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Functional Recognition Theory and Type 2 Immunity: Insights and Uncertainties

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Abstract

Type 2 immunity plays an important role in host defense against helminths and toxins while driving allergic diseases. Despite progress in understanding the biology of type 2 immunity, the fundamental mechanisms regulating the type 2 immune module remain unclear. In contrast with structural recognition used by pattern recognition receptors, type 2 immunogens are sensed through their functional properties. Functional recognition theory has arisen as the paradigm for the initiation of type 2 immunity. However, the vast array of structurally unrelated type 2 immunogens makes it challenging to advance our understanding of type 2 immunity. In this article, we review functional recognition theory and organize type 2 immunogens into distinct classes based on how they fit into the concept of functional recognition. Lastly, we discuss areas of uncertainty in functional recognition theory with the goal of providing a framework to further define the logic of type 2 immunity in host protection and immunopathology.

INTRODUCTION

The immune system evolved to protect hosts from pathogens and toxins, as well as promote tissue repair (1, 2). To combat the extensive diversity of pathogens and toxins, the adaptive immune system developed the capacity to generate lymphocytes with an enormous number of clonally diverse Ag receptors (1). Consequently, the adaptive immune system possesses the ability to respond to virtually any threat, regardless of the antigenic composition. Beyond Ag recognition, adaptive immunity provides host protection only if it couples Ag recognition with an effector program that successfully targets the specific pathogen or toxin. To combat classes of pathogens and toxins, distinct immune modules have evolved that generate unique

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effector mechanisms (3). Each immune module possesses lymphocyte effector cells from both the innate and adaptive immune systems, which contribute to the response through production of specialized cytokines. Type 1 immunity is induced by intracellular pathogens and orchestrated by type 1 innate lymphoid cells (ILC1s) and $CD4^+$ Th1 cells, as well as $CD8^+$ cytotoxic T cells, which all produce the cytokine IFN-γ. Type 2 immunity is induced by helminths, toxins, and allergens, being orchestrated by ILC2s and $CD4^+$ Th2 cells, which produce the cytokines IL-4, IL-5, IL-9, and IL-13. Type 3 immunity is induced by extracellular pathogens and orchestrated by ILC3s and $CD4^+$ Th17 cells, which produce the cytokines IL-17 and IL-22. The cytokines from each immune module provide help to innate immune cells, as well as structural cells and neurons, to promote a targeted host defense response. In addition, the differentiation of specialized $CD4^+$ T follicular helper (Tfh) cells provides B cell help and promotes class-switch recombination to specific Ab isotypes, thereby dictating the Ab-mediated effector response (4). Notably, although one module is generally dominant during an immune response, most immune responses exhibit a spectrum of activated modules in vivo.

The innate immune system controls the induction of all adaptive immune modules with type 1 and type 3 immune modules using distinct receptors, but a shared structural-based approach of sensing (3). Pathogens inducing type 1 and type 3 immunity are recognized via pattern recognition receptors (PRRs), which bind evolutionarily conserved pathogen-associated molecular patterns (PAMPs) (3). PRR sensing of PAMPs by innate immune cells leads to an initial innate effector response. In addition, PAMP detection by dendritic cells (DCs) at barrier surfaces leads to DC maturation and trafficking to the draining lymph nodes with Ag presentation, costimulation, and skewing cytokines instructing a specific $CD4^+$ T cell differentiation program (5). For example, the intracellular bacterium *Listeria monocytogenes* possesses multiple PAMPs, including lipoproteins, flagellin, and unmethylated CpG sequences, among others, which promote $CD4^+$ Th1 cell differentiation (6). *Candida albicans* possesses distinct PAMPs, such as α-mannan molecules, which are structurally recognized by Dectin-2 on DCs, leading to $CD4^+$ Th17 cell differentiation (7, 8). Consequently, structural recognition theory serves as the conceptional foundation for the induction of type 1 and type 3 immunity. Type 1 and type 3 immunogens can be organized into classes based on their respective PRR, which provides a clear framework of immune sensing.

In contrast with the essential role of PRRs in the induction of type 1 and 3 immunity, the type 2 immune module can be regulated by PRRs without absolutely requiring structural recognition. Type 2 immunogens can contain PRR ligands that play an important regulatory role in the host response. For instance, house dust mites contain the TLR4 ligand LPS, and the house dust mite allergen Der p 2 exhibits structural homology with MD-2, the LPS-binding component of the TLR4 signaling complex, which can directly promote TLR4 complex signaling (9, 10). Furthermore, house dust mites contain glycans that can activate Dectin-1 and Dectin-2 signaling (11). However, these PRRs can exhibit remarkably variable influence over type 2 immunity depending on the context. TLR4 expression in structural cells has been reported to promote type 2 immunity to house dust mites, whereas others have found that TLR4 is not required (9, 12). Numerous reports have suggested that the level of TLR4 signaling dictates the variable responses in vivo, with low-dose LPS

promoting type 2 immunity, whereas high-dose LPS inhibits type 2 immunity (13–16). LPS activity appears to switch from promoting to inhibiting type 2 immunity depending on the production of GM-CSF and TNF-α by monocyte-derived cells (12). Similarly, Dectin-1 can play distinct roles in type 2 immunity with engagement of Dectin-1 by house dust mites promoting DC migration to the draining lymph node and induction of $CD4^+$ Th2 immunity, whereas Dectin-1 expression in lung epithelial cells inhibits $CD4^+$ Th2 immunity (17, 18). Such findings indicate that PRRs can play a regulatory role but are not required for the induction of type 2 immunity. In support of such a model, type 2 immunogens can induce type 2 immunity in the absence of structural recognition. For instance, the papaya-derived allergen papain, which lacks Dectin-1 or Dectin-2 ligands, induces type 2 immunity in vivo in *Tlr2*/*Tlr4* double-knockout mice and MyD88-deficient mice (19). Rather than requiring structural recognition, papain-induced type 2 immunity is completely dependent on its cysteine protease activity (19). Notably, there are data suggesting that proteases from *Aspergillus orzyzae* cleave fibrinogen, with the cleavage products activating TLR4 to promote allergic immunity (20). Nevertheless, even if PRRs are used, the essential mechanisms of sensing type 2 immunogens appear to be distinct from structural recognition used by the type 1 and 3 immune modules.

How does the immune system sense the enormous number of structurally distinct type 2 immunogens? In contrast with structural recognition, the immune system senses type 2 immunogens through their functional properties, which include the ability to promote the release of damage-associated molecular patterns and activate sensory neurons (3, 21, 22). Functional recognition theory has arisen as the paradigm for the initiation of type 2 immunity. However, the vast array of structurally unrelated type 2 immunogens and numerous experimental models make it challenging to advance our understanding of type 2 immunity in vivo. In this article, we review functional recognition theory and organize type 2 immunogens into distinct classes based on how each class fits into the foundational concepts of functional recognition. Lastly, we discuss areas of uncertainty in functional recognition theory, including how Ags lacking intrinsic adjuvanticity generate an adaptive type 2 immune response, how innate and adaptive arms of the type 2 immune module can be differentially activated in vivo, and how functional recognition at barrier sites changes after previous type 2 inflammation. Our goal is to provide a framework to help further define the logic of type 2 immunity in host protection and immunopathology.

FUNCTIONAL RECOGNITION THEORY IN TYPE 2 IMMUNITY

Type 2 immunity evolved, in part, to provide host protection against parasitic helminths, including either mediating parasite expulsion or tolerance to the helminth in peripheral tissues (23). For instance, in mice, *Nippostrongylus brasiliensis* primary expulsion and *Heligmosomoides polygyrus* secondary expulsion require $CD4^+$ Th2 cells (24). In contrast with the host protective functions of type 2 immunity in the context of helminth infection, inappropriate type 2 immunity to noninfectious Ags drives allergic diseases. However, macroscopic helminths and microscopic allergens are very distinct immunogens, raising the question as to the shared mechanism(s) inducing type 2 immunity. Although type 2 immunogens lack conserved structural features, many exhibit the shared property of being noxious to the host (22). Even seemingly harmless environmental allergens often exhibit

enzymatic activity, which is required for their ability to induce type 2 immunity (19, 25). The toxin hypothesis of allergic disease posits that type 2 immunity evolved to combat harmful toxins with Ag-specific, adaptive immunity providing protection to future exposures (26). In support of the toxin hypothesis, mice treated with low doses of bee or snake venom are protected from the effects of secondary challenges with sublethal and lethal doses of venom in an IgE and mast cell–dependent manner (27–29). As a result, these findings suggest that molecules capable of causing a specific type of tissue "stress" activate the type 2 immune module. Furthermore, it is well established that the effector mechanisms employed by type 2 immunity promote tissue repair pathways, suggesting that this immune module evolved to couple recognition of tissue stress to immune effector mechanisms capable of expelling noxious Ags while maintaining tissue integrity and promoting repair (2, 30). Damage or stress to tissues promotes the release of a class of molecules termed damage-associated molecular patterns (DAMPs), which transmit the signal of tissue injury to the innate immune system (31). In murine models, DAMPs such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) play an important role in the initiation of type 2 immunity (3, 32). In addition, genome-wide association studies in humans have found that polymorphisms in IL-33 and the IL-33 receptor are associated with the development of allergic asthma (33, 34). Although there are multiple cellular sources of DAMPs, epithelial cells and adventitial stromal cells represent major sites of DAMP production, indicating specialized roles of these structural cells in sensing noxious stimuli and tissue stress (35, 36). Notably, while the above DAMPs play an important role in type 2 immunity, genetic deletion of individual DAMPs causes a reduction, but not complete abrogation, of type 2 immunity (27, 37–41). Even triple-knockout mice lacking the IL-33 receptor, TSLP receptor, and the cytokine IL-25 exhibit no defect in initial $CD4^+$ Th2 cell differentiation in the lymph node on infection with the helminth *N. brasiliensis*, although effector $CD4^+$ Th2 cell function at barrier sites was significantly impaired (42). As a result, the three conventional type 2 DAMPs promote type 2 immunity, but there are additional sensing pathways to initiate the type 2 immune module.

Over the last several years, growing evidence supports a central role for sensory neuron-derived neuropeptides in the regulation of both innate and adaptive type 2 immunity (21, 22). First, allergens directly activate sensory neurons to induce itch and pain in mice (43). Sensory neuron activation promotes avoidance behaviors in the organism, as well as plays a central role in initiating type 2 immune responses. Activated sensory neurons release neuropeptides that can cross-talk with local immune cells, leading to innate effector responses. For example, sensory neurons intertwine with mast cells in peripheral tissues with these two cell types forming physical synapses poised for intercellular communication (21, 44–49). Release of substance P and vasoactive peptide (VIP) from activated sensory neurons directly promotes mast cell degranulation (50–53). This may be sufficient for the IgE-independent mast cell protection against primary venom exposure, which requires degranulation and release of carboxypeptidase A and other proteases that degrade venom components (54). In addition, neuropeptide-induced mast cell degranulation may also act to coordinate type 2 inflammatory responses. Primary exposure to house dust mite allergen directly activates sensory neurons to promote release of substance P, which promotes mast cell degranulation and local inflammatory responses (55). In contrast, models

of contact hypersensitivity suggest that the neuropeptide calcitonin gene–related peptide inhibits mast cell function, indicating that sensory neurons can tune the responsiveness of mast cells (52, 56). Along with mast cells, neuropeptides regulate the function of other innate type 2 immune cells. ILC2s express the receptor for the neuropeptide neuromedin U, which promotes ILC2 production of IL-5 and IL-13 (57–59). Furthermore, VIP also directly promotes ILC2 production of IL-5, although the functional role of VIP in vivo remains less clear (60, 61). Similar to mast cells, calcitonin gene–related peptide plays an immunomodulatory role in ILC2 activation in response to DAMPs, suggesting that distinct neuropeptides can differentially regulate ILC2 effector function (62, 63).

In addition to the innate effector response, neuropeptides also play a role in initiating the adaptive immune response to type 2 immunogens through their effects on DCs. A specialized population of IRF4- and KLF4-dependent, type 2 conventional DCs (cDC2s) is required for $CD4^+$ Th2 cell differentiation (64–66). Unlike $CD4^+$ Th1- and $CD4^+$ Th17-skewing DCs, $CD4^+$ Th2-skewing cDC2s do not appear to respond directly to allergens. In the skin, sensory neuron-derived substance P stimulates $CD4^+$ Th2-skewing cDC2s via the receptor MRGPRA1, promoting migration to the draining lymph node and the induction of $CD4^+$ Th2 cell differentiation (43). Notably, substance P alone is insufficient for $CD4^+$ Th2 cell differentiation, suggesting that additional signals, such as DAMPs, collaborate with substance P to promote $CD4^+$ Th2 cell differentiation (43). In summary, although type 2 immunogens lack shared structural features, they are recognized functionally via release of DAMPs and the activation of sensory neurons (Fig. 1). However, it remains unclear how the immune system integrates signals from DAMPs and neuropeptides: do they simply act to amplify a generic activation signal, or do they activate and instruct specific type 2 immune outcomes? This second possibility is supported by observations from type 1 responses, where DAMP release leads to ILC2 activation to promote tissue repair without inducing an adaptive type 2 response (67–69). Such observations suggest the existence of a DAMP/neuropeptide code for the induction of specific type 2 immune responses.

Although the cellular sensors of type 2 immunogens are becoming clearer, whether these cellular pathways apply to all type 2 immunogens in vivo remains a mystery. For instance, while the enzymatic activity of protease allergens may imbue them with inherent adjuvanticity, many food allergens are seemingly inert and characterized mainly by their stability to heat and acid degradation. Modeling food allergy in vivo often relies on the use of exogenous adjuvants like cholera toxin (CT), but is this relevant to food allergy in humans? In addition, during type 1 or type 3 immune responses to pathogens, type 2 immunity can be activated to promote tissue repair or host defense. How are type 2 immunogens sensed and regulated during a dominant type 1 or 3 immune response? Lastly, although functional recognition is generally studied in the naive state in mice, there is growing evidence that induction of type 2 immunity at a barrier site induces tissue-resident memory that durably changes local functional recognition. How does functional recognition at a barrier site change after previous type 2 inflammation? One challenge to addressing these areas of uncertainty is the significant breadth of type 2 immunogens and murine models available for mechanistic studies. To further define such biology, we will review the unique features of different classes of type 2 immunogens and place them in the conceptual framework of functional recognition.

CLASSES OF TYPE 2 IMMUNOGENS

Allergenic proteins from plants, animals, and fungi are marked by significant structural heterogeneity that makes any classification scheme imprecise. However, by classifying allergens by function, which provides enzymatically active allergens with their inherent adjuvanticity, instead of structural or phylogenetic relatedness, certain major themes become apparent (Table I) (70, 71). The first theme is the enrichment of enzymatically active proteins as allergens, specifically those that are active against proteins (proteases) and carbohydrates (carbohydrate-active enzymes [CAZymes]). Protease allergens include cysteine, serine, and aspartic proteases, as well as metalloproteases. These allergenic proteases display a variety of targeted peptide sequences and are enriched in dust mite, cockroach, and fungi, although they can also be detected in some food plants (kiwi, papaya, pineapple, and muskmelon) and environmental pollens (ragweed, timothy grass, Bermuda grass). The enzymatic activity of cysteine and serine protease allergens has been clearly shown to act as an allergic adjuvant (19, 72, 73). How proteases exert this adjuvant activity is not entirely clear, but allergic proteases have been shown to degrade tight junction proteins and activate protease-activated receptors, indicating possible routes for indirect and direct adjuvant effects (74, 75). Finally, cysteine protease allergens have been shown to cleave CD25, leading to the hypothesis that it could target $CD25^{hi}$ regulatory T cells (76). However, the relevance of this in vitro finding remains unclear in the setting of in vivo data supporting a role for cysteine protease allergens in the indirect activation of $CD25^{hi}$ ILC2s and mast cell production of IL-2, which promotes regulatory T cell function in vivo (77, 78). Clearly, there remains much to be determined about how protease allergens drive allergic inflammation.

CAZymes include the well-described chitinase family (found in dust mite, cockroach, and food plants), as well as lysozymes from chicken egg and milks, and the pectin lyases found mainly in pollens (ragweed, mugwort, juniper) (79). CAZymes can be exogenous, as in the form of allergens, or endogenous. It is well described that worm or fungal chitins can induce the expression of mammalian chitinase enzymes leading to type 2 inflammation (80). Finally, CAZymes are also found in venom allergens, which are enriched in hyaluronidases that can act as type 2 adjuvants (81). In addition to these major classes are those enzymes involved in metabolic pathways, specifically the enolase and arginine kinase allergens, as well as those with detoxification roles (82). Although little is known about how these allergens might be recognized, the enrichment of enzymes in allergens across plant, animal, and fungal kingdoms underscores the potential role for their functional activity in driving their allergenicity.

Enzymes easily lend themselves to functional grouping, but many other immunodominant allergens, even if lacking in enzymatic activity, have functional activities that may be related to their allergenicity. Many food allergens are characterized by their stability to heat (cooking) and acid (digestion), but these same allergenic proteins also share in common the ability to bind bioactive lipids and small molecule ligands (83). The ubiquitous ligand binding proteins such as albumins and globulins, found in both plant food and environmental animal allergens (e.g., cat and dog), do not have enzymatic activity but can exert major physiological effects through the binding and release of bioactive small molecules and xenobiotics. Lipid transfer proteins from plants and lipocalins from animals get their name

from their ability to bind bioactive lipid mediators and hormones (84). Furthermore, there is evidence that the ubiquitous PR-10 family of allergenic proteins in both pollens and plant foods bind phytohormones and flavonoids in a shared hydrophobic cavity (85). These findings raise the possibility that otherwise “inert” proteins may exert a functional effect on the host by either binding host-derived bioactive small molecules or, alternatively, that they may carry small molecular adjuvants that exert functional effects on the host.

The last major class of functional allergens includes those that may impact the structural or membrane integrity of eukaryotic cells. This group includes the actin-binding profilins, which integrate membrane signaling with cytoskeletal dynamics and can even activate PI3K/Akt signaling pathways when encountered extracellularly (86). It also includes the plasma membrane toxins in allergenic venoms such as bee venom phospholipase A_2 ($bvPLA_2$) (Api m 1) and the pore-forming toxin melittin (Api m 4). In addition, given their described role in membrane targeting and disruption, we consider the defensin subset of allergens seen in both food plants and pollens to be another member of this group (87). Each of these groups has the ability to directly cause toxicity to membrane integrity, signaling pathways, and cytoskeletal structure, but some members may act to amplify another group’s functions. For example, the pore-forming toxin melittin has been shown to increase the toxicity of $bvPLA_2$ by facilitating its entry into membranes (88).

If allergens can be classified based on their functional principles, then certain predictions can be made. First, allergens that share functional activity, and not structural features or phylogenetic origin, will lead to similar DAMP release, neuropeptide release, and immune outcomes. There are data supporting this between the cysteine proteases (e.g., Der p 1 and papain), but data are mixed concerning families within the same functional class (e.g., cysteine versus serine proteases) (43, 55). The second prediction is that secreted products, such as bacterial toxins, that come from these functional classes may promote a type 2 immune pathway. This has recently been illustrated for the LasB metalloprotease toxin from *Pseudomonas aeruginosa* (89). The third prediction is that these broad classes of allergens would be sensed by shared pathways that detect alterations in host homeostasis or damage. However, these fundamental pathways may be different between the protease allergens and other classes. DAMPs consist of one such shared pathway for the functional detection of protease allergens and the membrane toxin $bvPLA_2$ (27, 77). In this case, the allergen’s activity, and therefore adjuvanticity, is relayed through a host-derived molecule in response to cellular damage. But how does the DAMP system detect “inert” proteins or their small molecule ligands? Could mammals have a conserved pathway to detect altered self through sacrificial decoy proteins? If such a pathway existed in mammals, it could provide the detection mechanism driving allergic responses to naturally occurring small molecules, as well as xenobiotics like penicillin.

AREAS OF UNCERTAINTY IN FUNCTIONAL RECOGNITION

As outlined earlier, many type 2 immunogens exhibit intrinsic adjuvanticity, offering a mechanism that couples induction of adaptive immunity with antigenic recognition. However, it remains less clear how Ags without intrinsic adjuvanticity, such as many food allergens, induce type 2 immunity (22). In such circumstances, the Ag is sensed

in association with some noxious stimulus that may not be defined. The latter substance may not be a protein and consequently serves as an adjuvant without being an Ag. Given that food Ags promote oral tolerance, murine models of food allergy aiming to induce sensitization via the oral route require addition of an adjuvant such as CT or staphylococcal enterotoxin B (90). Although CT has been shown to induce IL-33 release in the gut, it remains unclear whether oral adjuvants used in murine models are truly recapitulating the biology of type 2 immunity to food Ags that occurs in humans (91). Specifically, growing evidence suggests that early-life allergen exposure through the skin induces Ag-specific type 2 immunity, whereas early oral ingestion promotes immune tolerance (92). For example, a number of genetic mutations that disrupt skin barrier function are associated with atopic dermatitis, which is associated with an increased risk for allergic sensitization to foods (93–95). In addition, among children with high-risk atopic disease, early oral introduction of peanut significantly decreases the frequency of the development of peanut allergy (96). Even in the absence of skin barrier dys-function, the skin has distinct features of type 2 immunity from other barrier sites. In the murine skin, basal IL-13 from dermal ILC2 promotes the differentiation of $CD4^+$ Th2-skewing cDC2s in a STAT6- and KLF4-dependent manner (97). In the absence of IL-13 signaling, dermal cDC2s were unchanged in number but exhibited a reduced $CD4^+$ Th2-skewing phenotype, as well as reduced ability to promote $CD4^+$ Th2 cell differentiation, whereas $CD4^+$ Th17 cell differentiation was increased (97). Such an IL-13–dependent mechanism for promoting $CD4^+$ Th2-skewing cDC2s did not exist in the lungs or small intestine (97). In support of these findings, human cDC2s from the skin also exhibit an IL-4 and IL-13 signaling gene signature, which was absent in cDC2s from the blood, spleen, or lungs (97). As a result, the threshold of functional recognition and initiation of adaptive type 2 immunity may be distinct in the skin compared with other barrier tissues. Ags without intrinsic adjuvanticity may be more likely to be sensed in association with another noxious stimulus and trigger adaptive type 2 immunity in the skin, particularly in the context of barrier disruption, rather than other barrier sites such as the gut. Consequently, defining the unique features of functional recognition in the skin may yield new insight into the mechanisms whereby Ags without intrinsic adjuvanticity induce adaptive type 2 immunity.

Another area of uncertainty involves defining how innate type 2 immunity can be activated during type 1 or type 3 immunity to promote tissue repair without inducing an Ag-specific type 2 response. One hypothesis is that DAMP production promotes ILC2 activation, but the concomitant presence of PAMPs inhibits the induction of an adaptive type 2 response (2). Such a mechanism would allow the host to use the tissue reparative functions of innate type 2 immunity without engaging an adaptive type 2 response that may be inappropriate to combat a pathogen that is eliminated by type 1 or type 3 immunity. In support of such a model, high-dose LPS exposure, as would occur during an infection with an endotoxin-producing bacteria, is capable of inhibiting an adaptive type 2 immune response (12–16, 98). However, one challenge to the high-dose PAMP-inhibition model in adaptive type 2 immunity is that toxin-producing bacteria such as *Staphylococcus aureus* induce Ag-specific IgE, demonstrating that adaptive type 2 immunity can be activated even in the presence of high levels of PAMPs (99). Notably, *Staphylococcus aureus* induces a specialized subset of $CD4^+$ Tfh cells that produce IL-13 (99). Tfh13 cells represent a unique population of $CD4^+$ Tfh cells that are induced by allergens, but not helminths (100, 101). Tfh13

cells coexpress the canonical $CD4^+$ Tfh and $CD4^+$ Th2 cell transcription factors Bcl6 and Gata3, respectively, and are required for the instruction of high-affinity IgE, which causes anaphylaxis in the context of allergic disease (100, 101). The observation that both allergens and toxins, but not helminths, induce Tfh13 cell differentiation is intriguing. The fact that all of these type 2 immunogens induce DAMP release suggests that some other sensing mechanism dictates the differentiation of Tfh13 cells. Given that allergens directly activate sensory neurons and sensory neuron–derived neuropeptides play an important role in inducing adaptive type 2 immunity, it is possible that neuropeptides play an important role in engaging an Ag-specific type 2 immune response even in the presence of high levels of PAMPs. Could the presence of DAMPs and either activating or regulatory neuropeptides dictate engagement of adaptive type 2 immunity (21)? Defining how the immune system integrates signals from PAMPs, DAMPs, and neuropeptides to regulate type 2 immunity represents an area of central importance to the field.

Most models of functional recognition focus on the naive state. However, prior type 2 immunity leads to long-term changes in functional recognition and the capacity to induce type 2 inflammation. For instance, ILC2s can be “trained” by previous inflammation to acquire memory-like properties (102, 103). On activation, ILC2s proliferate in situ and produce type 2 cytokines to induce inflammation (104). While the ILC2 population subsequently contracts, the number of memory-like ILC2s remains greater than the naive state (102, 105). In addition, ILC2 can acquire cell-intrinsic, memory-like properties, including an enhanced responsiveness to DAMPs via epigenetic changes that are responsible for a poised effector program (102, 105). ATAC-seq analysis has shown that trained ILC2s possess alterations in accessibility of Bach2 and AP1 motifs, which play an important role in the memory-like program that allows activation to previous subthreshold stimulation (105). Furthermore, induction of adaptive type 2 immunity in a particular barrier tissue produces long-term, tissue-resident memory. After allergic inflammation within the lungs, memory $CD4^+$ Th2 cells establish residency and promote recurrent allergic inflammation in an allergen-specific manner (106–109). Tissue-resident memory $CD4^+$ Th2 cells are transcriptionally distinct from their circulating counterparts and durably persist in the lung parenchyma without the need for replenishment from circulating memory $CD4^+$ Th2 cells (108). Beyond canonical $CD4^+$ Th2 cells, a distinct subset of $CD4^+$ Th2 cells that acquire the capacity to express IL-9 (Th9 cells) are well described in human allergic diseases (110–112). IL-9 promotes type 2 immunity via activation of mast cells, enhancing eosinophil recruitment, activating macrophages, and promoting mucous metaplasia (113–115). Notably, IL-9 is predominantly expressed in highly differentiated $CD4^+$ Th2 cells, indicating that chronic stimulation is necessary for induction of the Th9 program (110). In murine models of allergic lung inflammation, short-term allergen exposure protocols do not seem to induce a significant Th9 cell subset, whereas chronic allergen treatments yield a distinct subset of Th9 cells (109, 116). After chronic allergen exposure, IL-9 is predominantly derived from a population of tissue-resident memory $CD4^+$ T cells that exhibit a distinct chromatin and transcriptional signature from $CD4^+$ Th2 cells (109). Tissue-resident memory Th9 cells produced IL-9 in an allergen-specific manner, which is enhanced by IL-33 (109). Beyond $CD4^+$ Th2 and Th9 cells, the induction of IgE significantly enhances the ability of mast cells to respond in an Ag-specific manner (117). Furthermore, both type 2 cytokines and

IgE can regulate the function of nociceptive neurons that participate in type 2 immunity. For example, nociceptive neurons express IL-4Rα and the high-affinity IgE receptor FceR1 and can directly respond to IL-4 and IgE (118, 119). Specifically, $TRPV1^+$ sensory neurons respond to IgE-allergen immune complexes by releasing substance P, which, in turn, amplifies $CD4^+$ Th2 cell production of IL-5 and IL-13 (118, 120–122). Consequently, the induction of Ag-specific type 2 immunity allows sensory neurons to broaden their sensing function to include Ag-specific recognition to regulate type 2 immunity. Along with changes in the responsiveness of cells involved in type 2 immunity, there are clearly changes in the niches supporting these cellular networks. For example, ILC2s and $CD4^+$ Th2 cells persist in adventitial stromal niches that line the outermost regions of large vessels, ducts, and airways, which include specialized stromal cells that produce IL-33 and TSLP (123–126). In models of early-life skin inflammation, a population of $CD4^+$ Th2 cells persists into adulthood via interactions with expanded fascial fibroblasts (127). Establishment of the microanatomical niche of $CD4^+$ Th2 cells and $CD4^+$ Th2-interacting fascial fibroblasts in the skin results in altered reparative responses to tissue injury (127). In sum, after type 2 immunity, ILC2s can acquire enhanced sensitivity to DAMPs; tissue-resident memory $CD4^+$ Th2 and Th9 cells, as well as IgE, provide the barrier tissue with the capacity to broaden the mode of immunosurveillance from functional recognition to include Ag-specific recognition; and there are changes to the supporting microanatomical niches within tissues. Defining the cellular networks and niches that support type 2 immune cells in barrier tissues and how these niches durably change in response to various type 2 immunogens represents a critically important area in type 2 immunity.

Although the topics outlined earlier cannot be exhaustive, we believe such areas represent important gaps in our working model of functional recognition and type 2 immunity. Notably, it is clear that the rules of functional recognition exhibit shared and immunogen-, tissue-, and context-specific features. To help advance our understanding of type 2 immunity in vivo, we need clearer delineation as to whether particular pathways or mechanisms are specific to a model/context or represent a fundamental feature of functional recognition. Delineating both shared and context-specific mechanisms regulating type 2 immunity will be critical to advancing our insight of type 2 immunity in vivo.

CONCLUSIONS

Functional recognition theory serves as the conceptual foundation for understanding type 2 immune recognition. Although there have been many advancements in delineating the biology of type 2 immunity, several important areas of uncertainty remain. The dizzying array of stimuli and models remain a challenge for the field, impairing our ability to define the logic of type 2 immunity in vivo. Further defining the rules regulating shared and context-specific type 2 immunity will be critical to develop novel approaches to target the type 2 immune module to promote host protection and prevent or limit immune-mediated disease states.

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Abbreviations used in this article:

bvPLA$_2$	bee venom phospholipase A$_2$
CAZyme	carbohydrate-active enzyme
cDC2	type 2 conventional dendritic cell
CT	cholera toxin
DAMP	damage-associated molecular pattern
DC	dendritic cell
ILC1	type 1 innate lymphoid cell
PAMP	pathogen-associated molecular pattern
PRR	pattern recognition receptor
Tfh	CD4$^+$ T follicular helper
TSLP	thymic stromal lymphopoietin
VIP	vasoactive peptide

REFERENCES

1. Hirano M, Das S, Guo P, and Cooper MD. 2011. The evolution of adaptive immunity in vertebrates. Adv. Immunol 109: 125–157. [PubMed: 21569914]
2. Gause WC, Wynn TA, and Allen JE. 2013. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. Nat. Rev. Immunol 13: 607–614. [PubMed: 23827958]
3. Iwasaki A, and Medzhitov R. 2015. Control of adaptive immunity by the innate immune system. Nat. Immunol 16: 343–353. [PubMed: 25789684]
4. Eisenbarth SC, Baumjohann D, Craft J, Fazilleau N, Ma CS, Tangye SG, Vinuesa CG, and Linterman MA. 2021. CD4$^+$ T cells that help B cells – a proposal for uniform nomenclature. Trends Immunol. 42: 658–669. [PubMed: 34244056]
5. Cabeza-Cabrerizo M, Cardoso A, Minutti CM, Pereira da Costa M, and Reis e Sousa C. 2021. Dendritic cells revisited. Annu. Rev. Immunol 39: 131–166. [PubMed: 33481643]
6. Regan T, MacSharry J, and Brint E. 2014. Tracing innate immune defences along the path of *Listeria monocytogenes* infection. Immunol. Cell Biol 92: 563–569. [PubMed: 24732075]
7. Robinson MJ, Osorio F, Rosas M, Freitas RP, Schweighoffer E, Gross O, Verbeek JS, Ruland J, Tybulewicz V, Brown GD, et al. 2009. Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. J. Exp. Med 206: 2037–2051. [PubMed: 19703985]
8. Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung SH, et al. 2010. Dectin-2 recognition of alpha-mannans and induction of Th17 cell

differentiation is essential for host defense against *Candida albicans*. Immunity 32: 681–691. [PubMed: 20493731]

9. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, and Lambrecht BN. 2009. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. Nat. Med 15: 410–416. [PubMed: 19330007]
10. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R, Thorne PS, Wills-Karp M, Gioannini TL, Weiss JP, and Karp CL. 2009. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. Nature 457: 585–588. [PubMed: 19060881]
11. Lamiable O, Mayer JU, Munoz-Erazo L, and Ronchese F. 2020. Dendritic cells in Th2 immune responses and allergic sensitization. Immunol. Cell Biol 98: 807–818. [PubMed: 32738152]
12. Kaur K, Bachus H, Lewis C, Papillion AM, Rosenberg AF, Ballesteros-Tato A, and León B. 2021. GM-CSF production by non-classical monocytes controls antagonistic LPS-driven functions in allergic inflammation. Cell Rep. 37: 110178. [PubMed: 34965421]
13. Bortolatto J, Borducchi E, Rodriguez D, Keller AC, Faquim-Mauro E, Bortoluci KR, Mucida D, Gomes E, Christ A, Schnyder-Candrian S, et al. 2008. Toll-like receptor 4 agonists adsorbed to aluminium hydroxide adjuvant attenuate ovalbumin-specific allergic airway disease: role of MyD88 adaptor molecule and interleukin-12/interferon-gamma axis. Clin. Exp. Allergy 38: 1668–1679. [PubMed: 18631348]
14. Delayre-Orthez C, de Blay F, Frossard N, and Pons F. 2004. Dose-dependent effects of endotoxins on allergen sensitization and challenge in the mouse. Clin. Exp. Allergy 34: 1789–1795. [PubMed: 15544606]
15. Eisenbarth SC, Piggott DA, Huleatt JW, Visintin I, Herrick CA, and Bottomly K. 2002. Lipopolysaccharide-enhanced, toll-like receptor 4-dependent T helper cell type 2 responses to inhaled antigen. J. Exp. Med 196: 1645–1651. [PubMed: 12486107]
16. Kim Y-K, Oh S-Y, Jeon SG, Park H-W, Lee S-Y, Chun E-Y, Bang B, Lee H-S, Oh M-H, Kim Y-S, et al. 2007. Airway exposure levels of lipopolysaccharide determine type 1 versus type 2 experimental asthma. J. Immunol 178: 5375–5382. [PubMed: 17404323]
17. Ito T, Hirose K, Norimoto A, Tamachi T, Yokota M, Saku A, Takatori H, Saijo S, Iwakura Y, and Nakajima H. 2017. Dectin-1 plays an important role in house dust mite-induced allergic airway inflammation through the activation of CD11b+ dendritic cells. J. Immunol 198: 61–70. [PubMed: 27852745]
18. Gour N, Lajoie S, Smole U, White M, Hu D, Goddard P, Huntsman S, Eng C, Mak A, Oh S, et al. 2018. Dysregulated invertebrate tropomyosin-dectin-1 interaction confers susceptibility to allergic diseases. Sci. Immunol 3: eaam9841. [PubMed: 29475849]
19. Sokol CL, Barton GM, Farr AG, and Medzhitov R. 2008. A mechanism for the initiation of allergen-induced T helper type 2 responses. Nat. Immunol 9: 310–318. [PubMed: 18300366]
20. Millien VO, Lu W, Shaw J, Yuan X, Mak G, Roberts L, Song L-Z, Knight JM, Creighton CJ, Luong A, et al. 2013. Cleavage of fibrinogen by proteinases elicits allergic responses through Toll-like receptor 4. Science 341: 792–796. [PubMed: 23950537]
21. Flayer CH, Perner C, and Sokol CL. 2021. A decision tree model for neuroimmune guidance of allergic immunity. Immunol. Cell Biol 99: 936–948. [PubMed: 34115905]
22. Florsheim EB, Sullivan ZA, Khoury-Hanold W, and Medzhitov R. 2021. Food allergy as a biological food quality control system. Cell 184: 1440–1454. [PubMed: 33450204]
23. Vacca F, and Le Gros G. 2022. Tissue-specific immunity in helminth infections. Mucosal Immunol. DOI: 10.1038/s41385-022-00531-w.
24. Anthony RM, Rutitzky LI, Urban JF Jr., Stadecker MJ, and Gause WC. 2007. Protective immune mechanisms in helminth infection. Nat. Rev. Immunol 7: 975–987. [PubMed: 18007680]
25. Yang ZY, Werner HC, Kong WP, Leung K, Traggiai E, Lanzavecchia A, and Nabel GJ. 2005. Evasion of antibody neutralization in emerging severe acute respiratory syndrome corona-viruses. Proc. Natl. Acad. Sci. USA 102: 797–801. [PubMed: 15642942]
26. Profet M 1991. The function of allergy: immunological defense against toxins. Q. Rev. Biol 66: 23–62. [PubMed: 2052671]

27. Palm NW, Rosenstein RK, Yu S, Schenten DD, Florsheim E, and Medzhitov R. 2013. Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity. Immunity 39: 976–985. [PubMed: 24210353]
28. Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, Metz M, and Galli SJ. 2013. A beneficial role for immunoglobulin E in host defense against honeybee venom. Immunity 39: 963–975. [PubMed: 24210352]
29. Starkl P, Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, and Galli SJ. 2016. IgE antibodies, FceRIα, and IgE-mediated local anaphylaxis can limit snake venom toxicity. J. Allergy Clin. Immunol 137: 246–257.e11. [PubMed: 26410782]
30. Gieseck III RL, Wilson MS, and Wynn TA. 2018. Type 2 immunity in tissue repair and fibrosis. Nat. Rev. Immunol 18: 62–76. [PubMed: 28853443]
31. Gong T, Liu L, Jiang W, and Zhou R. 2020. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat. Rev. Immunol 20: 95–112. [PubMed: 31558839]
32. El-Naccache DW, Haskó G, and Gause WC. 2021. Early events triggering the initiation of a type 2 immune response. Trends Immunol. 42: 151–164. [PubMed: 33386241]
33. Grotenboer NS, Ketelaar ME, Koppelman GH, and Nawijn MC. 2013. Decoding asthma: translating genetic variation in IL33 and IL1RL1 into disease pathophysiology. J. Allergy Clin. Immunol 131: 856–865. [PubMed: 23380221]
34. Ketelaar ME, Portelli MA, Dijk FN, Shrine N, Faiz A, Vermeulen CJ, Xu CJ, Hankinson J, Bhaker S, Henry AP, et al. 2021. Phenotypic and functional translation of IL33 genetics in asthma. J. Allergy Clin. Immunol 147: 144–157. [PubMed: 32442646]
35. Roan F, Obata-Ninomiya K, and Ziegler SF. 2019. Epithelial cell-derived cytokines: more than just signaling the alarm. J. Clin. Invest 129: 1441–1451. [PubMed: 30932910]
36. Sbierski-Kind J, Mroz N, and Molofsky AB. 2021. Perivascular stromal cells: directors of tissue immune niches. Immunol. Rev 302: 10–31. [PubMed: 34075598]
37. Townsend MJ, Fallon PG, Matthews DJ, Jolin HE, and McKenzie AN. 2000. T1/ST2-deficient mice demonstrate the importance of T1/ST2 in developing primary T helper cell type 2 responses. J. Exp. Med 191: 1069–1076. [PubMed: 10727469]
38. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TKA, Bucks C, Kane CM, Fallon PG, Pannell R, et al. 2010. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature 464: 1367–1370. [PubMed: 20200518]
39. Tang H, Cao W, Kasturi SP, Ravindran R, Nakaya HI, Kundu K, Murthy N, Kepler TB, Malissen B, and Pulendran B. 2010. The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. Nat. Immunol 11: 608–617. [PubMed: 20495560]
40. Besnard A-G, Togbe D, Guillou N, Erard F, Quesniaux V, and Ryffel B. 2011. IL-33-activated dendritic cells are critical for allergic airway inflammation. Eur. J. Immunol 41: 1675–1686. [PubMed: 21469105]
41. Halim TYF, Steer CA, Mathä L, Gold MJ, Martinez-Gonzalez I, McNagny KM, McKenzie ANJ, and Takei F. 2014. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. Immunity 40: 425–435. [PubMed: 24613091]
42. Van Dyken SJ, Nussbaum JC, Lee J, Molofsky AB, Liang HE, Pollack JL, Gate RE, Haliburton GE, Ye CJ, Marson A, et al. 2016. A tissue checkpoint regulates type 2 immunity. Nat. Immunol 17: 1381–1387. [PubMed: 27749840]
43. Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan ZNA, Voisin T, Camire RB, Chow OA, Chiu IM, and Sokol CL. 2020. Substance P release by sensory neurons triggers dendritic cell migration and initiates the type-2 immune response to allergens. Immunity 53: 1063–1077.e7. [PubMed: 33098765]
44. Heine H, and Förster FJ. 1975. Histophysiology of mast cells in skin and other organs. Arch. Dermatol. Res 253: 225–228. [PubMed: 1200702]
45. Botchkarev VA, Eichmüller S, Peters EM, Pietsch P, Johansson O, Maurer M, and Paus R. 1997. A simple immunofluorescence technique for simultaneous visualization of mast cells and nerve fibers reveals selectivity and hair cycle–dependent changes in mast cell–nerve fiber contacts in murine skin. Arch. Dermatol. Res 289: 292–302. [PubMed: 9164640]

46. Ito A, and Oonuma J. 2006. Direct interaction between nerves and mast cells mediated by the SgIGSF/SynCAM adhesion molecule. J. Pharmacol. Sci 102: 1–5. [PubMed: 16936456]
47. Furuno T, Ito A, Koma Y, Watabe K, Yokozaki H, Bienenstock J, Nakanishi M, and Kitamura Y. 2005. The spermatogenic Ig super-family/synaptic cell adhesion molecule mast-cell adhesion molecule promotes interaction with nerves. J. Immunol 174: 6934–6942. [PubMed: 15905536]
48. Kleij HP, and Bienenstock J. 2005. Significance of conversation between mast cells and nerves. Allergy Asthma Clin. Immunol 1: 65–80. [PubMed: 20529227]
49. Sumpter TL, Balmert SC, and Kaplan DH. 2019. Cutaneous immune responses mediated by dendritic cells and mast cells. JCI Insight 4: e123947. [PubMed: 30626752]
50. Johnson AR, and Erdös EG. 1973. Release of histamine from mast cells by vasoactive peptides. Proc. Soc. Exp. Biol. Med 142: 1252–1256. [PubMed: 4121082]
51. Matsuda H, Kawakita K, Kiso Y, Nakano T, and Kitamura Y. 1989. Substance P induces granulocyte infiltration through degranulation of mast cells. J. Immunol 142: 927–931. [PubMed: 2464033]
52. Kulka M, Sheen CH, Tancowny BP, Grammer LC, and Schleimer RP. 2008. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 123: 398–410. [PubMed: 17922833]
53. Li W-W, Guo T-Z, Liang DY, Sun Y, Kingery WS, and Clark JD. 2012. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. Anesthesiology 116: 882–895. [PubMed: 22343473]
54. Metz M, Piliponsky AM, Chen C-C, Lammel V, Abrink M, Pejler G, Tsai M, and Galli SJ. 2006. Mast cells can enhance resistance to snake and honeybee venoms. Science 313: 526–530. [PubMed: 16873664]
55. Serhan N, Basso L, Sibilano R, Petitfils C, Meixiong J, Bonnart C, Reber LL, Marichal T, Starkl P, Cenac N, et al. 2019. House dust mites activate nociceptor-mast cell clusters to drive type 2 skin inflammation. Nat. Immunol 20: 1435–1443. [PubMed: 31591569]
56. Niizeki H, Alard P, and Streilein JW. 1997. Calcitonin gene-related peptide is necessary for ultraviolet B-impaired induction of contact hypersensitivity. J. Immunol 159: 5183–5186. [PubMed: 9548453]
57. Cardoso V, Chesné J, Ribeiro H, García-Cassani B, Carvalho T, Bouchery T, Shah K, Barbosa-Morais NL, Harris N, and Veiga-Fernandes H. 2017. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. Nature 549: 277–281. [PubMed: 28869974]
58. Klose CSN, Mahlakõiv T, Moeller JB, Rankin LC, Flamar A-L, Kabata H, Monticelli LA, Moriyama S, Putzel GG, Rakhilin N, et al. 2017. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. Nature 549: 282–286. [PubMed: 28869965]
59. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour R-EE, Nyman J, Dionne D, Hofree M, Cuoco MS, Rodman C, Farouq D, et al. 2017. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. [Published erratum appears in 2017 Nature 551: 658.] Nature 549: 351–356. [PubMed: 28902842]
60. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, Thornton EE, Krummel MF, Chawla A, Liang H-E, and Locksley RM. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 502: 245–248. [PubMed: 24037376]
61. Talbot S, Abdulnour R-EE, Burkett PR, Lee S, Cronin SJF, Pascal MA, Laedermann C, Foster SL, Tran JV, Lai N, et al. 2015. Silencing nociceptor neurons reduces allergic airway inflammation. Neuron 87: 341–354. [PubMed: 26119026]
62. Wallrapp A, Burkett PR, Riesenfeld SJ, Kim S-J, Christian E, Abdulnour R-EE, Thakore PI, Schnell A, Lambden C, Herbst RH, et al. 2019. Calcitonin gene-related peptide negatively regulates alarmin-driven type 2 innate lymphoid cell responses. Immunity 51: 709–723.e6. [PubMed: 31604686]
63. Xu H, Ding J, Porter CBM, Wallrapp A, Tabaka M, Ma S, Fu S, Guo X, Riesenfeld SJ, Su C, et al. 2019. Transcriptional atlas of intestinal immune cells reveals that neuropeptide α-CGRP modulates group 2 innate lymphoid cell responses. Immunity 51: 696–708.e9. [PubMed: 31618654]

64. Kumamoto Y, Linehan M, Weinstein JS, Laidlaw BJ, Craft JE, and Iwasaki A. 2013. CD301b$^+$ dermal dendritic cells drive T helper 2 cell-mediated immunity. Immunity 39: 733–743. [PubMed: 24076051]

65. Gao Y, Nish SA, Jiang R, Hou L, Licona-Limón P, Weinstein JS, Zhao H, and Medzhitov R. 2013. Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells. Immunity 39: 722–732. [PubMed: 24076050]

66. Tussiwand R, Everts B, Grajales-Reyes GE, Kretzer NM, Iwata A, Bagaitkar J, Wu X, Wong R, Anderson DA, Murphy TL, et al. 2015. Klf4 expression in conventional dendritic cells is required for T helper 2 cell responses. Immunity 42: 916–928. [PubMed: 25992862]

67. Monticelli LA, Sonnenberg GF, Abt MC, Alenghat T, Ziegler CGK, Doering TA, Angelosanto JM, Laidlaw BJ, Yang CY, Sathaliyawala T, et al. 2011. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. Nat. Immunol 12: 1045–1054. [PubMed: 21946417]

68. Guo XJ, Dash P, Crawford JC, Allen EK, Zamora AE, Boyd DF, Duan S, Bajracharya R, Awad WA, Apiwattanakul N, et al. 2018. Lung γδ T cells mediate protective responses during neonatal influenza infection that are associated with type 2 immunity. Immunity 49: 531–544.e6. [PubMed: 30170813]

69. Wu X, Kasmani MY, Zheng S, Khatun A, Chen Y, Winkler W, Zander R, Burns R, Taparowsky EJ, Sun J, and Cui W. 2022. BATF promotes group 2 innate lymphoid cell-mediated lung tissue protection during acute respiratory virus infection. Sci. Immunol 7: eabc9934. [PubMed: 35030033]

70. Chapman MD, Pomés A, Breiteneder H, and Ferreira F. 2007. Nomenclature and structural biology of allergens. J. Allergy Clin. Immunol 119: 414–420. [PubMed: 17166572]

71. Radauer C, Bublin M, Wagner S, Mari A, and Breiteneder H. 2008. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. J. Allergy Clin. Immunol 121: 847–852.e7. [PubMed: 18395549]

72. Gough L, Schulz O, Sewell HF, and Shakib F. 1999. The cysteine protease activity of the major dust mite allergen Der p 1 selectively enhances the immunoglobulin E antibody response. J. Exp. Med 190: 1897–1902. [PubMed: 10601364]

73. Kale SL, Agrawal K, Gaur SN, and Arora N. 2017. Cockroach protease allergen induces allergic airway inflammation via epithelial cell activation. Sci. Rep 7: 42341. [PubMed: 28198394]

74. Kouzaki H, O'Grady SM, Lawrence CB, and Kita H. 2009. Pro-teases induce production of thymic stromal lymphopoietin by airway epithelial cells through protease-activated receptor-2. J. Immunol 183: 1427–1434. [PubMed: 19561109]

75. Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ, Stewart GA, Taylor GW, Garrod DR, Cannell MB, and Robinson C. 1999. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. J. Clin. Invest 104: 123–133. [PubMed: 10393706]

76. Schulz O, Sewell HF, and Shakib F. 1998. Proteolytic cleavage of CD25, the alpha subunit of the human T cell interleukin 2 receptor, by Der p 1, a major mite allergen with cysteine protease activity. J. Exp. Med 187: 271–275. [PubMed: 9432986]

77. Halim TYF, Krauss RH, Sun AC, and Takei F. 2012. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. Immunity 36: 451–463. [PubMed: 22425247]

78. Morita H, Arae K, Unno H, Miyauchi K, Toyama S, Nambu A, Oboki K, Ohno T, Motomura K, Matsuda A, et al. 2015. An inter-leukin-33-mast cell-interleukin-2 axis suppresses papain-induced allergic inflammation by promoting regulatory T cell numbers. Immunity 43: 175–186. [PubMed: 26200013]

79. Leoni C, Volpicella M, Dileo M, Gattulli BAR, and Ceci LR. 2019. Chitinases as food allergens. Molecules 24: 2087. [PubMed: 31159327]

80. Zhu Z, Zheng T, Homer RJ, Kim Y-K, Chen NY, Cohn L, Hamid Q, and Elias JA. 2004. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science 304: 1678–1682. [PubMed: 15192232]

81. King TP, and Wittkowski KM. 2011. Hyaluronidase and hyaluronan in insect venom allergy. Int. Arch. Allergy Immunol 156: 205–211. [PubMed: 21597301]

82. Morales-Amparano MB, Huerta-Ocampo JÁ, Pastor-Palacios G, and Teran LM. 2021. The role of enolases in allergic disease. J. Allergy Clin. Immunol. Pract 9: 3026–3032. [PubMed: 33862268]
83. Chruszcz M, Chew FT, Hoffmann-Sommergruber K, Hurlburt BK, Mueller GA, Pomés A, Rouvinen J, Villalba M, Wöhrl BM, and Breiteneder H. 2021. Allergens and their associated small molecule ligands-their dual role in sensitization. Allergy 76: 2367–2382. [PubMed: 33866585]
84. Foo ACY, Thompson PM, and Mueller GA. 2021. Removal and replacement of endogenous ligands from lipid-bound proteins and allergens. J. Vis. Exp 168: e61780.
85. Aglas L, Soh WT, Kraiem A, Wenger M, Brandstetter H, and Ferreira F. 2020. Ligand binding of PR-10 proteins with a particular focus on the Bet v 1 allergen family. Curr. Allergy Asthma Rep 20: 25. [PubMed: 32430735]
86. Davey RJ, and Moens PD. 2020. Profilin: many facets of a small protein. Biophys. Rev 12: 827–849. [PubMed: 32661903]
87. Petersen A, Kull S, Rennert S, Becker W-M, Krause S, Ernst M, Gutsmann T, Bauer J, Lindner B, and Jappe U. 2015. Peanut defensins: novel allergens isolated from lipophilic peanut extract. J. Allergy Clin. Immunol 136: 1295–1301.e1–5. [PubMed: 26037551]
88. Pucca MB, Ahmadi S, Cerni FA, Ledsgaard L, Sørensen CV, McGeoghan FTS, Stewart T, Schoof E, Lomonte B, Auf dem Keller U, et al. 2020. Unity makes strength: exploring intraspecies and interspecies toxin synergism between phospholipases A_2 and cytotoxins. Front. Pharmacol 11: 611. [PubMed: 32457615]
89. Agaronyan K, Sharma L, Vaidyanathan B, Glenn K, Yu S, Annicelli C, Wiggen TD, Penningroth MR, Hunter RC, Dela Cruz CS, and Medzhitov R. 2022. Tissue remodeling by an opportunistic pathogen triggers allergic inflammation. Immunity 55: 895–911.e10. [PubMed: 35483356]
90. Benedé S, and Berin MC. 2021. Applications of mouse models to the study of food allergy. Methods Mol. Biol 2223: 1–17. [PubMed: 33226583]
91. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, Moore CL, Seunghyun In T, Waserman S, Coyle AJ, et al. 2013. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. J. Allergy Clin. Immunol 131: 187–200.e1–8. [PubMed: 23006545]
92. Brough HA, Lanser BJ, Sindher SB, Teng JMC, Leung DYM, Venter C, Chan SM, Santos AF, Bahnson HT, Guttman-Yassky E, et al. 2022. Early intervention and prevention of allergic diseases. Allergy 77: 416–441. [PubMed: 34255344]
93. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJD, et al. 2006. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat. Genet 38: 441–446. [PubMed: 16550169]
94. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, Curtin JA, Bønnelykke K, Tian C, Takahashi A, et al. 2015. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat. Genet 47: 1449–1456. [PubMed: 26482879]
95. Carlsten C, Dimich-Ward H, Ferguson A, Watson W, Rousseau R, Dybuncio A, Becker A, and Chan-Yeung M. 2013. Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors. Ann. Allergy Asthma Immunol 110: 24–28. [PubMed: 23244654]
96. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, et al. ; LEAP Study Team. 2015. Randomized trial of peanut consumption in infants at risk for peanut allergy. N. Engl. J. Med 372: 803–813. [PubMed: 25705822]
97. Mayer JU, Hilligan KL, Chandler JS, Eccles DA, Old SI, Domingues RG, Yang J, Webb GR, Munoz-Erazo L, Hyde EJ, et al. 2021. Homeostatic IL-13 in healthy skin directs dendritic cell differentiation to promote T_H2 and inhibit T_H17 cell polarization. [Published erratum appears in 12022 Nat. Immunol. 23: 985.] Nat. Immunol 22: 1538–1550. [PubMed: 34795444]
98. Bachus H, Kaur K, Papillion AM, Marquez-Lago TT, Yu Z, Ballesteros-Tato A, Matalon S, and León B. 2019. Impaired tumor-necrosis-factor-α-driven dendritic cell activation limits lipopolysaccharide-induced protection from allergic inflammation in infants. Immunity 50: 225–240.e4. [PubMed: 30635238]

99. Starkl P, Watzenboeck ML, Popov LM, Zahalka S, Hladik A, Lakovits K, Radhouani M, Haschemi A, Marichal T, Reber LL, et al. 2020. IgE effector mechanisms, in concert with mast cells, contribute to acquired host defense against Staphylococcusaureus. [Published erratum appears in 2020 Immunity 53: 1333.] Immunity 53: 793–804.e9. [PubMed: 32910906]
100. Gowthaman U, Chen JS, Zhang B, Flynn WF, Lu Y, Song W, Joseph J, Gertie JA, Xu L, Collet MA, et al. 2019. Identification of a T follicular helper cell subset that drives anaphylactic IgE. Science 365: eaaw6433. [PubMed: 31371561]
101. Clement RL, Daccache J, Mohammed MT, Diallo A, Blazar BR, Kuchroo VK, Lovitch SB, Sharpe AH, and Sage PT. 2019. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. Nat. Immunol 20: 1360–1371. [PubMed: 31477921]
102. Martinez-Gonzalez I, Mathä L, Steer CA, Ghaedi M, Poon GFT, and Takei F. 2016. Allergen-experienced group 2 innate lymphoid cells acquire memory-like properties and enhance allergic lung inflammation. Immunity 45: 198–208. [PubMed: 27421705]
103. Martinez-Gonzalez I, Ghaedi M, Steer CA, Mathä L, Vivier E, and Takei F. 2018. ILC2 memory: recollection of previous activation. Immunol. Rev 283: 41–53. [PubMed: 29664572]
104. de Lucía Finkel P, Xia W, and Jefferies WA. 2021. Beyond unconventional: what do we really know about group 2 innate lymphoid cells? J. Immunol 206: 1409–1417. [PubMed: 33753565]
105. Verma M, Michalec L, Sripada A, McKay J, Sirohi K, Verma D, Sheth D, Martin R, Dyjack N, Seibold MA, et al. 2021. The molecular and epigenetic mechanisms of innate lymphoid cell (ILC) memory and its relevance for asthma. J. Exp. Med 218: e20201354. [PubMed: 34076685]
106. Hondowicz BD, An D, Schenkel JM, Kim KS, Steach HR, Krishnamurty AT, Keitany GJ, Garza EN, Fraser KA, Moon JJ, et al. 2016. Interleukin-2-dependent allergen-specific tissue-resident memory cells drive asthma. Immunity 44: 155–166. [PubMed: 26750312]
107. Turner DL, Goldklang M, Cvetkovski F, Paik D, Trischler J, Barahona J, Cao M, Dave R, Tanna N, D'Armiento JM, and Farber DL. 2018. Biased generation and in situ activation of lung tissue-resident memory CD4 T cells in the pathogenesis of allergic asthma. J. Immunol 200: 1561–1569. [PubMed: 29343554]
108. Rahimi RA, Nepal K, Cetinbas M, Sadreyev RI, and Luster AD. 2020. Distinct functions of tissue-resident and circulating memory Th2 cells in allergic airway disease. J. Exp. Med 217: e20190865. [PubMed: 32579670]
109. Ulrich BJ, Kharwadkar R, Chu M, Pajulas A, Muralidharan C, Koh B, Fu Y, Gao H, Hayes TA, Zhou H-M, et al. 2022. Allergic airway recall responses require IL-9 from resident memory $CD4^+$ T cells. Sci. Immunol 7: eabg9296. [PubMed: 35302861]
110. Wambre E, Bajzik V, DeLong JH, O'Brien K, Nguyen Q-A, Speake C, Gersuk VH, DeBerg HA, Whalen E, Ni C, et al. 2017. A phenotypically and functionally distinct human T_H2 cell subpopulation is associated with allergic disorders. Sci. Transl. Med 9: eaam9171. [PubMed: 28768806]
111. Micossé C, von Meyenn L, Steck O, Kipfer E, Adam C, Simillion C, Seyed Jafari SM, Olah P, Yawlkar N, Simon D, et al. 2019. Human "T_H9" cells are a subpopulation of PPAR-γ^+ T_H2 cells. Sci. Immunol 4: eaat5943. [PubMed: 30658968]
112. Seumois G, Ramírez-Suástegui C, Schmiedel BJ, Liang S, Peters B, Sette A, and Vijayanand P. 2020. Single-cell transcriptomic analysis of allergen-specific T cells in allergy and asthma. Sci. Immunol 5: eaba6087. [PubMed: 32532832]
113. Richard M, Grencis RK, Humphreys NE, Renauld JC, and Van Snick J. 2000. Anti-IL-9 vaccination prevents worm expulsion and blood eosinophilia in Trichuris muris-infected mice. Proc. Natl. Acad. Sci. USA 97: 767–772. [PubMed: 10639154]
114. Townsend JM, Fallon GP, Matthews JD, Smith P, Jolin EH, and McKenzie NA. 2000. IL-9-deficient mice establish fundamental roles for IL-9 in pulmonary mastocytosis and goblet cell hyperplasia but not T cell development. Immunity 13: 573–583. [PubMed: 11070175]
115. Fu Y, Wang J, Zhou B, Pajulas A, Gao H, Ramdas B, Koh B, Ulrich BJ, Yang S, Kapur R, et al. 2022. An IL-9-pulmonary macrophage axis defines the allergic lung inflammatory environment. Sci. Immunol 7: eabi9768. [PubMed: 35179949]

116. Tibbitt CA, Stark JM, Martens L, Ma J, Mold JE, Deswarte K, Oliynyk G, Feng X, Lambrecht BN, De Bleser P, et al. 2019. Single-cell RNA sequencing of the T helper cell response to house dust mites defines a distinct gene expression signature in airway Th2 cells. Immunity 51: 169–184.e5. [PubMed: 31231035]

117. Olivera A, Beaven MA, and Metcalfe DD. 2018. Mast cells signal their importance in health and disease. J. Allergy Clin. Immunol 142: 381–393. [PubMed: 29454835]

118. Crosson T, Wang J-C, Doyle B, Merrison H, Balood M, Parrin A, Pascal M, Mindt BC, Seehus CR, Ozcan A, et al. 2021. FceR1-expressing nociceptors trigger allergic airway inflammation. J. Allergy Clin. Immunol 147: 2330–2342. [PubMed: 33453289]

119. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, Chen S, Trier AM, Xu AZ, Tripathi SV, et al. 2017. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell 171: 217–228.e13. [PubMed: 28890086]

120. Mack M, Tonc E, Ashbaugh A, Wetzel A, Sykes A, Engblom C, Shabani E, Mora-Solano C, Trier A, Swanson L, et al. 2014. Clonal differences in IgE antibodies affect cutaneous anaphylaxis-associated thermal sensitivity in mice. Immunol. Lett 162(1 Pt A): 149–158. [PubMed: 25149207]

121. Rijnierse A, Kroese ABA, Redegeld FA, Blokhuis BRJ, van der Heijden MW, Koster AS, Timmermans J-P, Nijkamp FP, and Kraneveld AD. 2009. Immunoglobulin-free light chains mediate antigen-specific responses of murine dorsal root ganglion neurons. J. Neuroimmunol 208: 80–86. [PubMed: 19232443]

122. van der Kleij H, Charles N, Karimi K, Mao Y-K, Foster J, Janssen L, Chang Yang P, Kunze W, Rivera J, and Bienenstock J. 2010. Evidence for neuronal expression of functional Fc (epsilon and gamma) receptors. J. Allergy Clin. Immunol 125: 757–760. [PubMed: 20132972]

123. Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, et al. 2019. Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. Immunity 50: 707–722.e6. [PubMed: 30824323]

124. Mahlakõiv T, Flamar A-L, Johnston LK, Moriyama S, Putzel GG, Bryce PJ, and Artis D. 2019. Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33. Sci. Immunol 4: eaax0416. [PubMed: 31053655]

125. Rana BMJ, Jou E, Barlow JL, Rodriguez-Rodriguez N, Walker JA, Knox C, Jolin HE, Hardman CS, Sivasubramaniam M, Szeto A, et al. 2019. A stromal cell niche sustains ILC2-mediated type-2 conditioning in adipose tissue. J. Exp. Med 216: 1999–2009. [PubMed: 31248899]

126. Puttur F, Denney L, Gregory LG, Vuononvirta J, Oliver R, Entwistle LJ, Walker SA, Headley MB, McGhee EJ, Pease JE, et al. 2019. Pulmonary environmental cues drive group 2 innate lymphoid cell dynamics in mice and humans. Sci. Immunol 4: eaav7638. [PubMed: 31175176]

127. Boothby IC, Kinet MJ, Boda DP, Kwan EY, Clancy S, Cohen JN, Habrylo I, Lowe MM, Pauli M, Yates AE, et al. 2021. Early-life inflammation primes a T helper 2 cell-fibroblast niche in skin. Nature 599: 667–672. [PubMed: 34707292]

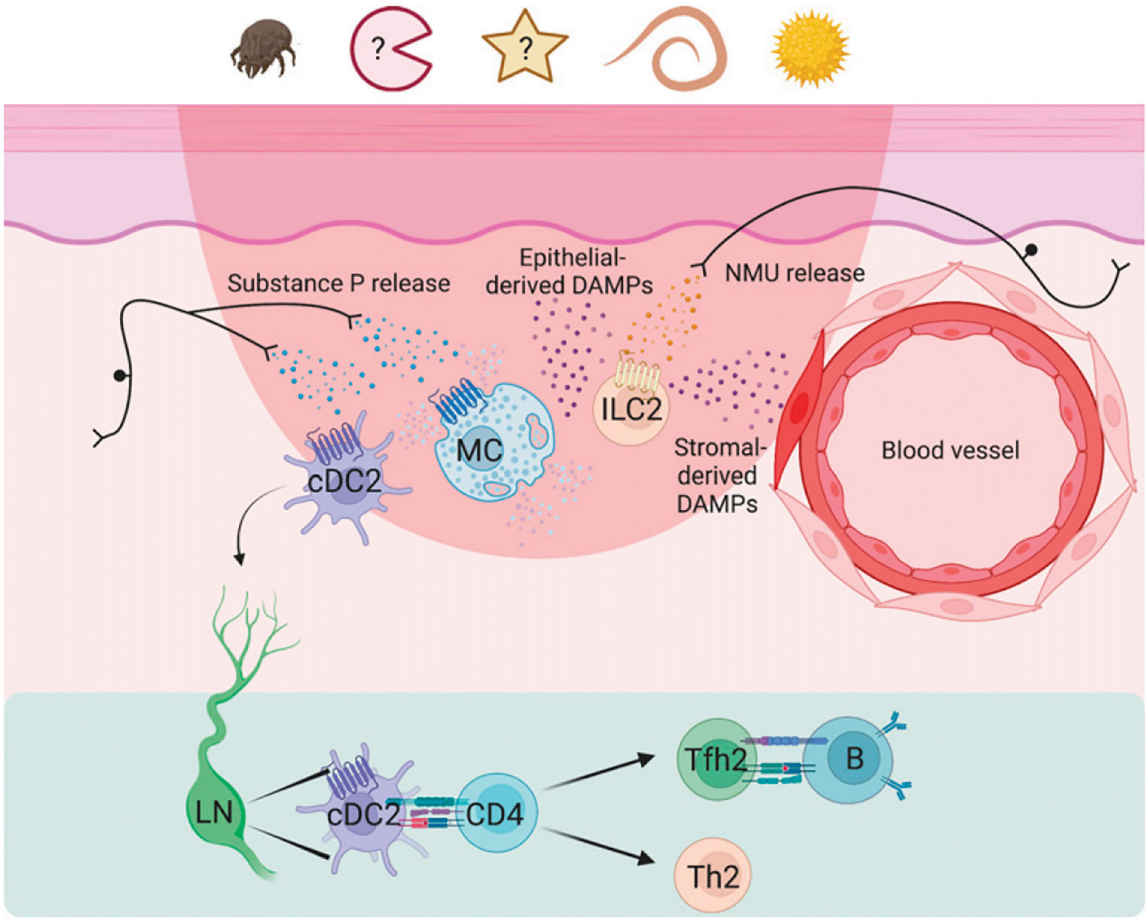

FIGURE 1. Functional recognition in the initiation of type 2 immunity at barrier surfaces.
Structurally unrelated type 2 immunogens, including those with undefined activities (question marks), are sensed at barrier surfaces by their shared ability to induce production of DAMPs and neuropeptides. DAMPs derived from epithelial cells and adventitial stromal cells, as well as other cell types, activate innate immune effectors such as mast cells and ILC2s. Neuropeptides such as neuromedin U promote the activation of ILC2s. The neuropeptide substance P enhances mast cell activation via MRGPRB2 and $CD4^+$ Th2-skewing cDC2 trafficking via MRGPRA1, the latter promoting the differentiation of $CD4^+$ Th2 and Tfh2 cells. Created with BioRender.com.

Table I.

Functional classes of allergens

Functional Group	Class	Endogenous Function	Example Allergens (Plant, Animal, Fungus, Venom)					
Proteases	Cysteine Protease	Protein cleavage	Act d 1 Blo t 1	Amb a 11 Der f 1	Ana c 2 Der p 1	Cari p 2	Cyn d CP	Phl p CP
	Serine protease	Protein cleavage	Cuc m 1 Alt a 15 Pen b 13	Der f 3 Asp f 13 Api m 7	Der f 6 Asp f 18 Pol e 4	Der p 6 Asp n 18	Der p 9 Cla c 9	Per a 10 Fus p 9
	Aspartate protease	Protein cleavage	Per a 2	Asp f 10	Rhi o 1	Aed a 11		
	Metalloprotease	Protein cleavage	Asp f 5					
CAZymes	Polygalacturonase	Hydrolysis of alpha-1,4 glycosidic bonds (fruit ripening)	Cari p 1	Cup s 2	Phl p 13			
	Chitinase	Hydrolysis of glycosidic bonds (pathogen resistance in plants, shell growth in animals)	Cas s 5 Bla g 12	Cof a 1 Der f 15	Man i 1 Der p 15	Mus a 2 Per a 12	Pers a 1	Zea m 8
	Amylase	Hydrolysis of starch into sugars (Digestive enzyme)	Hor v 16 Bla g 11	Tri a 17 Blo t 4	Der f 4	Der p 4	Per a 11	Asp o 2
	Lysozyme	Hydrolysis of peptidoglycan residues (host defense)	Equ a 6	Equ c 6	Gal d 4			
	Pectin Lyase	Hydrolysis of structural polysaccharides	Amb a 1	Art v 6	Cup a 1	Jun a 1	Pen c 32	
	Hyaluronidase	Hydrolysis of hyaluronan (degrade extracellular matrix)	Api m 2 Ves m 2	Dol m 2 Ves v 2	Pol a 2 Vesp ma 2	Pol d 2	Poly p 2	
Metabolic enzymes	Enolase	Catalyzes last step of glycolysis	Amb a 12 Sal s 2	Cyn d 22 Thu a 2	Cyp c 2 Alt a 6	Gad m 2 Asp f 22	Gal d 9 Cla h 6	Per a 14 Pen c 22
	Arginine kinase	Arginine and proline metabolism	Bla g 9 Der f 20	Can f 5 Der p 20	Cra a 2 Per a 9	Cra c 2		
Detoxification enzyme	Aldehyde dehydrogenase	Conversion of aldehydes to carboxylic acids	Tyr p 35	Alt a 10	Cla h 10	Har a 2		
	Manganese superoxide dismutase	Elimination of reactive oxygen species	Amb t 13 Alt a 14	Hev b 10 Asp f 6	Ole e 5 Mala s 11	Pis v 4		
	Glutathione-S-transferase	Catalyze binding of glutathione to xenobiotic substances	Bet v 8	Der p 8	Der f 8	Per a 5	Alt a 13	
Ligand binding proteins	Albumin	Soluble proteins that bind to various ligands	Act d 13 Ana o 3 Can f 3 Cav p 4	Ara h 2 Ara h 6 Ara h 7 Clu h 1 Gad c 1	Ber e 1 Car i 1 Cor a 14 Gal d 2 Gal d 5	Cuc ma 5 Gly m 8 Jug r 1 Fel d 2 Mus m 1	Ses i 1 Ses i 2 Sal s 1 Sus s 1	Bos d 4 Bos d 6 Thu a 1 Xip g 1
	Globulin	Soluble proteins that bind to various ligands. Act as protein storage in plants	Act d 12 Ara h 1 Ara h 3 Bos d 5	Ber e 2 Car i 2 Car i 4 Fel d 5	Cor a 9 Cor a 11 Cuc ma 4 Fel d 6	Gly m 5 Gly m 6 Jug r 4 Rat n 1	Jug r 6 Pis v 2 Pis v 5	Pru du 6 Ses i 3 Ses i 6
	Lipid Transfer Protein	Phospholipids and other fatty acid transport between cell membranes	Amb a 6 Cor a 8 Mus a 3	Api g 2 Fra a 3 Pru av 3	Ara h9 Hev b 12 Pru d 3	Art v 3 Jug r 3 Rub i 3	Cas s 8 Len c 3 Sola l 3	Cit l 3 Mal d 3 Tri a 14
	Cholesterol binding protein	Cholesterol transport	Der f 2	Der p 2	Tyr p 2			
	Fatty acid binding protein	Fatty acid transport between cell membranes	Der f 13	Der p 13	Lit v 13	Pen m 13		
	Lipocalins	Transport of small hydrophobic molecules (e.g., steroids)	Bla g 4 Bos d 4	Can f 1 Can f 2	Can f 4 Equ c 1	Equ c 2 Mes a 1	Mus m 1 Ory c 1	Per a 4 Rat n 1
	Transferrin	Transport iron through blood	Bos d lactoferrin		Gal d 3			
	PR-10	Pathogen defense	Act d 8 Cor a 1 Mal d 1	Aln g 1 Dau c 1 Pru ar 1	Api g 1 Fag s 1 Pru av 1	Ara h 8 Fra a 1 Pru du 1	Bet v 1 Gly m 4 Pru p 1	Cas s 1 Jug r 5 Que a 1
Structural integrity	Profilin	Actin binding protein	Act d 9 Bet v 2 Cuc m 2 Jug r 7 Pru av 4	Amb a 8 Cap a 2 Cyn d 12 Mal d 4 Pru du 4	Ana c 1 Che a 2 Dau c 4 Man l 4 Sola i 1	Api g 4 Citr l 2 Fra a 4 Mus a 1 Sola m 1	Ara h 5 Cit s 2 Gly m 3 Ole e 2 Tri a 12	Art v 4 Cor a 2 Hev b 8 Phl p 12 Tyr p 36
	Phospholipase	Hydrolysis of phospholipids	Api m 1 Sol i 1	Bom p 1 Vesp c 1	Bom t 1 Vesp m 1	Dol m 1 Vesp v 1	Pol a 1 Ves m 1	Pol d 1 Ves s 1
	Pore forming toxins	Pore formation	Api m 4					
	Defensin	Membrane disruption	Amb a 4	Api g 7	Ara h 12	Art v 1	Gly m 2	Par h 1

Allergens can be divided into distinct groups based on their functional properties. Example allergens for each group and class are listed based on their source: plant, animal, fungal, and venom. World Health Organization/International Union of Immunological Societies nomenclature is used throughout the table.