacterial toxins, lysozyme, cytokines, viruses, peptides complexed to α_2 -macroglobulin	Hepatocytes, dermal dendritic cells, fibroblasts, monocytes, macrophages, astrocytes, adipocytes
Serpin receptor I	Trypsin, thrombin, elastase, Factor IXa, chymotrypsin, cathepsin G complexed to appropriate protease inhibitors such as α_1 -protease inhibitor, anti-thrombin III, α_1 -antichymotrypsin	Monocytes, macrophages, hepatocytes
Anti-plasmin receptor	Plasmin, trypsin complexed to α_2 -antiplasmin	Hepatocytes, macrophages
Cell surface proteases	α_1 -protease inhibitor, soybean protease inhibitor	Fibroblasts, neutrophils, B cells, macrophages

See text for references

action of trypsin-like *Der f* III allergen is similar to that of human kallikrein, both with regard to substrate specificity and function (39–40). Further study showed that this allergen induced vascular permeability in guinea pig skin which was ascribed to the activation of the kallikrein-kinin system (41). In this regard, it is clear that the mite serine proteases, in general, show marked N-terminal sequence homology with a range of mammalian proteases possessing pro-inflammatory activity (Table 3).

Finally, it is also possible that epithelial changes may be induced due to osmotic changes. This possibility has been raised by Baraniuk and colleagues (42) who showed that the theoretical initial local concentration of proteins eluting from a pollen grain on a mucosal surface may be as high as 350 mg/ml. If validated, the release of such concentrations of allergen may have a marked influence on epithelial integrity.

Interaction with respiratory secretions – In addition to the above properties, it is possible that allergens possess other features which could contribute to immunogenicity. For example, hen egg white lysozyme, cat *Fel d* I and the rodent urinary allergens are all similar to proteins which are normally found in respiratory mucosa *per se*. (reviewed 4). These proteins are all highly soluble and diffuse easily within respiratory secretions, and it would be anticipated that allergens with similar structures would behave accordingly. Studies have also shown that proteins such as human respiratory lysozyme and endogenous protease inhibitors bind to the sialic acid rich mucins present in high concentration in respiratory secretions. These interactions are mediated through electrostatic interactions (43–45) and, on this basis, it is possible that many basic allergens might also bind. It is also feasible that any allergen with carbohydrase activ-

ity could bind to specific carbohydrate moieties comprising respiratory mucins due to enzyme-substrate interactions. At present, however, the importance of these properties in facilitating or increasing the chances of allergen being recognised by immunocompetent cells is unclear.

Allergens and receptor-mediated endocytosis

Several of the potentially important antigen presenting cells such as the macrophage have been shown to possess receptors which bind many different kinds of ligand. These receptors are thought to have evolved prior to the development of adaptive immune recognition systems to cope either with the invasion of the host by pathogenic microorganisms or the release of host hydrolytic enzymes occurring as a result of inflammatory stimuli (reviewed 46, 47). The receptors characterised so far have been shown to recognise either carbohydrates, lipopolysaccharide, proteases, lipids, matrix components, humoral immune components, interleukins, or transport proteins (reviewed 48). Once bound, receptor-ligand complexes are endocytosed and proceed to intracellular compartments where dissociation may occur. Following endocytosis, cells may become activated, resulting in the release of mediators such as cytokines, hydrolytic enzymes and superoxide.

Many allergens possess characteristics which could facilitate receptor mediated endocytosis, and it is feasible that such interactions play a role in the processing and/or presentation of allergen, thus contributing to immunogenicity. Such a concept is consistent with a substantial body of data which show that antigen capture and presentation (i.e. immunogenicity) is increased by several orders of magnitude if mediated via cell surface receptors (49). This has been demonstrated for antigen presentation by B cells using specific membrane im-

Table 5. Properties of allergens which could contribute to immunogenicity

Property	Mechanism	Allergen
Carbohydrate	Lectin receptor mediated endocytosis	Bromelain, bacterial subtilisins, wheat CM16, barley CMB, <i>Amb a</i> III, <i>Fel d</i> I, <i>Rat n</i> I and II, <i>Cl a</i> h II, fungal amylase, <i>Bet v</i> I, <i>Ole e</i> I, <i>Cry j</i> I, <i>Gal d</i> I, II and III, grass pollen groups I and IV, <i>Art v</i> I and II, <i>Par o</i> I and <i>Par j</i> I
Protease activity	Protease-protease inhibitor mediated endocytosis; epithelial permeability	Group I mite allergens, papain, actinidin, bromelain Group III mite trypsin, group VI mite chymotrypsins, mammalian trypsin, mammalian chymotrypsin, bacterial subtilisins, group II mite allergens
Charge	Interaction with respiratory mucins	<i>Amb a</i> V and VI, <i>Cry j</i> I, egg white lysozyme, grass pollen groups III, IV, V and X, <i>Ric c</i> I, <i>Sin a</i> I bromelain, papain
Solubility	Solubility in respiratory secretions	<i>Fel d</i> I(?), <i>Mus m</i> I, <i>Rat n</i> II, lysozyme, mite group II allergens

See text and (1–4, 9) for references

munoglobulin (including both IgG and IgE) and by macrophages via receptors for IgG Fc, protease-protease inhibitor complexes and transferrin (50–52).

Protease inhibitors – The respiratory system contains many protease inhibitors which function to protect the lungs from the consequences of proteases such as elastase. They include the serine protease inhibitors α_1 -anti-protease and bronchial leucocyte protease inhibitor, the cysteine protease inhibitor, cystatin C, and the serine and cysteine protease inhibitor, α_2 -macroglobulin. Several cell types, including macrophages and monocytes, possess at least 3 different high affinity receptors which recognize protease-inhibitor complexes with subsequent endocytosis (Table 4). They include the serpin receptor I (which binds a variety of serine protease inhibitors such as α_1 -anti-protease, anti-thrombin III and α_1 -antichymotrypsin), the anti-plasmin receptor and the α_2 -macroglobulin receptor (53–58). Once bound to protease, all inhibitors undergo conformational change which results in the exposure of specific sites recognized by receptors on phagocytic cells (58, 59).

The α_2 -macroglobulin inhibitor is unusual in that it possesses a "trap" region to which both serine and cysteine proteases bind (60). The trapping process may comprise non-covalent interactions between inhibitor and protease but covalent binding may occur via ϵ -lysyl- γ -glutamyl amide bonds formed due to nucleophilic substitution. Because of this, α_2 -macroglobulin may also bind proteins such as lysozyme, insulin, hormones and cytokines (61, 62). Of particular interest, however, are the observations which show that the immunogenicity of an antigen is significantly enhanced when combined with α_2 -macroglobulin (51, 63, 64). Thus, it is plausible to suggest that such a mechanism could serve to direct allergens expressing proteolytic activity (and/or lysozyme) to relevant immunocompetent cells within the respiratory tree.

A number of allergens from domestic and occupational settings have been identified which could potentially be endocytosed by mechanisms such as those described above. They include the dust mite, bacterial and pancreatic serine proteases (14, 18, 39, 65–67), the dust mite and plant cysteine proteases (12, 16), and dust mite and hen egg lysozyme (13, 68, 17) (Table 5). Unpublished studies from our laboratory show that the individual serine proteases and the cysteine protease, *Der p* I from *D. pteronyssinus* bind to α_2 -macroglobulin isolated from both rat and human serum although it has been reported that the kallikrein-kinin activating serine protease allergen, *Der f* III, did not bind to either α_2 -macroglobulin or α_1 -antiprotease (41). Further studies are now required to determine whether protease allergen-inhibitor complexes contribute to immunogenicity either under normal physiological conditions or during inflammatory responses in the respiratory system where extravasation of α_2 -macroglobulin rich serum into the lumen has been demonstrated (29).

In addition to the binding of protease-protease inhibitor complexes to potential antigen presenting cells as described above, protease inhibitors *per se* can bind directly to cell surface membranes (69). This binding is due to the direct interaction between the inhibitor and membrane bound proteases which are thought to play an important role in cell proliferation. For example, it has been shown that soybean protease inhibitor binds to cells and is subsequently endocytosed (70). This finding is of particular significance given that the major occupational wheat and barley allergens (CM16 and NMAI-1, and CMB and BDAI-1 respectively) (71, 72) and seed allergens such as the 2S napin related proteins from mustard seed (*Sin a* I) and castor bean (*Ric c* I) show sequence homology with known plant derived protease inhibitors (73–76).

Lectin receptors – Macrophages also possess a va-

Table 6. Carbohydrate binding receptors on cells

Receptor	Ligand	Cell type distribution
Mannose receptor	Mannose, fucose, N-acetylglucosamine	Macrophages
β -Glucan receptor	β -1,3 glucose	Monocytes, macrophages
Galactose-specific particle receptor	Galactosylated particles	Kupffer cells
Asialoglycoprotein binding protein	Galactose or N-acetylgalactose	Macrophages
Mac 2	Galactose	Macrophages
Fucosyl receptor	L-Fucose	Kupffer cells
Advanced glycosylation endproduct receptor	Glucose modified proteins	Macrophages, monocytes
LPS-LBP complex	Lipopolysaccharide	Macrophages

See text for references

riety of receptors which recognise terminal sugars comprising the N-linked oligosaccharide moieties of glycoproteins (reviewed 46–48). As with the protease-protease inhibitor complexes, interaction between glycoprotein and receptor result in endocytosis. A number of receptors may have been described which bind sugars such as mannose, fucose, galactose and glucose (Table 6), and they are particularly important in the removal of bacteria, soluble bacterial proteins and host glycoproteins such as lysosomal enzymes, and in host defence. In this regard, it has been shown that the binding of glycosylated proteins to receptors such as the macrophage mannose receptor stimulate the release of cytokines. Recent observations indicate that tumor necrosis factor α may be released in this fashion (77) and, given this cytokine may also cause the release of a variety of inflammatory mediators (reviewed 78), these findings may be of particular importance to the development of immediate hypersensitivity.

It is unclear whether phagocytic cells endocytose glycoprotein allergens via lectin-like receptors or if such interactions can result in enhanced antigen presentation as described above. However, both biochemical and sequence analyses show that many allergens contain carbohydrate or appropriate glycosylation sites. Although yet to reveal the detailed structure of the oligosaccharides present on individual allergens, such studies indicate that galactose and mannose are common constituents (Table 5). In this regard, rye and Bermuda grass pollen Group I allergen (1, 79), the Groups I and II allergens from the weed *Artemisia vulgaris* (80, 81), the Group I allergens from *Parietaria* spp (82, 83), fungi (84, 85) and mites (86) have been shown to contain these carbohydrates. Indeed, the presence of carbohydrates such as mannose has formed the basis for the isolation of several allergens by lectin affinity chromatography (79). Thus, binding to sugar receptors on macrophages may represent a potent mechanism by which allergens can also be directed to relevant immuno-

competent cells or, alternatively, initiate the production and release of pro-inflammatory cytokines.

Allergens, receptor expression, cytokines and cellular proliferation

Proteases are involved in many diverse biological processes which could influence immune responses to allergens by mechanisms other than those discussed above. For example, exposure of mesenteric lymph node cells from rats immunized with dinitrophenylated ovalbumin to active serine proteases from *Schistosoma mansoni* not only increased the synthesis of IgE but also increased the expression of the low affinity Fc ϵ R II (CD 23) receptor (87). Interestingly, increased expression of IgG Fc receptors on eosinophils from both human and rat has also been reported after exposure to the same proteases (88), and the affinity of the low affinity Fc γ R II (CD 32) receptor has been shown to increase after exposure to serine proteases from granulocytes (89). In addition to the above studies, it has been shown that both serine and cysteine proteases such as trypsin, thrombin, chymotrypsin, pronase and papain are B cell mitogens (reviewed 69).

Studies also show that proteases may be important in the release of cytokines thought to be involved in IgE synthesis, and the effects observed are likely to be related to those described above. For example, it has recently been demonstrated that the injection of the cysteine protease, papain, into the footpads of mice resulted in the expression of messenger RNA for the cytokines, IL4, 5, and 9 but not interferon γ . Message was detected in both the footpad and draining popliteal lymph node (90) but the cell source was not ascertained. These data and those described above are all consistent with the possibility that protease activity may be important in directing the synthesis of IgE in certain circumstances.

The data may also be relevant to recent *in vitro* studies which suggest that the properties of an allergen may influence the nature of the CD4+ helper T cell response (e.g. Th₀, Th₁ or Th₂ type) and subsequent cytokine elicited after exposure. *In vitro* observations show that human T cell clones derived from peripheral blood leucocytes after exposure to a crude mixture of helminth components or soluble allergens (e.g. *Toxocara canis* and dust mite) were generally of the CD4+ helper T cell population and were comparable, on the basis of cytokine profiles, to the mouse Th₂ type population thought to be important in the generation of an IgE response. In contrast, those obtained after exposure to bacterial proteins such as purified protein derivative were usually similar to those of the mouse Th₁ type population (reviewed 90–94).

It is not clear whether the effects observed reflect differences in antigen processing by appropriate cells or if antigens are, in some way, influencing the T cells directly. However, it has been demonstrated that cell surface CD4 is particularly susceptible to proteolysis, in contrast to other cell surface proteins such as MHC Class I and II suggesting that further study of the effects of proteases on the different putative Th cell types may be in order (95). In addition, the differentiation of Th cells from a putative precursor pool may also be influenced by cytokines derived from cells such as natural killer cells, macrophages and mast cells (92). Such observations suggest that non-antibody dependent interactions between allergen and cells other than T cells may be more important than has been previously recognised.

Conclusions

It is clear that genetic predisposition plays an important role in IgE production and many studies are currently underway to determine the importance of candidate genes such as that reported to be located on chromosome 11q (96). It is, therefore, unlikely that the physicochemical nature of the allergen *per se* will account directly for the sensitization of atopic individuals but may do so in both atopic and non-atopic individuals exposed to helminthic infections. However, it is possible that the biochemical activities of allergens and/or the presence of post-translational modifications could influence immunogenicity *per se*. In those individuals predisposed towards atopy, this is likely to result in the production of IgE, whereas in non-atopic individuals, it is likely that either limited IgG production or tolerance will ensue (97). As yet, it is not clear whether such properties are major factors, but given that the host has developed a variety of non-adaptive defense mecha-

nisms to cope with both endogenous and exogenous (e.g. viral and bacterial) proteins that share many of the properties and structural characteristics displayed by clinically important allergens, it is not inconceivable that they make some contribution.

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