

Endogenous function and biological significance of aeroallergens: an update

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Significant advances have been made in delineating the structure and function of the clinically important aeroallergens. Most have now been characterized at the molecular level, and their endogenous function determined. In the period of review, however, several novel allergens have been identified. They include the house dust mite lipophorins and gelsolins, and the birch isoflavone reductase. In addition, the functions of previously described allergens have now been established or inferred on the basis of homology studies. For example, cat Fel d 1 and the grass pollen group 1 allergens possess proteolytic activity and the thaumatin-like plant and pollen allergens possess endo- β 1,3-glucanase activity. Similarly, the lipocalin allergens may possess endonuclease activity, and the mite group 2 allergens may bind cholesterol. The three-dimensional structure of the horse dander lipocalin Equ c 1 and the honey bee Api m 2 allergens have also been determined during the review period. Finally, in this period, a variety of novel or improved immunotherapeutic allergen reagents designed to redirect the host immune response from a T-helper-2 to a T-helper-1 cell phenotype have been described, in particular, allergen and immunostimulatory CpG motif conjugates. *Curr Opin Allergy Clin Immunol* 1:95–103. © 2001 Lippincott Williams & Wilkins.

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Abbreviation

PR pathogenesis-related protein

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Introduction

The introduction of molecular biology to the study of allergen structure and function was initiated just over a decade ago. Since then, the knowledge gained from these studies has made a major contribution to the study of allergic disease. Most of the clinically significant aeroallergens have now been described at the molecular level, and their endogenous biochemical activities determined. We now have more discriminating tools with which to determine the immunological bases for diseases such as allergic rhinitis, atopic dermatitis and allergic asthma. In the present review of allergen structure and function, we assess the most recent literature and summarize some of the major developments that have occurred with regard to the characterization of novel allergens and our understanding of their biological activities. In addition, we review developments in novel immunotherapeutic modalities. Extensive descriptions of the allergens is not attempted, but rather the reader is referred to a series of recently published reviews [1–4] in addition to the original papers quoted in this text. As always in this series, the choice of material for review is subjective, reflecting areas of allergen biology that have interested us.

Novel allergens and novel sources

A small number of proteins that belong to biochemical groups not previously associated with allergenicity or only previously described in species from other phyla have recently been reported (Table 1) [5–11,12[•],13–16]. They include allergens from birch pollen, grass pollen, fungi and mites. In addition, at least four species of mites have been recognized as new and potentially important occupational sources of allergen.

Tree pollen allergens

Two new allergens have been described in birch pollen, namely Bet v 5 and Bet v 7 [6,17], which share sequence identity with isoflavone reductase and cyclophilin, respectively. The Bet v 5 allergen shows approximately 60–80% sequence identity to the isoflavone reductase isolated from other plants, and is recognized by approximately 30% of patients who are allergic to birch pollen [6]. These cytosolic enzymes are involved in the biosynthesis of lignins and isoflavones, both of which play a role in plant defence, particularly against wood rotting fungi [7]. The cyclophilin Bet v 7 allergen is an 8-kDa protein and is recognized by approximately 20% of birch pollen-allergic individuals

[17]. It belongs to a group of ubiquitous and highly conserved group of cytosolic enzymes that possess peptidyl-proline isomerase activity. Their precise role within cells is still unclear, but they are known to bind to proteins and are targets of the transplantation drug cyclosporin A in humans [18]. The pollen cyclophilins have not previously been shown to be allergenic but are known to be so in fungi (e.g. Psi c 2, Mal f 6) [19,20]. On this basis, it has been suggested that, like profilin, they represent pan-allergens [17]. A low-molecular-weight olive pollen allergen (Ole e 7) of unknown function has also been characterized at the molecular level [8].

Grass pollen allergens

With regard to grass pollen allergens, Suck *et al.* [5] have described the isolation and characterization of a 55-kDa to 60-kDa allergen from Timothy pollen designated Ph1 p 13 (Table 1). This allergen showed significant homology to the pectin-degrading enzyme polygalacturonase, and was recognized by approximately 50% of patients who were allergic to grass pollen. Polygalacturonase is one of several classes of enzyme that are known to be involved in the degradation of pectin, and it is known to be present in pollen. Previously, however, this class of enzyme was only shown to be allergenic in pollen from trees such as Japanese and Mountain Cedar (e.g. Cry j 2) [21,22].

Fungal allergens

Several novel, major or minor allergens have recently been described in *Alternaria alternata* (Alt a 2), *Coprinus comatus* (Cop c 1) and *Malassezia furfur* (Mal f 7, Mal f 8 and Mal f 9) [9–11]. However, even though some of their sequences have been determined, such data have not revealed their endogenous function thus far (Table 1). However, the Alt a 2 allergen shows some homology with mouse RNA-dependent eukaryote initiation factor-2 α kinase [9].

Dust mite allergens

At least three new mite groups of allergens have been described, including a lipophorin [12 $\bullet\bullet$], a gelsolin and a EF-hand calcium-binding protein (Table 1) [13].

With regard to lipophorin, a 190-kDa allergen from this family has been cloned from *Euroglyphus maynei* (Eur m 14). These proteins are thought to play a major role in the transport of lipid from the gut to surrounding tissues in insects, and 50% of the molecule may comprise lipid material. These studies have also clarified our understanding of the group of allergens previously designated Mag 1 and Mag 3 [13,23], because both are represented in the structure of the *E. maynei* allergen.

The gelsolin and EF-hand calcium-binding mite allergen are both recognized by approximately 35% of mite-allergic

Table 1. Recently described groups and sources of allergens

Allergen	Frequency of reactivity (%)	Molecular weight (kDa)	Function	Reference
Pollens				
Timothy pollen	50	55–60	Polygalacturonase	[5]
Birch pollen				
Bet v 5	32	35	Isoflavone reductase	[6]
Bet v 7	21	18	Proline isomerase	[7]
Olive pollen				
Ole e 7	47	10	Function unknown	[8]
Fungi				
<i>Alternaria alternata</i>				
Alt a 2	61	27	Shows homology with mouse RNA-dependent eukaryote initiation factor-2 α kinase	[9]
<i>Coprinus camatus</i>				
Cop c 1	25	9	Function unknown	[10]
<i>Malassezia furfur</i>				
Mal f 7	89	16	Function unknown	[11]
Mal f 8	?	19	Function unknown	[11]
Mal f 9	44	14	Function unknown	[11]
Mites				
<i>Euroglyphus maynei</i>				
Eur m 14 (M-177)	70	190	Lipophorin	[12 $\bullet\bullet$]
<i>Dermatophagoides farinae</i>				
Mag 15	35	53	Gelsolin	[13]
Mag 50	35	30	EF-hand calcium-binding protein	[13]
<i>Panonychus citri</i>	–	–	–	[14]
<i>Panonychus ulmi</i>	–	–	–	[15]
<i>Tetranychus urticae</i>	–	–	–	[15]
<i>Hemisarcoptes cooremani</i>	–	–	–	[16]

Based on binding with *Dermatophagoides farinae* Mag 3 portion of the intact molecule [12 $\bullet\bullet$].

individuals. Although calcium-binding proteins from other sources have been shown to be allergenic [13], the mite allergen has not. In this regard, the mite allergen does not show any sequence similarity with these other allergens. In contrast, the gelsolins have not previously been shown to be allergenic. Elsewhere, these proteins bind to a range of proteins including actin (where they play a role in the polymerization and depolymerization) and tropomyosin [24]. Interestingly, tropomyosin as well as paramyosin, which form part of the cytoskeleton of most cells, have also been shown to be allergenic in mites [25,26]. These data suggest that cellular debris is a significant component of faecal pellets, perhaps derived from gastrointestinal epithelial cells that are involved in mite digestive processes.

In addition to these studies on specific mite allergens, at least four new species of mites have been implicated as sources of both domestic and occupational allergen. They include the European red mite, the two-spotted mites, the citrus mite and the *Hemisarcoptes cooremani* mite [14–16].

Endogenous allergen biochemistry

A number of allergens have been described that have been characterized at the molecular level, but their endogenous biochemical function has remained elusive. Recently, however, insight into the possible functions of some of these allergens has emerged, particularly with regard to tree and grass pollen allergens, mite allergens, cockroach allergens, cat allergens and the lipocalin allergens (Table 2) [12•,27•,28•,29,30,31•,32•,33•].

Tree pollen and fruit allergens

A number of tree pollen and fruit allergens belong to the group of plant proteins that are known as pathogenesis-related proteins (PRs). These proteins are either constitutively expressed or produced in response to developmental signals, physical stress and infection. There are currently 14 groups, with most of the denominated allergens belonging to PR-2, -3, -4, -5, -10 and -14 [4•]. Many of the groups are characterized by enzymatic

activity, particularly carbohydrases (PR-2, -3, -4) and ribonucleases (PR-10), as well as thaumatin-like proteins (PR-5). The PR-5 thaumatin-like proteins demonstrate some homology with the sweet tasting protein thaumatin from the fruit of the plant *Thaumatococcus danielli*, and at least three allergens have been shown to belong to this group, including the cherry allergen Pru av 2 [34], the apple allergen Mal d 2 [35] and the Mountain Cedar pollen allergen Jun a 3 [29]. However, the PR-5 proteins per se do not possess the property of sweetness. Their true function in plants has been unclear, although they have been shown to possess antifungal properties. Recently, however, studies have shown that these proteins, including the purified cherry allergen, possess endo β -1,3-glucanase activity. However, sequence homology studies indicate they belong to a different group of enzymes from that previously described [27•].

Grass pollen allergens

The biochemical function of the group 1 and 2 allergens from the grasses and pollens has also been unclear for some time, despite our knowledge of their sequences. However, Grobe *et al.* [28•] recently reported that the group 1 allergens from Timothy grass and maize pollens possess cysteine protease activity that is consistent with marked sequence homology with papain in the regions involved in catalysis. The allergens were shown to be activated by reducing agents and inhibited by *N*-ethylmaleimide and iodoacetic acid, both of which are characteristic features of cysteine proteases. However, this view has been challenged by Cosgrove and co-workers [36•], who failed to demonstrate proteolytic activity using the maize group 1 allergen. They showed that the group 1 allergens share sequence homology with a group of proteins designated β -expansins, which play a major role in plant cell wall growth by a process known as cell-wall loosening. This process may be particularly important in pollen tube growth *per se*, as well as penetration of the pollen tube into the style. Although it is argued that the biochemical mechanism(s) that is involved in this process is yet to be determined, those investigators suggest that the group 1 allergens are endoglucanases because the amino-terminal regions share sequence homology with the family-45 endoglucanases, and that the characteristic catalytic triad of such enzymes can be identified in this group of allergens. It is also argued that the β -expansin-like group 1 allergens may be two-domain proteins that comprise a catalytic domain and a carbohydrate-binding domain, based on the three-dimensional structure of the Timothy group 2 allergen, which is very similar to the carboxyl-terminal portions of the group 1 allergens.

Dust mite allergens

With regard to mite allergens, the functions of the groups 2, 5 and 7, and Mag allergens have proven to be

Table 2. Potential biochemical properties of previously described major allergens

Allergen	Function	References
Grass pollen Group 1	Cysteine protease/ endoglucanase	[27•,28•]
Tree pollen Jun a 3	Endo β -1,3-glucanases	[29]
Dust mites Group 2	Cholesterol binding	[30,31•]
Group 14	Lipid binding	[12•]
Mammals and insects Fel d 1	Serine-like protease	[32•]
Lipocalins	Endonucleases	[33•]

enigmatic. The function of the group 2 of allergens is still to be determined, despite recent data [30] that suggest a role in reproduction, given their sequence similarity with a group of phylogenetically conserved mammalian epidymal proteins. However, this role has been difficult to reconcile on the basis of data [37,38] that show that the allergen is restricted to the mite gut and faecal pellets. However, recent studies [31•] indicate that analogous mammalian epidymal proteins bind cholesterol, thus raising the possibility that the group 2 allergens are also be involved in the transfer of such a ligand, a proposal that could easily be tested. These data are also of interest given the description of the mite lipophorin allergens described above.

Cockroach allergens

Although described before the period over which this review extends, interesting information regarding the function of the cockroach allergen Bla g 2 has emerged. This allergen shows marked sequence similarity to porcine pepsin, although it is proteolytically inactive due to amino-acid substitutions in the catalytic region [39•]. However, further studies suggest that the allergen may be related to a large group of pregnancy-associated glycoproteins that are found in artiodactyl species such as cow and sheep. These aspartate protease-related proteins are associated with placental tissue and are expressed in the mononuclear and invasive binucleate cells in the epithelial layer of the trophectoderm [40]. The function of these proteins is unknown, but they possess the characteristic bilobed aspartate protease structure with a cleft capable of binding peptide ligands. Data suggest that they may play an immunosuppressive role in animals such as the cow, and it has been shown that they can stimulate the release of the α chemokine granulocyte chemotactic protein-2 from endometrium [41]. In the cockroach, however, just as in the case of the mite group 2 allergens, which show homology with proteins that are present in the mammalian reproductive system, the cockroach allergen is expressed predominantly in the gut and its true function remains unclear. This association between proteins of mammalian reproductive organs also extends to the bee venom groups 2 (hyaluronidase) and 4 (sperm acrosin protease-like) allergens, and the wasp venom group 5 allergens (cysteine-rich epididymal and salivary gland protein) [1•].

Cat allergens

The function of the cat allergen Fel d 1 is also unclear, although it is known to be a noncovalently linked 2-chain structure with one of the chains (chain 1) showing homology with uteroglobin and the α -subunit of the mouse salivary gland androgen-binding protein. Recently, however, data have been obtained [32••] that show that the Fel d 1 allergen may possess serine

protease activity toward gelatin and fibronectin. If this activity is confirmed, then the cat allergen may represent a novel group of proteases.

Lipocalin allergens

The lipocalins are a group of proteins that are thought to be involved in the transport of small, hydrophobic molecules. At least five major mammalian lipocalin allergens [Can f 1 (dog), Bos d 2 (cow), Bos d 5 (β -lactoglobulin; cow), Mus m 1 (mouse) and Equ c 1 (horse)] have now been described [42•]. Unlike allergens such as Bos d 2 and Mus m 1, which exist as monomers, Equ c 1 and Bos d 5 (β -lactoglobulin) are homodimers. The nature of the ligands bound by the mammalian lipocalins is unclear, although the mouse allergen is thought to bind pheromones and there are data to suggest that the horse allergen may bind histamine. Recently, however, it has been shown that the Bos d 5 lipocalin allergen, along with other nonallergenic lipocalins, possess nonspecific endonuclease activity [33••]. The catalytically important glutamic acid at position 134 in Bos d 5 that is necessary for phosphodiester bond cleavage is also conserved in Bos d 2, Equ c 1, Can f 1 (but not Can f 2) and Mus m 1 allergens, as well as the cockroach Bla g 4 lipocalin allergen, suggesting that they too may possess such activity.

Allergens yet to be biochemically characterized

While describing the biochemical functions of a number of groups of allergens, it is worth while drawing attention to those allergens that have been characterized at the molecular level, but whose endogenous function remains unclear (Table 3). It can be seen that the function of a number of mite, pollen, insect and, particularly, fungal allergens remain to be biochemically characterized.

Three-dimensional structures of allergens

The availability of recombinant proteins has greatly facilitated the ability of crystallographers to determine the three-dimensional structures of a variety of allergens. During the period of review, the crystal structures of two

Table 3. Allergens of unknown function

Type of allergen	Allergens
Fungal	Alt a 1, Alt a 4, Alt a 8, Alt a 9, Asp f 2, Asp f 4, Asp f 7, Asp f 9, Cla h 1, Cla h 1, Cla h 1, Cla h 7, Cla h 8, Cla h 9, Cop c 1, Mal f 1, Mal f 7, Mal f 8, Mal f 9
Dust mite	Group 5, Group 7, Blo t 1, Blo t 12
Insect	Sol i 2, Myr p 1, Myr p 2, Bla g 1, Per a 1, Aed a 2
Grass and weed pollen	Group 2, Group 3, Group 6, Group 11, Amb a 5
Olive pollen	Group 1, Group 6
Peanut	Gly m (Bd 28k)

This list is restricted to allergens that have been denominated by either the International Union of Immunological Societies Allergen Nomenclature Sub-Committee, or according to this Committee's guidelines.

allergens have been determined, namely the lipocalin allergen from horse dander (Equ c 1) [43] and hyaluronidase (Api m 2) from honey bee [44] (Table 4).

The structure of the horse allergen [43] is similar to that of the cow Bos d 2 allergen, and shows the characteristic β -barrel structure that contributes to their ligand-binding function, and a carboxyl-terminal α -helix.

The bee venom hyaluronidases are commonly recognized, 40-kDa allergens that are present in both bee and hornet venoms that hydrolyze hyaluronic acid (which comprises repeating *D*-glucuronic acid and *N*-acetyl glucosamine disaccharides). The three-dimensional structure of this allergen has now been determined and found to be a single-domained globular protein, which is similar in structure to a number of hydrolases, including bacterial chitinase A. The bee venom enzyme possesses a seven-stranded β/α -barrel, which is in contrast to the usual eight-stranded structure [44].

In addition to these allergens, a structure for the Jun a 3 allergen from Mountain Cedar pollen has been modelled on the basis of previously determined structures of homologous but nonallergenic thaumatin-like proteins [29], in a similar manner to that used to determine a structure for the mite allergen Der p 1 [45]. The Jun a 3 structure was modelled on the structures of the PR-5D protein from tobacco and thaumatin from the African berry, which show 52 and 47% sequence identity, respectively, and Der p 1 was modelled on papain and actinidin. In addition, the first description of a major aeroallergen complexed to the Fab fragment of a mouse

immunoglobulin G monoclonal antibody has been determined [46••]. The antibody used was known to block the binding of allergen-specific immunoglobulin E to Bet v 1, and thus the epitope bound by the monoclonal Fab fragment probably represents an immunoglobulin E epitope, with obvious relevance.

Allergens and immunotherapy

Immunotherapy has regained momentum because of the introduction of molecular biology to the study of allergens. It is now feasible to express recombinant allergens or epitopes using a variety of expression vectors, including bacteria (e.g. *Escherichia coli*), yeast (*Pichia pastoris*) and, more recently, tobacco leaves [47•]. This technology is capable of providing large quantities of well-characterized proteins with appropriate post-translational modifications, as well as providing proteins that are sufficiently mutated to be immunogenic but not allergenic [3•], as well as monovalent epitopes or mimotopes [48,49].

These reagents are currently being married to novel adjuvants, for example immunostimulatory DNA sequences that comprise unmethylated CpG motifs flanked by two purines 5' and two pyrimidines 3', which are commonly found in bacteria but not mammalian DNA [50••], to modulate allergic disease. These dinucleotide motifs are recognized by both intracellular CpG-binding proteins [51] and the cell-surface receptors [52•] that are present in mammalian cells to activate natural killer cells, monocytes, dendritic cells and B cells, resulting in the secretion of a variety of cytokines, such as interleukin-6, interleukin-10 and interferon- γ [50••]. A

Table 4. Allergens of unknown three-dimensional structure

Source	Allergen	Function	Technique used to determine structure	Protein database code or reference
Pollens				
Birch	Bet v 1	Ribonuclease	X-ray diffraction	1BV1
	Bet v 1-Fab complex	—	X-ray diffraction	1FSK
	Bet v 2	Profilin	X-ray diffraction	1CQA
Timothy grass	Phl p 2	Unknown	X-ray diffraction	1WA8
Ragweed	Amb t 5	Unknown	NMR	2BBG
Mountain Cedar	Jun a 3	PR-5 protein	Modelling; based on structure of mouse urinary protein Mus m 1	[29]
Latex	Heb v 8	Profilin	X-ray diffraction 1	G5U
Stinging insect venom				
Bee	Api m 2	Hyaluronidase	X-ray diffraction	[44]
Wasp	Ves v 5	Unknown	X-ray diffraction	1QNX
Mammalian dander				
Horse	Equ c 1	Lipocalin	X-ray diffraction	1EW3
Cow	Bos d 2	Lipocalin	X-ray diffraction	1BJ7
Mouse	Mus m 1	Lipocalin	X-ray diffraction	1MUP
Dust mites				
<i>Dermatophagoides pteronyssinus</i>	Dep p 1	Cysteine protease	Modelling; based on structure of papain and actinidin	[45]
	Der p 2	Unknown	NMR	1A9V
<i>Dermatophagoides farinae</i>	Der f 2	Unknown	NMR	1AHK

NRM, nuclear magnetic resonance; PR, pathogenesis-related protein.

number of animal model studies show that administration of CpG reagents stimulates T-helper-1 immune responses, resulting in the downregulation of allergic inflammation [53,54] as well as the enhancement of immunogenicity, but not allergenicity of allergens such as ragweed Amb a 1 and Bet v 1 [55,56]. These agents appear to be nontoxic and offer significant advantages over other types of allergen modification techniques such as chemical modification. The efficacy of the allergen DNA vaccines may owe much to the presence of such motifs [50••].

Allergen nomenclature

Over the years, allergen chemists have developed their own terminology to help bring consistency and enlightenment to a confusing field when little structural data were available. Now, however, the structures of many of the clinically important allergens have been determined, and it can be seen that the majority (and perhaps eventually all) belong to previously described groups of proteins. Thus, it may now be the time to debate whether it is still appropriate to denominate allergens on the basis of genus and species source, combined with priority of publication or clinical importance.

In this regard, pre-existing and precise nomenclatures exist, for example the Enzyme Commission nomenclature (which clarifies the type of enzyme, e.g. the serine protease EC 3.4.21.4) and the trivial name (e.g. trypsin). Mites contain a serine protease with significant sequence homology and substrate specificity to a range of enzymes classified as trypsins from many species. This allergen has been denominated the 'group 3' allergen, but this description tells us little about its endogenous enzymatic function, in contrast to the term 'mite trypsin'.

The current allergen nomenclature system also has the potential to confuse, because a biochemically similar allergenic protein found in many species across different phyla may be given a different group name in different species. For example, profilins are ubiquitous, but they have been denominated the groups 11 or 12 allergens in grasses [57,58]; the group 2 allergens in Birch, Birch-related tree pollens and sunflower pollen [59,60]; the group 4 allergen in celery [61]; the group 3 allergen in soybean [62]; and the group 8 allergen in latex [63]. In the nonallergy literature, such proteins are known simply as profilins and, as such, their function and interrelationships are clear [64]. This situation is not restricted to the minor profilin allergens, and has the potential to continue as the functions of more allergens become apparent.

Consistent denomination cannot at present occur because the appropriate group designation may already be

in use. Finally, the current terminology used by allergists is ignored by biochemists, who were often the first to characterize the proteins that have subsequently been shown to be allergenic.

Allergens and particulates

The majority of allergen immunochemical studies so far performed have concentrated primarily on individual allergens. However, the immune systems of most individuals are not necessarily exposed to allergen in this manner, but rather in particulate form, either as pollens or their starch granules, fungal spores or faecal pellets, or they may become associated with exogenous particulate material such as diesel exhaust particles. Such particles are currently being investigated, because they may contribute to resulting immune responses by facilitating physical contact between the allergen source and the local network of antigen-presenting cells within the lung, by acting as adjuvants or by carrying the allergen.

For example, it has been shown that, after inhalation, fungal spores are forced through the aqueous layer lining both airways and alveoli onto the epithelial surface by surfactant [65•]. In addition, some particulates such as pollen are known to release smaller particles such as starch granules on contact with moist surfaces, resulting in enhanced capacity to enter deep into the respiratory tract and trigger sensitization or provocation of allergic symptoms [66–68]. Interestingly, these granules may not only carry allergen, but also act as adjuvants because they have been shown to bind to alveolar macrophages via both integrin and c-type lectin receptors with subsequent phagocytosis [69••] and stimulate the production of cytokines and mediators such as nitric oxide. Similarly, fungal spores that comprise the cell-wall polymer β 1–3 glucan may also possess adjuvant properties [70]. This carbohydrate polymer has recently been found in pollen, and therefore may also contribute to the allergenicity of these particulates [71].

Other particles, including house dust and diesel exhaust particles, have also been shown to carry allergens such as house dust mite, cat, dog and birch allergens on their surface, as well as possessing adjuvant activity [72–75]. The nature of the adjuvant in these particulates is unclear, but may be related to the presence of metal constituents [75].

Conclusion

In the present review, we describe a number of new allergen groups and discuss recent advances in our understanding of their actual and potential endogenous biochemical activities, as well as the nature of the particles that may carry them into the lung. In addition, the impact of this knowledge of their molecular biology

on the development of novel immunotherapeutic regimens is described.

We now know much about the allergens associated with allergic disease, and these data continue to converge with those emerging from many other disciplines. We see that the protein allergens fall, not unexpectedly, into previously delineated protein groups. Given that allergens are proteins with intrinsic activity, it follows that these functions may have implications for the development of immune responses after exposure of host tissues to these allergens. Because it is now generally believed there is no single defining structural characteristic that confers allergenicity on a protein [2•], the potential of properties such as proteolytic activity and size, etc., on immunogenicity and allergenicity are currently being investigated [76•,77,78•]. In such studies, we must also be aware that there are likely to be other factors, such as the nature of the allergen carrier, that impact on this process.

We are now entering a new phase in which the recent technologies, combined with advances in our understanding of the immune system, the pharmacology of allergic diseases and the genetics that underlie mediator production, promise much in the new millennium. Whether the immunologists or the pharmacologists triumph in alleviating allergic disease remains to be determined.

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