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Allergic Host Defenses

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Abstract

Allergies are generally thought to be a detrimental outcome of a mistargeted immune response that evolved to provide immunity to macro-parasites. Here we present arguments to suggest that allergic immunity plays an important role in host defense against noxious environmental substances, including venoms, hematophagous fluids, environmental xenobiotics and irritants. We argue that appropriately targeted allergic reactions are beneficial, although they can become detrimental when excessive. Furthermore, we suggest that allergic hypersensitivity evolved to elicit anticipatory responses and to promote avoidance of suboptimal environments.

Introduction

The immune system protects the host from a variety of infectious agents, ranging from microscopic RNA viruses to 40 foot long tapeworms. Mammalian hosts can employ several defense strategies to deal with different classes of pathogens. Immune defense against microorganisms (viruses, bacteria, fungi and protozoa), referred to as type 1 immunity, relies primarily on direct killing of pathogens or infected host cells. The adaptive arm of type 1 immunity is mediated by T helper type 1 (Th1) and Th17 cells, cytotoxic T cells, and IgM, IgA and several IgG antibody classes. In contrast, type 2 immunity protects against macroparasites (helminthes and parasite expulsion. Type 2 immune responses are mediated by Th2 cells and IgE and ectoparasites, such as ticks) and relies primarily on barrier defenses and IgG1 antibodies, as well as several components of the innate immune system, including epithelial barriers, innate lymphoid cells (ILC), eosinophils, mast cells, basophils and alternatively-activated macrophages¹⁻³. While their role in host defense against macroparasites is well appreciated, type 2 immune responses can notoriously be activated in response to a broad variety of environmental challenges. Non-infectious environmental stimuli that can trigger type 2 immune response are referred to as allergens, and the allergic reactions they elicit are thought to be a purely detrimental consequence of a mistargeted response that normally operates to protect from parasitic worms.

Here we will argue that defence against macroparasites is only one of several functions of type 2 immunity. Specifically, we propose that type 2 immune responses evolved to protect from at least four different classes of environmental challenges, including: (1) helminthes; (2) noxious xenobiotics; (3) venoms and hematophagous fluids; and (4) environmental irritants. Accordingly, there may be multiple pathways that lead to activation of Th2 immune responses that are specialized to protect against these environmental challenges. All of these responses, however, share a common defense strategy and their effector functions converge on the surface epithelia (skin and mucosa), smooth muscles and vasculature to

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promote barrier defenses and expulsion. While activation of these target tissues is intended to protect from the four types of environmental challenges, exacerbation of these defenses leads to overlapping immunopathologies commonly known as allergies. These include rhinorrhea (runny nose), hay fever, hives, itch and allergic dermatitis. At the extreme, allergic hypersensitivity can result in life-threatening anaphylaxis. Notably, unlike other immunopathologies, allergic disorders exclusively affect tissues that interface with the environment.

Allergic immunity

Allergic reactivity remains one of the biggest mysteries of the immune system. The prevailing paradigm holds that Th2-IgE mediated immune responses evolved to provide protection against multicellular parasites also lead to allergy when inadvertently activated by non-infectious environmental antigens⁴. The allergic response is thus considered a misdirected and unintended type 2 immune response. There are several problems with this view: First, while some allergens (for example, chitin and cysteine proteases) can indeed mimic the immunogenic activities of macroparasites⁵, most allergens do not have any obvious relationship with parasitic worms. Second, anaphylactic responses to allergens are extremely rapid, occurring within minutes of exposure. However, there is no obvious reason to respond with such extreme urgency when dealing with slowly replicating macroparasites – even immune responses to bacteria and viruses, which have replication rates that are orders of magnitude faster than helminthes, occur on the time scale of hours to days⁶. Third, allergic hypersensitivity is largely dependent on IgE-mediated activation of mast cells and basophils⁷. In contrast, while IgE levels are elevated in mice and people with helminth infections, IgE itself is dispensable for immunity to most helminthes for which its role has been tested⁸. Finally, allergic hypersensitivity can develop against a huge variety of allergens that have little common in terms of their structure or origin. Pollen, shellfish, peanuts, bee venom, latex, penicillin and Ni⁺ are all common allergens, yet they do not share any chemical characteristics and there is no unifying framework to explain their allergenicity⁹.

An alternative, but largely ignored, explanation for the existence of the allergic reactivity is that it can provide protection against environmental toxins^{6, 10, 11}. According to this view, the allergic response can be intended and beneficial, and not simply a pathological consequence of immunity to parasites. Here we present arguments to support the view that allergic immunity is an important component of host defense against non-infectious noxious environmental factors, including venoms and hematophagous fluids, noxious xenobiotics and irritants (Fig. 1). The diversity and prevalence of allergens may in turn reflect an important role of allergic reactivity in defense against these three classes of non-infectious stimuli, which we discuss in more detail next.

Allergens as noxious environmental stimuli

The most enigmatic feature of type 2 immunity is its propensity to be activated in response to a wide variety of environmental substances known as allergens. Allergens have defied all attempts at a comprehensive and rational classification, and they do not share any one property that would universally define them as allergens⁹. Consequently, allergens can only be defined operationally as substances that elicit an allergic response. We believe that the difficulty in establishing a rational framework for understanding allergens may stem from the fact that there are several distinct classes of allergens, including venoms and hematophagous fluids, xenobiotics and irritants. The common feature of these allergens is that they are noxious to the host, and therefore specific mechanisms have likely evolved for their detection and to provide protection from their noxious effects.

Venoms are complex mixtures of enzymes, peptides and small chemicals that are produced by various species of arthropods, Cnidaria, amphibians and reptiles for predation and defense and are usually delivered to their victims via bites or stings¹². Envenomation can cause severe and life-threatening tissue damage. In addition, venoms can induce Th2-IgE responses and can cause systemic anaphylaxis, which can be deadly in its own right^{13, 14}. However, allergic responses triggered by venoms may have evolved to protect the host from the direct damage caused by venoms, while anaphylaxis may be an unfortunate result of over-reaction, particularly when the response is triggered systemically^{10, 11, 15}. In this sense, allergic anaphylaxis is analogous to septic shock, which can be elicited by systemic stimulation of TLR4 by bacterial LPS. Just as the response to LPS evolved to protect from bacterial infections but can result in sepsis, the anaphylactic response may have evolved to protect from venoms and noxious xenobiotics but can result in potentially lethal systemic anaphylaxis. This would explain the apparent urgency of the anaphylactic reaction, which operates within minutes or even seconds – a time scale that is appropriate when dealing with deadly substances⁶.

Hematophagous fluids are used by a variety of ectoparasites, including ticks and mosquitos, to enable feeding on the blood of target species. Venoms and hematophagous fluids are evolutionarily related as both are produced by modified salivary glands and share many molecular components and properties¹³. Hematophagous species also act as vectors for many pathogens; for example, deer ticks harbor *Borellia burgdorferi*, the causative agent of Lyme disease, and mosquitos harbor *Plasmodium falciparum*, the causative agent of malaria¹⁶. Notably, hematophagous fluids can also induce a Th2 response¹⁷, and IgE, mast cell and basophil-dependent immune responses can prevent tick feeding¹⁸. Therefore, the immune system can sense hematophagous fluids and induce an allergic immune response that can prevent blood feeding (and transmission of vector-borne pathogens)¹⁹. To be effective, this response must be very rapid thus providing a clear rationale for the urgency of IgE-mediated responses. Importantly, helminthes also use salivary excretions to feed on host tissues²⁰. Recognition of salivary components from macroparasites may therefore contribute to defense against both hematophagous ectoparasites and helminthes, as well as from transmission of vector-borne microbes. Thus, defensive immune response to venoms and hematophagous fluids can explain allergies to arthropod bites and stings.

Noxious xenobiotics and toxins, including phytochemicals like urushiol from poison ivy and ricin, can also cause tissue and organ damage^{6, 21}. For the purpose of this discussion there are two classes of xenobiotics that differ in their site and mode of action. Hydrophobic xenobiotics can enter and accumulate inside cells where they can cause various toxic effects. This class of xenobiotics is detected by various intracellular sensors, including the Aryl hydrocarbon receptor (AhR), and the nuclear receptors CAR and FXR, that operate primarily in the liver²². These xenobiotics are primarily inactivated by the cytochrome P450 system and ultimately are excreted in the urine²²; however, at least in some cases they may cause allergic responses if the cytochrome P450 detoxification system is insufficient to prevent their noxious effects. The second class of noxious xenobiotics are haptens – reactive chemicals that have the propensity to form adducts with proteins. These xenobiotics are noxious because adduct formation can alter protein conformation and functions leading to various toxic effects²³. Interestingly, haptenation makes otherwise inert proteins immunogenic, leading to IgG1 antibody production, which may promote their clearance²⁴. Exposure to reactive haptens can also stimulate inflammasome activation²⁵ and induction of contact hypersensitivity reactions in the skin, which are mediated primarily by Th1 and CD8 T cells²⁶. However, if the skin barrier is breached, reactive haptens induce a largely Th2-based response²⁷, which may provide an allergic immune protection from reactive chemicals. Allergic responses may protect from xenobiotics via increased mucus production, keratinocyte hyperplasia, itch and bronchoconstriction (to reduce entry), vomiting and

diarrhea (to promote expulsion), complement activation (to promote clearance) and vascular leakage (to dilute the noxious substance). When excessive, these defensive reactions can result in allergic disease.

Reactivity to noxious xenobiotics presumably explains the existence of drug allergies. For example, penicillin allergy can develop in some people because penicillin can undergo metabolic transformation resulting in a reactive product that can form protein adducts²³. This property of the reactive form of penicillin is shared with noxious xenobiotics, except that penicillin transformation is very inefficient in most individuals. Free (non-conjugated) penicillin is immunologically inert in non-sensitized people and it is the hapten (conjugated) form of penicillin that appears to be immunogenic. However, once the response to the haptenated form is elicited, a hypersensitivity to free (non-conjugated) penicillin may develop, resulting in penicillin allergy²³. Many idiosyncratic drug reactions of allergic etiology presumably develop by the same mechanism and, more generally, small molecule allergens may elicit allergic reactions because they either have noxious xenobiotic activity (even if that activity is very low), or because they mimic something that has noxious activity. Therefore, while the xenobiotic-elicited response can be intended and protective, unintended allergic responses can develop to xenobiotics that are not intrinsically noxious.

Environmental irritants are chemicals (e.g., mild detergents) and particulates (e.g., dust and diesel exhaust particles) that can cause damage to the mucosal epithelium and skin²⁸. Airway reflexes (bronchoconstriction, sneezing and coughing) and itch have an obvious protective effect against environmental irritants. When excessively and persistently engaged these responses can cause allergic diseases, including asthma and dermatitis, in susceptible individuals.

Environmental irritants are presumably sensed primarily as a result of their damaging effects on respiratory or gastrointestinal mucosa and skin. Because diverse substances can cause mild tissue damage to surface epithelia, this class of allergens can be extremely heterogeneous. For example, it is estimated that more than half of all major characterized allergens have lipid binding activity^{29, 30}. One reason for their immunogenicity could be that lipids associated with these proteins may have mild detergent (irritant) properties and therefore may be sensed as noxious. Some lipid binding allergens can also associate with LPS and stimulate TLR4, as is the case of Der p 2³¹, and in experimental settings, ovalbumin (OVA)³².

Importantly, host defense against venoms, xenobiotics and irritants relies on the same basic strategies used for the defense against helminthes: barrier enhancement, expulsion, inactivation, restriction and repair (Fig. 1). These defence strategies are well appreciated in the case of helminth infections^{1, 2}, but they are equally well suited to protect from other noxious environmental stimuli, as we discuss next.

Allergic Defenses

Barrier defenses

Skin and mucosal epithelial barriers prevent or minimize parasite settlement at the mucosal surfaces and entry into internal compartments². Epithelial barriers are also critical in protecting from noxious xenobiotics and environmental irritants and these defenses can be enhanced through multiple mechanisms. Goblet cell hyperplasia leads to production of mucus and other defense molecules at mucosal surfaces; keratinocyte hyperplasia leads to a thickening of the epidermis; and, metaplasia of columnar epithelium into squamous epithelium results in improved resistance to damage. All of these barrier-enhancing effects occur at the expense of normal epithelial functions, such as nutrient absorption and gas

exchange, and therefore are only activated transiently upon exposure to noxious stimuli. Prolonged or excessive mucus production is a common component of allergies and asthma, for example rhinitis, sinusitis and airway obstruction. IL-13 is the best characterized inducer of goblet cell hyperplasia and mucus production³³. The source of IL-13 is either type 2 innate lymphoid cells (ILC), also known as nuocytes and natural helper cells,³⁴⁻³⁷ or Th2 cells. ILCs secrete IL-13 in response to stimulation by IL-33 and IL-25, which are produced by epithelial cells³. The mechanism responsible for induction of these cytokines in epithelial cells is incompletely understood, except that cell damage appears to be an important stimulus for IL-33 release³⁸. Mast cells can also be a source of IL-33 for ILC activation³⁹. In addition, production of TSLP by epithelial cells can also contribute to barrier defenses⁴⁰ and has been linked to allergic dermatitis and induction of Th2 differentiation in humans^{41, 42}.

Expulsion

Removal or expulsion is a preferred host defense strategy when dealing with helminthes and noxious substances. Their expulsion can be enforced by various means, such as sneezing, coughing, vomiting and diarrhea. Regulation of these defensive reactions can occur locally through the effect of mast cell derived histamine on the smooth muscles in airways and the intestine, as well as by neuronal mechanisms. Expulsion of noxious particulates is also achieved through the effect of the 'ciliary elevator' of the airway epithelia, which functions cooperatively with the mucus layer to promote expulsion of unwanted materials^{43, 44}. Itch sensation is another important mechanism of barrier defense and a common symptom of allergic diseases. Itch can be caused by the activation of C-fibers by histamine produced by mast cells⁴⁵. The intended effect of itch is to induce mechanical removal of ectoparasites (e.g., ticks) and harmful environmental substances (e.g., noxious xenobiotics) through scratching⁴⁶. This intended effect, however, when prolonged or excessive is a common manifestation of allergic dermatitis. Likewise, sneezing, coughing, tearing and diarrhea, while intended to provide host defense by expulsion, are also common symptoms of many allergies.

Inactivation and destruction

Inactivation of noxious substances, including reactive xenobiotics, toxins and venoms can occur through detoxification, neutralization and degradation. Notably, heparin and proteases produced by mast cells can neutralize and destroy various venom components^{10, 1115}. IgG1 antibodies have a well-defined protective effect against venoms, presumably because they can neutralize and clear toxic venom proteins. Xenobiotics that trigger allergic reactions are presumably also detoxified. The mechanism of detoxification of this class of xenobiotics is not known, but may involve phagocytosis and degradation of damaged proteins and cells, which may be aided by IgG antibodies and complement.

Direct destruction of helminthes is problematic due to their large size and the potential for excessive collateral tissue damage. Nevertheless, eosinophils can kill parasite larvae and eggs, and in some cases even adult worms, during tissue dwelling phases of their life cycle¹.

Restriction

When barrier defenses are breached and direct elimination or expulsion is insufficient, restriction provides the next layer of defense. Restriction mechanisms help to prevent the spread of parasites, venoms and noxious chemicals through the body. Vascular restriction mechanisms including endothelial leakage, exudate formation and coagulation can be induced by mast cell-derived histamine and chymase⁴. Another restriction mechanism involves sequestration through granuloma formation. Collagen deposition by fibroblasts can also help restrict the spread of parasites and noxious substances. Finally, in the case of

macroparasites, macrophage, mast cell and eosinophil-derived mediators can act on host tissues to make them less desirable habitats for helminthes ¹, or restrict tick feeding on the host blood ¹⁸. At the extreme, restriction processes may also contribute to the pathogenesis of allergic diseases.

Repair

Repair mechanisms help to mend the damage caused by macroparasites, venoms and noxious substances. Alternatively-activated macrophages and fibroblasts play a critical role in orchestrating repair responses through production of growth factors and extracellular matrix deposition, respectively ⁴⁷. In addition, ILCs in the lung can produce amphiregulin, which promotes repair of lung epithelium ⁴⁸. It has been suggested that much of Th2 mediated immunity is devoted to promoting tissue tolerance to damage and repair of parasite inflicted tissue injury ⁴⁹ and the same argument can be applied to any other noxious stimuli that induce allergic responses. Thus, the physiological rationale for the induction of tissue repair as part of allergic defenses is obvious. However, when excessive, these reparative processes can lead to pathological sequelae, such as airway remodeling with epithelial metaplasia and fibrosis in asthma.

In summary, common defense mechanisms provide protection from helminthes, venoms, xenobiotics and irritants, even though the adaptive value of these defenses is only appreciated in the case of helminth infections. In case of allergens, these same defenses are primarily known or perceived as pathological. The type of allergic pathology that develops (for example, dermatitis versus rhinitis) depends on which specific defense mechanism is over-reacting. All allergic defenses, however, can be grouped into two major host defense modules.

Two modules of allergic immunity

Common defense mechanisms that protect from macroparasites, venoms, xenobiotics and irritants are activated by two major functional modules of type 2 immunity (Fig 2).

The first module centers around type 2 ILCs and their adaptive counterpart, Th2 cells. These cells produce IL-13 to activate barrier defenses by inducing goblet cell hyperplasia and increased mucus production. ILCs also produce growth factors that repair mucosal epithelium ⁴⁸ and possibly KGF to induce keratinocyte hyperplasia. The latter can also be achieved by IL-22 produced by ILCs or skin resident Th22 cells ⁵⁰, although this is not generally classified as part of allergic immunity. ILCs and Th2 cells can also produce IL-5 to induce eosinophil activation and recruitment to the site of infection ^{51, 52}. Th2 and ILC derived IL-4 and IL-13 likely also promote alternative activation of macrophages, which in turn contribute to defense against helminthes ^{47, 53} and possibly venoms, irritants and xenobiotics. ILC activation is induced by the epithelial-derived cytokines, including IL-33 and IL-25³, while Th2 production of cytokines must be triggered by antigen recognition, although the relevant antigen-presenting cell in the affected tissues is not well defined.

The second module centers around mast cells and basophils and can be activated by IgE, which is deposited on high affinity Fc_ε receptors (Fc_εR). Mast cells and basophils can also be activated directly, for example, by protease allergens and venoms ^{10, 11, 15, 54}. However, it is the IgE-mediated activation of mast cells and basophils that makes this module exquisitely sensitive to allergens. Cross-linking of cell surface IgE by antigens leads to mast cell degranulation and release of pre-formed mediators, including histamine, leukotrienes, prostaglandins, substance P and various proteases ⁴. An important feature of mast cell and basophil degranulation is that it can occur in an all-or-none fashion and is extremely rapid because it does not require new protein synthesis. The rapid kinetics of the mast cell

response underlies many features of allergic inflammation and, as argued above, presumably evolved for defense against venoms and noxious chemicals⁶. Mast cell-derived histamine and prostaglandins act on endothelium to cause vasodilation and exudation; on airway smooth muscles to cause bronchoconstriction; and on intestinal smooth muscles to promote peristalsis and diarrhea. Mast cell-derived histamine also acts on C-fibers to cause itching⁴⁵. Finally, mast cell-derived proteases can contribute to venom degradation¹⁵, while basophils and mast cells can restrict tick feeding¹⁸.

The two modules of allergic immunity can function independently in some settings, but are not functionally isolated. For example, Th2 cells produce IL-3 and IL-9, which lead to basophil and mast cell expansion. Furthermore, basophils can produce Th2-inducing cytokines such as IL-4, and mast cells can produce ILC-activating cytokines, such as IL-33³⁹.

Sensing pathways for type 2 immune responses

Given the diversity of stimuli that can elicit type 2 immune responses, it is likely that there are multiple mechanisms used for their detection. These mechanisms can be divided into three categories: pattern recognition, sensing noxious activities and sensing molecular proxies of noxious activities. In addition, the somatosensory system cooperates with immune recognition in sensing noxious substances.

Pattern recognition—Unlike innate sensing for the type 1 immune response, pattern recognition is of limited use for the initiation of type 2 immunity. The premise of microbial pattern recognition is based on the existence of conserved biochemical products unique to microorganisms. Because multicellular parasites are much more closely related to their hosts on an evolutionary scale (compared to microorganisms), biochemical distinctions in core metabolic processes are limited to only a few examples, such as chitin⁵⁵. Although helminthes have many unique glycoproteins, they are not conserved across species and may not be essential for parasite survival. Nevertheless, there are a few cases of pattern recognition of helminthes and noxious substances. The house dust mite allergen Der p 2 (bound to LPS) and contact allergen Ni⁺ can activate TLR4^{31, 56}, Schistosome egg antigen (SEA) can be sensed by Dectin 2⁵⁷, and Ara h 1 from peanuts can be detected by DC-SIGN⁵⁸. In addition, sensing of LPS in the respiratory tract by TLR4 can elicit Th2 responses in the lungs³². In this case, LPS is presumably detected as an environmental irritant, rather than as a sign of bacterial infection. Alternatively, commensal-derived LPS maybe sensed as a sign of a breach in epithelial barrier. Not all of these examples represent true, intentional pattern recognition: activation of TLR4 by Ni⁺ is likely to be purely accidental, as its recognition is not conserved across mammalian species⁵⁶, and it is unlikely that TLR4 evolved to recognize Ni⁺.

Sensing noxious activities—The more common mechanism of sensing helminthes and allergens is likely based on detection of their unique activities or their effects on host tissues. For example, many Th2 inducing stimuli are sensed via their enzymatic activities. These include proteases (e.g., Der p 1 from dust mites⁵⁹ and papain from papaya⁵⁴), phospholipases (e.g., phospholipase A2 from bee venom⁶⁰), and the ribonuclease omega-1 from SEA⁶¹. Additional classes of allergens, including noxious xenobiotics, non-enzymatic venom components, poisons and irritants are also likely to be sensed via their effects on host tissues. Notably, tissue damage itself has been associated with the induction of type 2 immune responses: IL-33 can be produced by epithelial cells upon damage³⁸ and ATP released from dying cells promotes allergic inflammation and Th2 response in the lung⁶². Mechanical injury induces TSLP expression in the skin⁶³, and surgery induces a transient rise in total IgE (but not other Igs) in humans⁶⁴. Additionally, epithelial stress signals

mediated by Rae1-NKG2D interactions on keratinocytes and intraepidermal T cells, respectively, can induce Th2 differentiation⁶⁵. At least some toxins, such as the ribosome inactivating proteins from plants (including the famously potent Ricin), also induce IgE responses when given at sublethal doses²¹. The NLRP3 inflammasome can be activated by membrane damaging haptens and produces IL-1 that regulates contact hypersensitivity responses⁶⁶. Tissue damage can also be sensed by nociceptors (see below).

Sensing by proxy—The immune system may be able to detect molecular proxies of at least some noxious stimuli to elicit anticipatory responses, and in some cases, to promote their avoidance. Sensing ‘by proxy’ is used in a variety of systems as it provides the clear benefit of a pre-emptive response. Pathogen presence in the environment can be detected through molecular proxies of high bacterial density, such as bacteria-specific metabolites (e.g., cadaverin and putrescine). When these molecular proxies are volatile, they can be detected by the olfactory system to induce avoidance⁶⁷; if they are not volatile, they trigger the gustatory system to prevent ingestion of contaminated substances or to promote their expulsion (vomiting)^{68, 69}. We propose that sensing by proxy may also be used to elicit type 2 immune responses to some noxious environmental substances. Thus, innocuous allergens might be sensed because they function as a proxy for a noxious stimulus. Alternatively, innocuous allergens may be mistakenly recognized as a proxy for a noxious stimulus, because sensing by proxy is more error-prone than direct sensing. Sensing by proxy is likely used primarily to promote avoidance of noxious substances.

Somatosensory detection of noxious substances—An interesting and perhaps unique aspect of recognition of the stimuli that induce allergic defenses is the involvement of somatosensory pathways (Fig. 3). Chemosensory C-fibers may be particularly relevant in the context of allergic inflammation as they can be activated by endogenous mediators of tissue damage, including bradykinin and extracellular ATP⁷⁰, and by reactive chemical allergens, including chemical irritants, chlorine, environmental pollutants, and reactive oxygen species through the triggering of TRPA1 and TRPV1 ion channels⁷¹. Substance P and Calcitonin Gene-Related Peptide (CGRP) produced by C-fibers have direct inflammatory activities and can induce mast cell degranulation⁴⁵, thus connecting sensing of tissue damage with the allergic inflammation. It is likely that C-fibers are also activated in tissues infected with helminthes. In addition, irritants and other noxious substances can be sensed by epithelial chromaffin cells. Serotonin produced by enteric and pulmonary chromaffin cells, in turn activates afferent neurons of the vagus nerve, triggering expulsion and aversion reactions, including vomiting, sneezing and diarrhea⁷². Importantly, in addition to direct stimulation by noxious substances, C-fiber neurons can also be activated by histamine and other mediators produced by mast cells upon degranulation⁴⁵. The outcome of this stimulation is itch sensation and other defensive reactions. Thus, IgE-mast cell module can provide an antigen-dependent entry point into the somatosensory pathways, thus allowing the activation of somatosensory pathways by any allergen detectable by IgE deposited on mast cells. This, in turn, may provide the basis for association between allergen recognition by IgE and sensory stimuli detected by the olfactory, gustatory and visual systems, resulting in the phenomenon of conditional allergic reactions⁷³. Conditional allergic reactions are elicited by neutral stimuli when they are temporally associated with an allergen. The famous, albeit anecdotal example of such response is an allergic reaction elicited by a painting of a flower in individuals that have allergy to the flower. Although this phenomenon was first described over one hundred years ago^{74, 75}, and is well documented in the literature^{73, 76, 77}, the mechanistic basis and physiological rationale for conditional allergic reactions remains poorly understood. The coupling between IgE-mast cell - somatosensory pathways and visual, olfactory and gustatory stimuli may conceivably result in classical (Pavlovian) conditioning with subsequent conditional allergic reactions to

otherwise neutral stimuli present in the environment. The biological rationale for such learned allergic reactions might have to do with the assessment of the environment for the presence of noxious substances, as we discuss next.

The allergic response as an avoidance strategy

If the allergic response indeed evolved for defense purposes, what might be the reason for the extraordinary level of sensitivity of allergen recognition? What is the purpose of sensing miniscule amounts of allergen when the level of exposure is clearly far too low to cause any harm? We suggest that allergic hypersensitivity evolved to survey the environment (including air, water and food) for the presence of noxious substances. Once exposure to noxious environmental substances has taken place and allergen-specific IgE is generated, memory of allergen exposure can develop. After such sensitization, subsequent exposure to even minute amounts of allergen in a given environment will result in an allergic reaction, which has two purposes: First, it will induce anticipatory allergic responses that will help minimize the potentially harmful effects of the allergen by restricting entry and spread, enhancing detoxification, and encouraging expulsion. Second, allergic responses will encourage avoidance of the environment that contains the allergen (which is typically a noxious substance). According to this view, exquisite sensitivity to allergens triggers avoidance of what is perceived as a suboptimal environment. Repeated exposure may also condition future avoidance of suboptimal environments as well as the specific sources of noxious substances, such as specific foods and plants.

There are several lines of evidence that support the view that allergic sensitization play a role in aversive behavior. Mice made allergic to OVA avoid drinking the otherwise preferred sweetened solution⁷⁸. This aversion was allergen-specific and dependent on the immune system⁷⁹. Furthermore, available evidence suggests that allergen-containing food aversion is dependent on functional C-fiber innervation^{80, 81}. Interestingly, allergen sensitized mice exhibited increased level of anxiety upon exposure to the allergen, consistent with avoidance of allergen-containing environment. Finally, OVA-sensitized mice avoided entering the environment containing traces of OVA. Strikingly, this aversive behavior was IgE and mast cell dependent^{82, 83}. Together, these studies strongly support the notion that allergic sensitization promotes avoidance of allergen-containing environment, food and water sources⁸⁴.

It should be noted here that allergy is a unique disease in that it only manifests itself when the allergen is present in the environment. As any allergy sufferer would know, the best way to deal with allergy is to avoid exposure to the allergen. As soon as the exposure to allergen is eliminated, which in a natural setting would entail moving to a different environment, allergic symptoms disappear. This is consistent with the view that allergic hyper-reactivity evolved to screen the quality of the environment, to elicit an anticipatory response, and to enforce a change of environment whenever allergens are encountered.

Conclusions and Perspectives

The existence of allergic hypersensitivity remains largely unexplained. The commonly held assumption is that allergies are misguided reactions that are intended to protect from macroparasites. However, it is not clear from that perspective why allergens would induce the same type 2 immune responses as helminth infections. Moreover, the exquisite sensitivity and urgency of the allergic response, as well as the enormous diversity of allergens that can trigger this response, are hard to explain if we are to assume that the only function of these responses is defense against helminthes.

Here we presented the argument that allergic immunity evolved to protect the host not only from parasitic infections, but also from noxious xenobiotics, environmental irritants, envenomation and hematophagous ectoparasites. Each of these stimuli also defines a different class of allergens. We propose that allergic responses to noxious allergens are intended and protective, though they can become detrimental when excessive. It is possible, however, that responses to allergens that are truly innocuous (if such allergens indeed exist) are likely to be purely detrimental and are due to mistargeting of the immune response. It should be noted that it is difficult to determine with certainty which, if any, allergens are truly innocuous because the noxious effects of allergens may not be immediately obvious. It will be important to evaluate specific allergens from this perspective in the future.

Another unexplained feature of allergic hypersensitivity is its idiosyncrasy. Why are some people hypersensitive to peanuts and pollen while others are not? Although genetic factors certainly contribute to differential predispositions to allergic diseases, genetics alone cannot explain the idiosyncrasy of allergic sensitization. Indeed, the dramatic rise in allergic diseases over the past few decades cannot be accounted for by genetic factors alone. Moreover, hypersensitivity can develop or be lost at almost any stage of an individual's life. We propose that the idiosyncrasy of the allergic response may be due to at least two factors: First, allergic sensitization may occur due to accidental temporal association of a noxious stimulus and a neutral antigen whereby allergic sensitivity develops towards the latter. The noxious stimulus in this case will function as an 'adjuvant' and may or may not be an allergen itself. Thus, the details of an individual's life history may account for acquisition of hypersensitivity to certain allergens. The second reason for idiosyncrasy may have to do with differential sensitivity among individuals to the noxious effects of allergens. For example, if protection from a noxious xenobiotic can be afforded by both barrier defenses and detoxification, the individual that has reduced detoxification capacity (due to genetic variation or physiological status) would have to rely excessively, or even exclusively, on barrier defenses. Exaggerated barrier defenses will compensate for reduced detoxification and may afford sufficient protection from noxious offenses. This protection, however, will come at a cost that may manifest itself as allergic disease. Mutations in filaggrin may provide an example of such compensatory allergic reactivity. Filaggrin encodes a structural epidermal protein and genetic deficiencies in filaggrin are associated with atopic dermatitis⁸⁵. One could argue that development of dermatitis in this case is an attempt to compensate for defects in barrier functions caused by filaggrin mutation.

Importantly, while hypersensitivity itself is idiosyncratic, sub-clinical allergic defenses presumably operate in all healthy individuals. It would be interesting to investigate in future studies the long-term consequences of deficient allergic defenses. Interestingly in this regard, some of the noxious environmental factors that elicit allergic defense responses are likely to be carcinogenic and some studies suggest that allergies are inversely correlated with incidence of several types of cancer⁸⁶.

In conclusion, allergic reactivity may provide an important defense mechanism that protects the host from noxious environmental factors. The very nature of allergic reactions (mucus overproduction, sneezing, itching, etc.) suggests that they are engaged to reduce exposure and promote expulsion of unwanted environmental substances. Furthermore, the extraordinary sensitivity of IgE-based recognition of allergens may have evolved to induce anticipatory response to noxious substances and to ensure avoidance of unfavorable environments.

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Figure 1. Diverse stimuli activate allergic host defenses

Four main classes of stimuli activate the allergic host defense response: helminthes, noxious xenobiotics (e.g., urushiol from poison ivy), venoms (e.g., venom from the honey bee *Apis mellifera*), and irritants (e.g., diesel exhaust particles). A variety of effector modules constitute the allergic host defense response. Keratinocyte and goblet cell hyperplasia (mucus secretion) enhance barrier functions to reduce exposure to noxious environmental allergens and to restrict helminth entry, feeding and growth. Sneezing, coughing, vomiting, diarrhea, and itch serve to remove or expel noxious xenobiotics, irritants, helminthes and ectoparasites. Eosinophils can mediate direct helminth killing, while heparin and proteases from mast cells can inactivate venoms through neutralization and detoxification. Granuloma formation and alternatively activated macrophages can restrict helminth spread, lead to disruption of niches and restrict feeding. Granuloma formation also restricts the damage caused by irritants. Additional allergic defense mechanisms, such as mast cell-induced hypotension and vasodilation, may restrict the spread of noxious xenobiotics and venoms. Fibroblasts and alternatively activated macrophages coordinate tissue protection and tissue repair through epithelial metaplasia, extracellular matrix deposition, and barrier restoration. Various allergic host defenses may also condition future avoidance of sources of noxious xenobiotics, irritants and venoms. For example, cutaneous hypersensitivity responses (e.g., itch and dermatitis) to noxious phytochemicals, such as urushiol, may condition future avoidance of poison ivy. Furthermore, anaphylactic responses to bee venom may condition avoidance of honey bees, and sneezing, coughing, vomiting, diarrhea, tearing and mucus production may condition avoidance of various irritants and other noxious environmental substances.

a

b

Figure 2. Functional modules of type 2 immunity

a) Innate lymphoid cells and Th2 cells secrete the canonical type 2 cytokines IL-4, IL-5, IL-9, and IL-13. The IL-4R⁺-activating cytokines, IL-4 and IL-13, induce epithelial barrier enhancement by promoting goblet cell hyperplasia and mucous secretion at mucosal surfaces, while contributing to epidermal thickening and keratinocyte hyperplasia in the skin. These cytokines also induce alternative activation of macrophages, which play an instrumental role in helminth restriction and tissue repair. IL-5 secretion induces eosinophil recruitment to tissues where they contribute to helminth killing. b) Mast cell secretion of proteases and heparin aids in detoxification, degradation, and clearance of venoms and noxious xenobiotics increasing resistance to these toxins. Mast cells mediate many responses by producing histamine and lipid mediators, such as prostaglandins. Histamine and prostaglandins contribute to activation of endothelial cells, inducing vasodilation and vascular leakage, and smooth muscle cells, inducing bronchoconstriction and various mechanisms that contribute to expulsion (coughing, sneezing, vomiting, diarrhea). Basophils also contribute to antibody-mediated tick resistance. Histamine release from mast cells also can activate C-fibers to induce itch. Notably, crosstalk between these two modules is also common. For example, Th2 cells produce IL-3, which leads to increased basophil and mast cell production, and IL-9, which leads to recruitment of mast cells. Furthermore, basophils can produce Th2-inducing cytokines such as IL-4, and mast cells can produce ILC-activating cytokines, such as IL-33.

Figure 3. Somatosensory pathways in allergic immunity

Noxious substances, including allergens can be detected by somatosensory neurons to elicit protective reflexes, including itch, coughing, sneezing, vomiting and diarrhea. These pathways can also elicit aversive behaviors that help to avoid exposure to the noxious allergens. Somatosensory neurons can sense noxious effects of allergens directly, for example through TRP channels expressed on C-fiber neurons. Afferent neurons of vagus nerve can be activated by serotonin produced by chromaffin cells in mucosal epithelia upon exposure to irritants and other noxious substances. Finally, C-fiber neurons can be activated in response to histamine produced by mast cells upon allergen recognition by IgE. The latter mechanism couples immune recognition of allergens with somatosensory pathways. Allergens recognized by IgE can come in three flavors: they can be intrinsically noxious, they can serve as proxies for noxious allergens, or they can be accidental. Neutral environmental stimuli perceived through olfactory, gustatory and visual systems can be temporally associated with somatosensory pathways resulting in Pavlovian conditioning of neutral cues with antigen specific response to allergens.