**FORUM:** Immunology

# Allergy challenged

**An article suggesting that allergic responses may not be an accident of an off-target immune system, but rather a deliberate defence against potential harm, provokes the question of whether our understanding of allergy needs an overhaul. Immunologists provide their opinions.** SEE PERSPECTIVE P.465

**THE PAPER IN BRIEF**

- Allergic responses replicate the immune reaction to parasites such as worms, and are therefore thought to arise from misdirected immune responses.
- Palm *et al.*[1] (page 465) propose instead that a range of allergic-type immune responses evolved as protection against environmental toxins, such as venom and irritants.
- The authors argue that allergies represent a subset of these responses that have been activated to excess.
- The idea of 'intentional' allergic reactions contradicts long-standing immunological dogma.

## A multitasking defence

DAVID ARTIS & RICK M. MAIZELS

The prevalence of allergic diseases has reached pandemic proportions in industrialized countries. Although our understanding of the pathways that promote allergy is growing, we still lack good answers to two central conundrums. First, why did allergic responses evolve when they are so damaging to the human body? And second, what do such unlikely triggers as pollen, shellfish and snake venom have in common that provokes similar allergic responses? Palm and colleagues[1] suggest that allergic reactions have evolved both as a defence against foreign toxins and to promote hazard-avoidance behaviour in animals. These challenging ideas should provoke new thinking in this critical area of research.

Conventional wisdom holds that allergic responses, which are mobilized by an arm of the immune system referred to as $T_H2$ immunity, are the body's first line of defence against macroparasites such as helminth worms and biting arthropods, and that these stimuli have provided the evolutionary driving force to maintain allergy (Fig. 1). However, a small but consistent body of literature has also highlighted the role of $T_H2$-associated immune cells in neutralizing venom from biting animals[2]. Palm *et al.* have developed this concept to suggest that allergic responses neutralize not only toxins but also other small-molecule chemicals and irritants that damage host tissues. Indeed, tissue damage might be the unifying trigger for allergy to diverse stimuli. In this context, both environmental toxins and helminth-derived products may share the capacity to elicit the positive effects of $T_H2$-associated responses — those of wound-healing and tissue repair.

One argument for the appropriateness of allergy in dealing with a multitude of chemical challenges is the speed of the severe allergic response known as anaphylaxis — if a paralysing venom is introduced, time is of the essence. However, the immune system must also race against the clock when parasites first penetrate the body's surface barriers, to prevent them from spreading through the bloodstream.

It is interesting to consider when and how allergic mechanisms evolved. Notably, mammals developed certain immune characteristics that promote allergic reactions, such as IgE antibodies and some granulocyte cells, whereas birds and reptiles lack this allergic 'machinery'. Furthermore, the triggers of allergy almost exclusively originate from eukaryotic organisms (such as plants, animals and fungi): only 1% of known allergens are derived from bacterial organisms. If allergy had evolved primarily to neutralize broad classes of toxins, one might expect these groups of organisms to elicit allergic responses in equal measure. Thus, although a multitude of stimuli provoke allergic responses, it is hard to abandon the hypothesis that allergy is, at least in part, a misdirected anti-macroparasite response.

These considerations bring us no closer to answering the second, and more perplexing, question: what do the several thousand diverse proteins that are known to be allergenic have in common? Palm and colleagues[1] suggest that this shared feature is their capacity to cause tissue damage. An alternative consideration is that all of the allergen families (such as plant storage proteins and pet dander) are also represented in macroparasites[3], such that our contemporary allergies to harmless proteins may have their roots in recognition of macroparasite-associated molecules. Consistent with this hypothesis, shared protein families can be found in venom, parasite secretions and the saliva of biting arthropods[4].

Collectively, these findings support a scenario in which the evolutionary pressure to maintain allergic mechanisms is their capacity to forestall tissue damage from either biological or chemical agents. Palm and colleagues have clearly advanced our thinking in this shadowy area of immunology, and their ideas should provoke studies to delineate how diverse stimuli, through common or distinct mechanisms, promote allergic responses.

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**Figure 1 | The serpent or the worm?** Historians have debated whether the Rod of Asclepius, a commonly used symbol of medicine, represents a venomous snake coiled around the Greek god of healing's staff, or the ancient tradition of using a stick to wind long parasitic guinea worms (*Dracunculus medinensis*) out of infected people's bodies. In a related debate, Palm *et al.*[1] propose that the immune pathways that now manifest themselves in allergy evolved not only to protect the host against parasites such as worms, as has long been thought, but also to combat a broad range of toxins, including venom.

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# The price we pay

FRED D. FINKELMAN

Palm and colleagues[1] propose that allergic responses are important for host defence against noxious environmental substances and that they evolved to promote avoidance of suboptimal environments. They suggest that the sensitivity and rapidity of the allergic response, together with the great diversity of known allergens, argue against the possibility that host protection against worm and insect macroparasites can fully explain the evolution of allergy. However, I believe that protection against macroparasites can explain all the characteristics of allergic responses, including those[2] that protect against toxins.

Allergic responses involve components of both the innate immune system, which generates inflammatory responses against certain classes of pathogen, and the adaptive immune system, which targets specific pathogens following infection. Immunologically naive animals already have the allergy-associated cells of the innate system, which include eosinophils, mast cells and basophils. By contrast, exposure to an allergen or pathogen is required to activate the adaptive allergic response, which includes the production of antibodies of the IgE class and cytokine proteins that enhance antiparasite activity[2]. Host protection against toxins and other inanimate stressors, however, is accomplished by innate immunity only[5]. In fact, IgE antibodies to these molecules increase the risk of inducing deleterious allergy[6]. If adaptive allergic-type responses had evolved to clear toxins also, advantageous involvement of IgE antibodies in these responses would be expected.

Contrary to the argument presented by Palm and colleagues[1], the great sensitivity and rapidity of the allergic response can promote host protection against multicellular parasites, particularly during a repeat infection with a specific parasite. For example, an animal that has previously been infested with a tick may generate tick-specific IgE antibodies that can trigger an allergic response if it is again infected by a tick of the same species. This response includes rapid activation of mast cells and basophils, which secrete products that cause swelling and fluid accumulation under the skin, making it difficult for the tick to invade[7]. Additionally, IgE-dependent rapid expulsion of some worms can inhibit parasite migration and accumulation that could severely injure the host's brain, lungs and other essential organs[8].

Although these allergic-type responses can cause 'bystander' damage to the host, they have a net protective effect. The cytokines produced by parasite-activated immune cells not only promote parasite expulsion, but also neutralize parasite toxins and promote healing of affected cells and tissues[9,10]. It is not surprising that some of these same mechanisms can also protect against other chemical hazards, but this does not mean that they evolved to do so.

This leaves the issue of how so many substances of diverse structure and function can act as allergens. The simplest answer is that an IgE response can be induced by any foreign protein that induces inflammation without stimulating production of large amounts of cytokines that suppress allergy, such as IL-12. Worms, insects and potent allergens are particularly good inducers of such inflammatory responses, and indeed often actively suppress IL-12 production.

This evidence that the adaptive immune system is required and uses the same mechanisms to protect against macroparasites and to induce allergy, but is not required to protect against noxious environmental agents, suggests that immunity against macroparasites and allergic disorders co-evolved, without the influence of other toxins. Worm infections in vertebrates, which actually suppress allergic responses, were common during the hundreds of millions of years of evolution and should have provided a selective pressure in favour of the evolution of allergic-type adaptive immunity to macroparasites. Now, however, the low prevalence of worm infections in humans in developed societies is revealing the deleterious potential of these co-evolved allergic responses.

Finally, I am aware of no evidence that the non-allergic majority of individuals are less protected against toxins and other inanimate stressors than allergic individuals, as would be expected if adaptive allergic responses protected against such agents. Taken together, these observations suggest that allergy is indeed the price we pay for the evolution of protection against multicellular parasites. ■

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DEVELOPMENTAL BIOLOGY

# Heart under construction

**Developing organs adapt dynamically to meet the changing needs of a growing organism. A study in zebrafish reveals surprising patterns of muscle growth that reshape the heart as it matures.** SEE ARTICLE P.479

DEBORAH YELON

Remodelling a developing organ without halting its functions must be as challenging as renovating a building without evacuating its occupants. How does the simple structure of an embryonic heart change into the complex architecture of the powerful adult organ? It is easy to imagine a simple model in which the heart grows through steady, gradual expansion, with many cells proliferating and contributing equally. However, the reality seems to be more complex, with considerable delegation of labour to small subpopulations of cells. On page 479 of this issue, Gupta and Poss[1] apply a sophisticated technique to track patterns of heart growth in zebrafish, and highlight that even a handful of cells can drive substantial changes in the shape of the organ.

Heart function depends on the specific dimensions of the heart chambers — the ventricles and atria that work in series to pump blood through the circulatory system. During organ development, the chambers must