Current perspectives

Nomenclature and structural biology of allergens

Martin D. Chapman, PhD,[a] Anna Pomés, PhD,[a] Heimo Breiteneder, PhD,[b] and Fatima Ferreira, PhD[c] *Charlottesville, Va, and Vienna and Salzburg, Austria*

Purified allergens are named using the systematic nomenclature of the Allergen Nomenclature Sub-Committee of the World Health Organization and International Union of Immunological Societies. The system uses abbreviated Linnean genus and species names and an Arabic number to indicate the chronology of allergen purification. Most major allergens from mites, animal dander, pollens, insects, and foods have been cloned, and more than 40 three-dimensional allergen structures are in the Protein Database. Allergens are derived from proteins with a variety of biologic functions, including proteases, ligand-binding proteins, structural proteins, pathogenesis-related proteins, lipid transfer proteins, profilins, and calcium-binding proteins. Biologic function, such as the proteolytic enzyme allergens of dust mites, might directly influence the development of IgE responses and might initiate inflammatory responses in the lung that are associated with asthma. Intrinsic structural or biologic properties might also influence the extent to which allergens persist in indoor and outdoor environments or retain their allergenicity in the digestive tract. Analyses of the protein family database suggest that the universe of allergens comprises more than 120 distinct protein families. Structural biology and proteomics define recombinant allergen targets for diagnostic and therapeutic purposes and identify motifs, patterns, and structures of immunologic significance. (J Allergy Clin Immunol 2007;119:414-20.)

Key words: *Allergen, nomenclature, IgE, asthma, protein families, allergic disease, protein structure, biologic function*

The biochemistry of allergens is underpinned by a Linnean system of nomenclature that is maintained by the World Health Organization (WHO) and International Union of Immunological Societies (IUIS) Allergen Nomenclature Sub-Committee. The systematic nomenclature was the brainchild of the late Dr David Marsh (Johns Hopkins University), who authored a seminal chapter on ''Allergens and the genetics of allergy'' in the 1970s. This chapter reviewed allergen structure, immune response, and immunogenetics and also provided the first definitions of major and minor allergens.[1] At that time, allergens were described using a variety of generic names, such as Antigen E, Rye 1, and Cat-1, and it was not uncommon for researchers to use different names for the same allergen. In 1980, Marsh, together with Dr Henning Lowenstein and Dr Thomas Platts-Mills, developed the systematic nomenclature during the 13th Symposium of the Collegium Internationale Allergologicum (Lake Bodensee, Germany). A committee, including Drs Te Piao King and Larry Goodfriend, drafted the nomenclature and developed criteria for biochemical properties and allergenic importance that would qualify allergens in the new system. The systematic nomenclature was adopted by the WHO/IUIS and published in the Bulletin of the WHO in 1986 and in revised form in 1994.[2-5] Allergens are named using the first 3 letters of the genus, followed by a single letter for the species and a number indicating the chronologic order of allergen purification. Thus the major cat allergen (formerly Cat-1) became *Felis domesticus* allergen 1 or Fel d 1.

The systematic allergen nomenclature proved to be robust and accommodated the explosion of data on new allergens that occurred in the 1980s and 1990s, when the most important allergens from mites, animal dander, insects, pollens, molds, and foods were cloned. Allergens entered into the nomenclature are being used to develop allergen-specific diagnostics and to formulate recombinant allergen vaccines.[6-8] Allergen biochemistry is now entering a new era of structural biology and proteomics that will require sophisticated tools for data processing and bioinformatics and might require further

From [a]Indoor Biotechnologies, Inc, Charlottesville; [b]the Medical University of Vienna; and [c]Christian Doppler Laboratory for Allergy Diagnosis and Therapy, University of Salzburg.

H. B. is supported by Austrian Science Fund Grant SFB F01802. F. F. is supported by the Christian Doppler Research Association, the Austrian Science Fund (Grants S8802 and P16456), and the Oesterreichische Nationalbank (Grant no. 10150).

Disclosure of potential conflict of interest: M. D. Chapman owns stock in Indoor Biotechologies, Inc; has received grant support from the National Institute of Environmental Health Sciences Small Business Innovation Research award program; and is employed by Indoor Biotechnologies, Inc. A. Pomés is employed by Indoor Biotechnologies, Inc. F. Ferreira has consulting arrangements with Indoor Biotechnologies, Inc, and has received grant support from Biomay AG. H. Breiteneder has declared that he has no conflict of interest.

Received for publication October 17, 2006; revised October 31, 2006; accepted for publication November 2, 2006.

Available online December 14, 2006.

Reprint request: Martin D. Chapman, PhD, INDOOR Biotechnologies, Inc, 1216 Harris St, Charlottesville, VA 22903. E-mail: mdc@inbio.com.

0091-6749/$32.00

doi:10.1016/j.jaci.2006.11.001

Abbreviations used
EF hand: Calcium-binding motif (E-helix-loop-F-helix) in a "hand" configuration
IUIS: International Union of Immunological Societies
PR-10: Pathogenesis-related group 10
WHO: World Health Organization

delineation of the nomenclature. Increasingly, the wealth of structural information is enabling the biologic function of allergens to be established and the assignment of allergen function to diverse protein families. In this article we review the allergen nomenclature system and recent advances in structural biology that have established the form and function of many important allergenic proteins.

CURRENT ALLERGEN NOMENCLATURE

The current allergen nomenclature was developed through 2 iterations in 1986 and 1994, since which it has been unchanged.[2-5] The nomenclature is not italicized, has a space after each of the first two elements, and uses Arabic numerals: hence Der p 1, Bet v 1, Fel d 1, and Amb a 1, for example. The nomenclature covers different molecular forms of the same allergen: isoallergens and isoforms (or variants). Isoallergens are multiple molecular forms of the same allergen that share extensive IgE cross-reactivity. They are defined in the nomenclature as allergens from a single species with 67% or greater amino acid sequence identity. The most prolific example is birch pollen allergen, Bet v 1, which has more than 40 sequences representing 31 isoallergens, showing 73% to 98% sequence identity.[9] The Bet v 1 isoallergens are distinguished by additional numbers: Bet v 1.01 through Bet v 1.31. Similarly, 4 isoallergens of ragweed allergen, Amb a 1, are listed as Amb a 1.01, Amb a 1.02, Amb a 1.03, and Amb a 1.04. The terms *isoform* or *variant* refer to polymorphic variants of the same allergen, which typically show greater than 90% sequence identity. Isoforms are distinguished in the nomenclature by 2 additional numbers. The 42 isoforms of Bet v 1 are listed as Bet v 1.0101, Bet v 1.0102, Bet v 1.0103, and so on. Recent studies have shown that mite allergen sequences derived from environmental isolates by means of high-fidelity PCRs show extensive numbers of isoforms: 23 for Der p 1 (Der p 1.0101 to Der p 1.0123) and 13 for Der p 2.[10-12] These polymorphisms might affect T-cell responses or alter antibody-binding sites and should be taken into account in designing allergen formulations for immunotherapy.[12]

The reader is referred to a recent review for finer points of the current nomenclature.[9] To submit a newly defined allergen, investigators should download the "New Allergen Name" form from the official website of the WHO/IUIS Sub-Committee on Allergen Nomenclature at www.allergen.org. The application is reviewed by the Allergen Nomenclature Sub-Committee, which is chaired by Dr Heimo Breiteneder (Medical University of Vienna, Vienna, Austria) and comprises 19 experts in the field (see Table E1 in the Online Repository at www.jacionline.org). The molecular properties of allergens to be included in the nomenclature must be unambiguously defined by submitting nucleotide and amino acid sequence data, by intrinsic molecular properties (molecular weight, isoelectric point, and secondary structure), by purification of the allergen to homogeneity, and by monospecific antibodies. The importance of the allergen in causing IgE responses should be demonstrated by *in vitro* testing, by biologic testing (histamine release or skin testing), and by comparing the prevalence of IgE antibody binding in a large group of allergic patients.[9] The goal of the Allergen Nomenclature Subcommittee is simply to provide systematic nomenclature and clear identification of allergens and not to grade allergens on their importance or assign any ownership rights. Allergens must be shown to cause IgE antibody production in at least 5 individuals to be included, but otherwise, researchers must demonstrate the merits and significance of their particular protein.

ADVANCES IN STRUCTURAL BIOLOGY AND PROTEOMICS

Molecular cloning and searches of GENBANK, EMBL, and other protein databases have allowed the biologic function of many allergens to be assigned based on their amino acid sequence homology to proteins of known function. Assignments based on sequence homology do not prove that an allergen has a given function but do provide evidence that can be used to investigate whether a particular allergen has the putative biologic activity. For example, the homology of Der p 1 to papain and actinidin strongly suggested that Der p 1 was a cysteine protease. This was later confirmed by using functional assays and by x-ray crystallography, which determined the structures of the proenzyme and mature forms of the allergen.[13,14] The Protein Database contains more than 40 three-dimensional structures of allergens. Structural studies often reveal features of biologic importance that might not be apparent from biologic assays.

Allergens belong to protein families with diverse biologic functions that can be summarized as follows:

(1) indoor allergens: enzymes (especially proteases), ligand-binding proteins or lipocalins, albumins, tropomyosins, and calcium-binding proteins;
(2) pollen allergens: pathogenesis-related proteins, calcium-binding proteins, pectate lyases, β-expansins, and trypsin inhibitors; and
(3) plant and animal food allergens: lipid transfer proteins, profilins, seed storage proteins, and tropomyosins.

Indoor allergens

In some cases the biologic function of an allergen might have direct effects on IgE responses and have

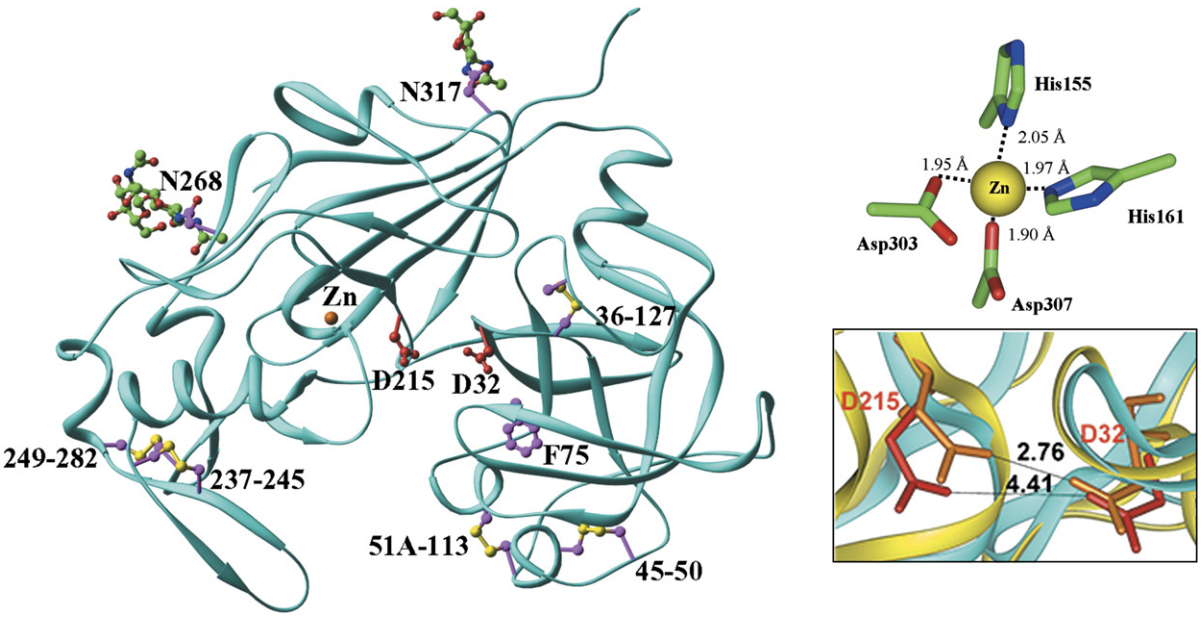

FIG 1. Crystal structure of the cockroach allergen Bla g 2. *Left,* Structure of Bla g 2 showing residues at the region of the catalytic site (D215, D32 [1yg9.pdb]).[19] *Right,* The zinc ion *(yellow sphere)* with coordinating residues and interatomic distances *(top)* and aspartate positions in Bla g 2 *(red aspartates on blue ribbon)* and in pepsin (*orange aspartates on yellow ribbon, bottom*). Reprinted with permission from Gustchina A, Li M, Wunschmann S, Chapman MD, Pomés A, Wlodawer A. Crystal structure of cockroach allergen Bla g 2, an unusual zinc binding protein with a novel mode of self-inhibition. J Mol Biol 2005;348:433-44.[19]

proinflammatory effects. Cysteine and serine protease dust mite allergens (Der p 1, Der p 3, Der p 6, and Der p 9) can cleave the low-affinity IgE receptor, can promote T_H2 responses, and have proinflammatory effects by initiating release of T_H2 cytokines. The enzyme hypothesis proposes that enzymatic activity has synergistic effects on IgE production and that enzymes can act directly to damage the bronchial epithelium and promote inflammation in the lung.[15,16] This has led to a wider interpretation that enzymatically active allergens have special importance in chronic asthma, whereas allergen sources (eg, animals) that are not enzymes are less associated with persistent asthma and more likely to induce tolerance. Other evidence suggests that this might not be the case. Important dust mite allergens (Der p 2, Der p 5, and Der p 7) are not enzymes. Cockroach is an important cause of chronic asthma in populations at lower socioeconomic status in the United States, but none of the cockroach allergens that have been cloned are active proteolytic enzymes.[17]

The cockroach allergen Bla g 2 is an interesting example of how sequence homology and structural data need to be combined to obtain a complete picture of the allergen. When Bla g 2 was cloned, it was considered to be an aspartic protease based on sequence homology. Molecular modeling revealed substitutions in the 2 aspartic protease motifs in the catalytic sites, indicating that the allergen was not an active protease (this was confirmed using *in vitro* aspartic protease assays).[18] Bla g 2 showed homology to a group of inactive aspartic proteases known as pregnancy-associated glycoproteins, which are found in horses, sheep, pigs, and cattle and are thought to have a ligand-binding function. X-ray crystallography of Bla g 2 confirmed that molecular distortions caused by amino acid substitutions in the catalytic site would inactivate the enzyme (by excluding a water molecule involved in catalysis) and also confirmed the presence of a deep ligand-binding cleft (Fig 1).[19] Bla g 2 also contained a zinc ion, indicating that the allergen was a zinc-binding protein, which was not predicted from the biologic assays.

Bla g 2 appears to be one of a growing number of allergens that has a ligand-binding function. The major mite allergen Der p 2 is homologous to MD-2 and Niemann-Pick disease C2-type protein, which are lipid-binding proteins.[20] Most mammalian allergens (cat, dog, rat, mouse, horse, and cow) are either lipocalins or albumins: Rat n 1 and Mus m 1 are pheromone-binding proteins that rodents use to mark their territories, and Can f 1 has the functional motif of a cysteine protease inhibitor, as does Fel d 3, a cystatin allergen that was cloned from a cat skin cDNA library.[6] Fel d 1 was homologous to uteroglobin, and x-ray crystallography of recombinant Fel d 1 showed that the allergen had a 480$Å^3$ asymmetric internal cavity capable of binding an endogenous ligand (Fig 2).[21] Although Fel d 1 and the animal lipocalins appear to bind ligands, these proteins have quite different structures: Fel d 1 is a complex heterodimeric protein with 8 α-helices, whereas the lipocalins usually have 8 β-sheets with a short α-helical C-terminus. Unlike mite proteolytic allergens, ligand-binding function *per se* does not appear to have direct effects on IgE production or inflammation. However,

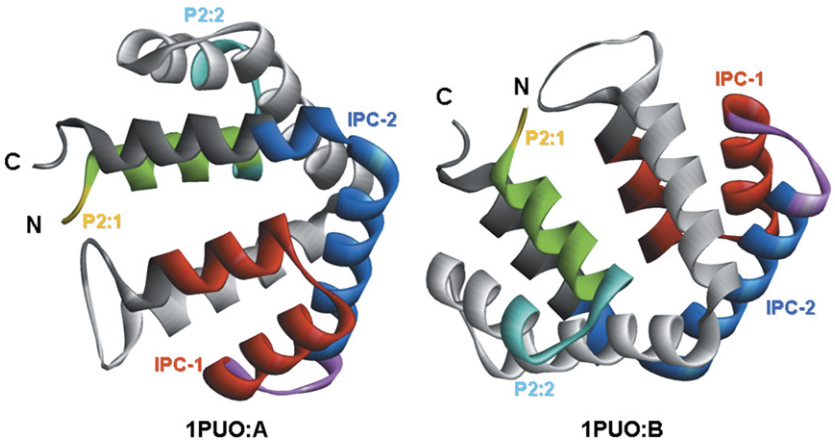

FIG 2. Crystal structure of recombinant cat allergen Fel d 1 (1puo.pdb). Fel d 1 is a 2-chain heterodimer with the C-terminus of chain 1 (in *gray*) and the N-terminus of chain 2 (in *white*).[21] The heterodimers associate together to form a larger dimeric structure. Also shown are various T-cell epitopes in chain 1 (*IPC-1* and *IPC-2*) and chain 2 (*P2:1* and *P2:2*).

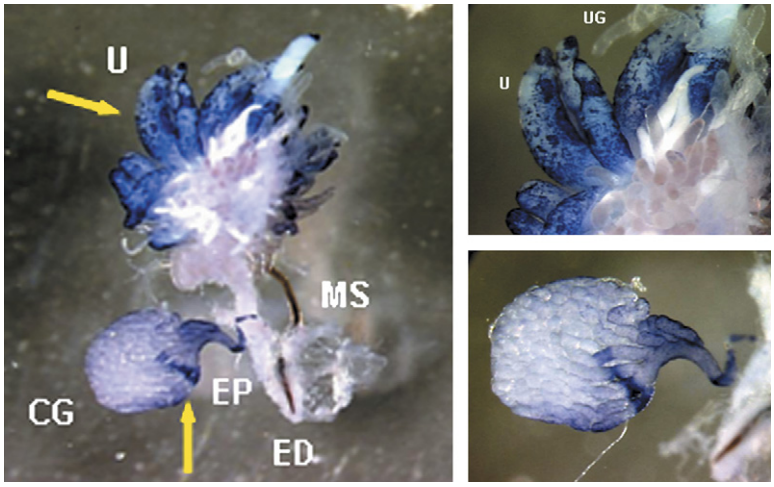

FIG 3. Localization of Bla g 4 in the male cockroach reproductive system by means of *in situ* hybridization. Blue staining shows deposition of Bla g 4 among the reproductive tissues *(left)*, with higher magnification of large apical utricles (*U, upper right*) and the conglobate gland (*C, lower right*). Reproduced with permission of Dr Coby Schal and Blackwells Scientific Publishing Company (Oxford, United Kingdom) from Fan et al.[24] *CG*, Conglobate gland; *EP*, ejaculatory pouch; *ED*, ejaculatory duct; *MS*, median sclerite; *UG*, uricose gland.

high-dose exposure to animal allergens (notably cat) is associated with tolerance and the production of a modified T_H2 response.[22] This appears to be related to the fact that exposure to animal allergens can be one or more orders of magnitude higher than exposure to other indoor allergens and that these allergens remain airborne for long periods, further increasing allergen exposure. It is difficult to establish the nature of the ligand or ligands bound by this class of allergens. Specific chemical ligands were identified in crystals of Rat n 1 and Mus m 1, and the strategy of using crystallography of natural allergens to analyze the ligand might be effective for other allergens.[23] Another approach that provides clues to function is to analyze tissue localization and expression. The cockroach allergen Bla g 4 is also a lipocalin and had been considered to be a pheromone- or pigment-binding protein similar to other insect lipocalins. However, recent ultrastructural localization studies with *in situ* hybridization showed that Bla g 4 is only found in accessory glands of the male cockroach reproductive system (conglobate gland and utricles) and is transferred to the female during copulation (Fig 3).[24] This suggests that Bla g 4 has a reproductive function and that dried seminal secretions or spermatophores might be the form by which the protein accumulates in the environment and becomes airborne as an allergen.

Pollen allergens

Comparison of 157 pollen allergen sequences within the Pfam protein family database (http://www.sanger.ac.uk/Software/Pfam) showed that pollen allergens are distributed within 29 protein families from a total of 2615 seed plant families.[25] Bet v 1 homologues (pathogenesis-related

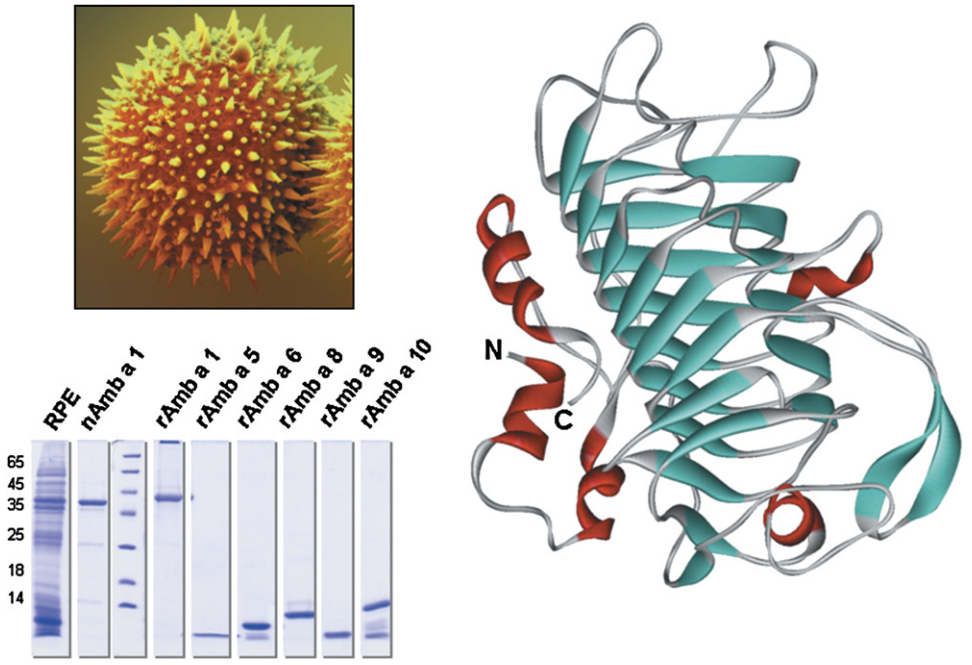

FIG 4. From pollen to protein. A short ragweed pollen grain *(left upper panel)* and a series of purified recombinant allergens from short ragweed *(lower left panel)* analyzed by means of gel electrophoresis. *Right,* Three-dimensional structure of Amb a 1 modeled from the x-ray coordinates of Jun a 1, a pectate lyase from mountain cedar pollen.

group 10 [PR-10] proteins), profilins, calcium-binding proteins, and expansins are the major pollen allergen families.[26] Profilins and Bet v 1 homologues are also the most relevant families that are responsible for pollen-food oral allergy syndromes.[27] PR-10 protein allergens from trees of the genus *Fagales* include Bet v 1, Cor a 1, Aln g 1, and Car b 1. These proteins exist as multiple isoforms with greater than 70% sequence identity that are encoded by alleles of orthologous and paralogous genes (orthologous = homologous genes from different species; paralogous = homologous genes derived from gene-duplication events).[28] Two families of paralogous genes, altogether 14 alleles of 7 different genes, encode Bet v 1 isoforms.[29] Sensitization by Bet v 1 frequently results in IgE antibody cross-reactions with homologues in soft fruits and vegetables, which share as little as 37% to 67% sequence homology with Bet v 1.[25] Other cross-reactive pollen-food homologues usually show at least 50% sequence conservation, suggesting that it is difficult to define a simple relationship between the degree of sequence homology and allergenic cross-reactivity. In terms of function, the crystal structure of Bet v 1 showed interaction with phytosteroids, suggesting that PR-10 proteins might function as plant-steroid carriers.[30]

Profilins are involved in the regulation of actin polymerization, and these ubiquitous allergens cause cross-reactions between a broad range of pollen and food sources. Calcium-binding proteins from pollens, another family of cross-reactive allergens, contain a molecular signature of 2 to 4 calcium-binding motifs (E-helix-loop-F-helix) in a ''hand'' configuration (EF hand) and are described as polcalcins because their expression is restricted to pollen grains.[31] Comparison of pollen allergens with 2-, 3-, and 4-EF hand domains showed that timothy grass Phl p 7 is the most cross-reactive.[32] Profilins and calcium-binding proteins show greater than 60% sequence similarity with cross-reactive members from different plant families.[25] However, sequence similarities between calcium-binding allergens from pollen and calmodulins, or calmodulin-like proteins, from vegetative plant tissue or from animals are quite low (39% to 42%) and are not cross-reactive.

Grass pollen group 1 allergens contain 7 conserved cysteine residues in the N-terminus and are homologous to plant β-expansins, which are involved in cell-wall loosening and extension.[33] Extensive cross-reactivity between group 1 allergens in different grass species has been described, which is restricted to proteins sharing more than 50% sequence identity.[25]

Although weeds are taxonomically quite diverse, data on structure-function relationships among allergens is derived mainly from ragweed, mugwort, and pellitory (a common weed in the Mediterranean area). Major allergens from weed pollen were classified into 4 protein families: (1) the ragweed Amb a 1 family of pectate lyases (Fig 4); (2) the defensin-like Art v 1 family from mugwort, feverfew, and sunflower; (3) the Ole e 1–like allergens Pla l 1 from plantain and Che a 1 from goosefoot; and (4) the nonspecific lipid transfer proteins Par j 1 and Par j 2 from pellitory.[34,35] Amb a 1 homologues have been identified in cypress, Juniper, and cedar (Fig 4).[36] There is considerable sequence divergence (45% to 49% identity) and

weak cross-reactivity between the allergenic pectate lyases from *Ambrosia* species, Cupressaceae, and homologues from fruits.[25] The low level of sequence similarity between Ole e 1, Pla l 1, and Che a 1 also matches their weak cross-reactivity. The nonspecific lipid transfer proteins are potent food allergens involved in the transport of lipids and phospholipids across membranes. These proteins also have antifungal and antibacterial activities and are members of pathogenesis-related group 14.

Plant and animal food allergens

Plant food allergens were classified based on their biologic function or on their membership to protein families.[37] Using the Pfam protein database, all plant food allergens could be assigned to 31 of 8296 protein families.[38] Likewise, all known pollen allergens are members of a restricted number of protein families.[38] The prolamin superfamily comprises the largest number of allergenic plant food proteins.[37,39] Prolamins are proline- and glutamine-rich α-helical proteins with a conserved skeleton of 8 cysteine residues that serve several biologic functions. They comprise 3 major groups of plant food allergens: the seed storage 2S albumins found in tree nuts and seeds, the defense-related nonspecific lipid transfer proteins found in soft fruits and vegetables, and cereal α-amylase/trypsin inhibitors.[37,40] The second major superfamily of plant food allergens, the cupins, are widely distributed among all kingdoms and share a conserved β-barrel fold.[41] The cupin family contains 2 groups of seed storage proteins called vicilins and legumins, which are important peanut and tree nut allergens, such as Ara h 1 from peanut and Jug r 2 from walnut. The profilin and Bet v 1 family includes tree pollinosis–associated food allergens with low stability that induce symptoms of the oral allergy syndrome. These 4 protein families contain approximately 65% of all plant food allergens. Of the remaining 27 allergen-containing protein families, more than 50% harbor allergenic proteins of the plant defense system or pathogenesis-related proteins, such as the cysteine proteinases, thaumatin-like proteins, or chitinases.[37]

The most important animal food allergens are present in milk, egg, and seafood. Mammalian milk allergens are found predominantly in 3 protein families. α-Lactalbumin, which is essential for milk production, is a member of glyosyl hydrolase family 22. β-Lactoglobulin is a lipocalin, and the casein family harbors the major constituents of milk. Ovomucoid, the most important egg allergen, is a Kazal-type serine protease. In seafood there are 2 major groups of allergenic proteins. The tropomyosins of crustacea and mollusks play a key regulatory role in muscle contraction, and the calcium-binding parvalbumins present in fish and amphibians are important for the relaxation of muscle fibers.

ALLERGEN DATABASES

The official Web site for the WHO/IUIS Sub-Committee on Allergen Nomenclature is www.allergen.org. This site lists all allergens and isoforms that are recognized by the committee and is updated on a regular basis (see Table E2 in the Online Repository at www.jacionline.org). The improved WHO/IUIS site contains allergen sequences, Protein Database numbers, and information on structural features related to allergenicity for a given allergen. Several other online databases provide sequences and features for structural analysis. The Structural Database for Allergenic Proteins has bioinformatic tools to screen candidate allergens or peptides for allergenic cross-reactivities and IgE epitopes.[42] The Food Allergy Research and Resource Program database provides ''bioinformatic allergen assessment reports'' that enable the potential allergenicity of genetically modified foods to be investigated. Allergome provides current literature references, as well as a list of suppliers of allergens and assays.

CONCLUSIONS

Nomenclature and structural biology play a crucial role in defining allergens for research studies and for the development of new clinical products. Classification of allergens into known protein families or superfamilies augments the nomenclature and allows biologic function to be investigated. For food and pollen allergens, intrinsic protein structure probably plays an important role in determining allergenicity by conferring, for example, heat stability or resistance to digestion in the digestive tract. Sequence comparisons and assignments to protein families provide a molecular basis for clinical cross-reactions between food, pollen, and latex allergens that give rise to oral allergy syndromes. Analysis of the Pfam database suggests that there are currently more than 120 molecular architectures that are responsible for eliciting IgE responses. In the future, it will be important to marry the systematic nomenclature with classification of allergens into protein families to provide complete delineation of allergens and their structure-function relationships as part of a comprehensive bioinformatics database. The practical consequences of this approach are seen most clearly with genetically modified foods, in which sequence comparisons can be used for safety assessment of genetically modified organisms.

The success of the WHO/IUIS systematic nomenclature lies in its simplicity and its Linnean roots. One can envision further expansion of the nomenclature to include as-yet-unidentified protein allergens, such as from pollens (or foods) in Asia and the Indian subcontinent, few of which have been identified to date. It might be possible to adapt the system to include engineered protein molecules, such as hypoallergens, CpG-modified allergens, allergens engineered with antibodies or receptors, T-cell peptides, and recently described nonprotein allergens and lipid and glycolipid antigens derived from cypress pollen that stimulate natural killer T cells.[43,44] The initial success of clinical trials with a multiallergen recombinant grass pollen vaccine underscores the need for a firm foundation of structural biology to develop new allergy therapeutics.[8] The exciting prospect with these approaches is the

translation of basic research on allergen biology to produce new diagnostic and therapeutic products that will benefit patients with allergic respiratory disease.

We thank Dr Wayne Thomas for his dedicated service as Chair of the WHO/IUIS Allergen Nomenclature Sub-Committee from 1997 through 2006.

REFERENCES

1. Marsh DG. Allergens and the genetics of allergy. In: Sela M, editor. The antigens, Vol. III. New York: Academic Press; 1975. p. 271-350.
2. Marsh DG, Goodfriend L, King TP, Lowenstein H, Platts-Mills TAE. Allergen nomenclature. Bull World Health Organ 1986;64:767-70.
3. King TP, Hoffman, Lowenstein H, Marsh DG, Platts-Mills TAE, Thomas WR. Allergen Nomenclature. Bull World Health Organ 1994;72:797-80.
4. King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TAE, Thomas WR. Allergen nomenclature. Int Arch Allergy Appl Immunol 1994;105:224-33.
5. King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TAE, Thomas W. Allergen nomenclature. Allergy 1995;9:765-74.
6. Chapman MD, Smith AM, Vailes LD, Arruda K, Dhanaraj V, Pomés A. Recombinant allergens for diagnosis and therapy of allergic diseases. J Allergy Clin Immunol 2000;106:409-18.
7. Ferreira F, Wallner M, Thalhamer J. Customized antigens for desensitizing allergic patients. Adv Immunol 2004;84:79-129.
8. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005;116:608-13.
9. Chapman MD. Allergen nomenclature. In: Lockey RF, Bukantz SC, Bousquet J, editors. Allergens and allergen immunotherapy. New York: Marcel Decker; 2003. p. 51-64.
10. Smith AS, Benjamin DC, Hozic N, Derewenda U, Smith WA, Thomas WR, et al. The molecular basis of antigenic cross-reactivity between the group 2 mite allergens. J Allergy Clin Immunol 2001;107:977-84.
11. Smith WA, Hales BJ, Jarnicki AG, Thomas WR. Allergens of wild house dust mites: environmental Der p 1 and Der p 2 sequence polymorphisms. J Allergy Clin Immunol 2001;107:985-92.
12. Piboonpocanun S, Malinual N, Jirapongsananuruk J, Vichyanond P, Thomas WR. Genetic polymorphisms of major house dust mite allergens. Clin Exp Allergy 2006;36:510-6.
13. Meno K, Thorsted PB, Ipsen H, Kristensen O, Larsen JN, Spangfort MD, et al. The crystal structure of recombinant proDer p 1, a major house dust mite proteolytic allergen. J Immunol 2005;175:3835-45.
14. de Halleux S, Stura E, VanderElst L, Carlier V, Jacquemin M, Saint-Remy JM. Three-dimensional structure and IgE-binding properties of mature fully active Der p 1, a clinically relevant major allergen. J Allergy Clin Immunol 2006;117:571-6.
15. Sharma S, Lackie PM, Holgate ST. Uneasy breather: the implications of dust mite allergens. Clin Exp Allergy 2003;33:163-5.
16. Asokanathan N, Graham PT, Stewart DJ, Bakker AJ, Eidne KA, Thompson PJ, et al. House dust mite allergens induce proinflammatory cytokines from respiratory epithelial cells: the cysteine protease allergen, Der p 1, activates protease-activated receptor (PAR)-2 and inactivates PAR-1. J Immunol 2002;169:4572-8.
17. Arruda LK, Vailes LD, Ferriani VPL, Santos ABR, Pomés A, Chapman MD. Cockroach allergens and asthma. J Allergy Clin Immunol 2001; 107:419-28.
18. Wünschmann S, Gustchina A, Chapman MD, Pomés A. Cockroach allergen Bla g 2: an unusual aspartic proteinase. J Allergy Clin Immunol 2005;116:140-5.
19. Gustchina A, Li M, Wünschmann S, Chapman MD, Pomés A, Wlodawer A. Crystal structure of cockroach allergen Bla g 2, an unusual zinc binding protein with a novel mode of self-inhibition. J Mol Biol 2005;348:433-44.
20. Gruber A, Mancek M, Wagner H, Kirschning CJ, Jerala R. Structural model of MD-2 and functional role of its basic amino acid clusters involved in cellular lipopolysaccharide recognition. J Biol Chem 2004; 279:28475-82.
21. Kaiser L, Grönlund H, Sandalova T, Ljunggren H-G, van Hage-Hamsten M, Achour A, et al. The crystal structure of the major cat allergen Fel d 1, a member of the secretoglobin family. J Biol Chem 2003;278:37730-5.
22. Platts-Mills TAE, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma and a modified Th2 response in children exposed to cat allergen: a population-based, cross-sectional study. Lancet 2001;357:752-5.
23. Bocskei Z, Groom CR, Flower DR, Wright CE, Phillips SE, Cavaggioni A, et al. Pheromone binding to two rodent urinary proteins revealed by x-ray crystallography. Nature 1992;360:186-8.
24. Fan Y, Gore JC, Redding KO, Vailes LD, Chapman MD, Schal C. Tissue localization and regulation by juvenile hormone of human allergen Bla g 4 from the German cockroach, *Blattella germanica* (L.). Insect Mol Biol 2005;14:45-53.
25. Radauer C, Breiteneder H. Pollen allergens are restricted to few protein families and show distinct patterns of species distribution. J Allergy Clin Immunol 2006;117:141-7.
26. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A. Allergic cross-reactivity: from gene to the clinic. Allergy 2004;59:243-67.
27. Vieths S, Scheurer S, Ballmer-Weber B. Current understanding of cross-reactivity of food allergens and pollen. Ann N Y Acad Sci 2002;964:47-68.
28. Ferreira F, Hirtenlehner K, Jilek A, Godnik-Cvar J, Breiteneder H, Grimm R, et al. Dissection of immunoglobulin E and T lymphocyte reactivity of isoforms of the major birch pollen allergen Bet v 1: potential use of hypoallergenic isoforms for immunotherapy. J Exp Med 1996; 183:599-609.
29. Schenk MF, Gilissen LJWJ, Esselink GD, Smulders MJM. Seven different genes encode a diverse mixture of isoforms of Bet v 1, the major birch pollen allergen. BMC Genomics 2006;7:168.
30. Markovic-Housley Z, Degano M, Lamba D, von Roepenack-Lahaye E, Clemens S, Susani M, et al. Crystal structure of a hypoallergenic isoform of the major birch pollen allergen Bet v 1 and its likely biological function as a plant steroid carrier. J Mol Biol 2003;325:123-33.
31. Valenta, Hayek B, Seiberler S, Bugajska-Schretter A, Niederberger V, Twardosz A, et al. Calcium-binding allergens: from plants to man. Int Arch Allergy Immunol 1998;117:160-6.
32. Tinghino R, Twardosz A, Barletta B, Puggioni EM, Iacovacci P, Butteroni C, et al. Molecular, structural, and immunologic relationships between different families of recombinant calcium-binding pollen allergens. J Allergy Clin Immunol 2002;109:314-20.
33. Cosgrove DJ. Loosening of plant cell walls by expansins. Nature 2000; 407:321-6.
34. Gadermaier G, Dedic A, Obermeyer G, Frank S, Himly M, Ferreira F. Biology of weed pollen allergens. Curr Allergy Asthma Rep 2004;4:391-400.
35. Wopfner N, Gadermaier G, Egger M, Asero R, Ebner C, Jahn-Schmid B, et al. The spectrum of allergens in ragweed and mugwort pollen. Int Arch Allergy Immunol 2005;138:337-46.
36. Czerwinski EW, Midori-Horiuti M, White MA, Brooks EG, Goldblum RM. Crystal structure of Jun a 1, the major cedar pollen allergen from *Juniperus ashei*, reveals a parallel beta-helical core. J Biol Chem 2005; 280:3740-6.
37. Breiteneder H, Radauer C. A classification of plant food allergens. J Allergy Clin Immunol 2004;113:821-30.
38. Jenkins JA, Griffiths-Jones S, Shewry PR, Breiteneder H, Mills EN. Structural relatedness of plant food allergens with specific reference to cross-reactive allergens: an in silico analysis. J Allergy Clin Immunol 2005;115:163-70.
39. Breiteneder H. Classifying food allergens. In: Koppelman SJ, Hefle SL, editors. Detecting allergens in foods. Cambridge (England): Woodhead Publishing; 2006. p. 37-43.
40. Kreis M, Forde BG, Rahman S, Miflin BJ, Shewry PR. Molecular evolution of the seed storage proteins of barley, rye and wheat. J Mol Biol 1985;183:499-502.
41. Dunwell JM, Khuri S, Gane PJ. Microbial relatives of the seed storage proteins of higher plants: conservation of structure and diversification of function during evolution of the cupin superfamily. Microbiol Mol Biol Rev 2000;64:153-79.
42. Ivancuic O, Schein CH, Braun W. SDAP: database and computational tools for allergenic proteins. Nucleic Acids Res 2003;31:359-62.
43. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley S, Khattignavong A, Lindblad R, et al. Immunotherapy with a ragweed-Toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med 2006; 355:1445-55.
44. Agea E, Russano A, Mannucci R, Nicoletti I, Corazzi L, Postle AD, et al. Human CD-1-restricted T cell recognition of lipids from pollens. J Exp Med 2005;202:295-308.