

Feature

Why did evolution give us allergies?

The questions of why allergies exist and why they are becoming more prevalent continue to puzzle immunologists. Recent research has uncovered a wealth of details and in the process grown an impenetrable hedge of acronyms around the issue, but the answers may be hidden elsewhere, in the ecology and evolution of our interactions with insects, worms and snakes. **Michael Gross** reports.

Peanuts, pollen and penicillin are completely harmless for most of us, yet to a small but growing part of the population these and other materials trigger a severe reaction of our adaptive immune system that can lead to a range of outcomes, from a skin rash through to fatal anaphylaxis. So far, so familiar — but why would a highly sophisticated immune system, which can administer finely balanced responses to a wide range of viral, bacterial and other threats, respond to a harmless substance by trying to kill its host organism? And why have allergies and other autoimmune diseases become much more common in the industrialised parts of the world throughout the last century?

Even though immunologists have unravelled many mechanistic details of the workings of our immune system in the past few decades, these two big why-questions remain fundamentally unanswered. The apparent lack of shared features between different classes of allergens made it impossible to identify a simple mechanistic chain linking trigger and response.

Rays of hope that were much discussed at the recent Cell Symposium *The Multifaceted Roles of Type 2 Immunity* at Bruges, Belgium, often came from areas beyond the inner workings of the immune system. Researchers increasingly ask themselves what kinds of challenges in nature may have produced this remarkable and at times dangerous response. They have studied, in particular, the interfaces of the human organism with the outside world, such as the endothelia of guts and lungs, as well as the skin. And they are looking at other species that may interact with us at these interfaces. Apart from the obvious suspects, like house dust mites and bees, this line of thinking also leads to a few more surprising species, such as parasitic worms and poisonous snakes.

Hygiene hypothesis

A widely discussed but still unproven hypothesis links the rising prevalence of allergies and autoimmune disease in the industrialised world to improvements in hygiene. Our immune system evolved to fight a wide range of foes, and to learn to distinguish between them during childhood. It is plausible to assume that children growing up in virtually sterile settings may end up with an immune system that is less educated and mature than it should be. But what specific processes could go wrong in this scenario and how that might cause allergy remains to be elucidated.

One important threat that is prevalent in developing countries but virtually absent in industrial ones is that of parasitic worms, such as hookworms, which colonise the small intestines. The intensively studied interaction of related helminths, such as *Heligmosomoides polygyrus bakeri*, with the rodents they infect has yielded striking parallels to the cellular and

molecular processes seen in allergy. Responses to chronic helminth infection involve the IgE as well as IgG antibodies, innate lymphoid cells and type 2 helper T cells (Th2 cells), but helminths have many means to hold off the immune system, such as stimulating regulatory T cells. Infection with helminths can thus protect mice against experimental allergies. As Rick Maizels from the University of Edinburgh, UK, reported at the Cell Symposium, transfer of certain regulatory immune cells from infected mice can also convey this protection in the absence of worms (*Mucosal Immunol.* (2014) 7, 1068–1078). Furthermore, Maizels revealed that a recently discovered protein molecule from the worm blocks the pathway that initiates the allergic response.

These findings raise the hope of similar application of parasite responses in the treatment of allergies in human patients without the need to infect them with actual parasites. “Although helminth parasites cause widespread disease, they are also adept at downregulating the host immune system; if we can isolate their anti-allergic effects as single molecules, we can take advantage of the benefits they



Helpful helminths: Parasitic worms have been shown to regulate parts of the host immune system and thereby also to suppress allergic responses. Their disappearance from modern life has been linked to the increasing prevalence of allergies. (Image: Wikimedia Commons/CDC.)



Bug's life: House dust mites are among the most significant airborne allergens. Studies using specific molecular agents from these tiny arthropods are now providing deeper insights into the molecular mechanisms behind common allergies. (Image: Wikimedia Commons/Gilles San Martin.)

can confer without incurring any of the harm," Maizels explained.

Nicola Harris from the EPF Lausanne, Switzerland, told the meeting that the situation is further complicated, as gut bacteria also play a role in this anti-allergic effect of helminths. Intriguingly, the worm-induced alterations of the immune system could be transferred to other animals by faecal transplants that did not contain live worms. Specifically, her team found that short chain fatty acids secreted by commensal bacteria play a crucial role.

Harris concluded that, while the hygiene hypothesis is traditionally seen as an alternative to the view that diet change caused the rise of allergies, the two explanations may be linked through the complex interactions going on in the digestive system between the immune system, commensal bacteria and the parasitic worms that may be more likely to show up with a diet rich in fibre.

Tackling toxins

While the hygiene hypothesis aims to explain why allergies are becoming more prevalent, the toxin hypothesis offers clues to why they evolved in the first place. In a paper published in 1991, Margie Profet suggested that most allergic responses are triggered by materials that sometimes (e.g. peanuts) or always (e.g. bee stings) contain poisonous substances. Accordingly, she proposed that the

characteristic immune response seen in allergies evolved as a defence mechanism against natural toxins.

As Profet came to the field as an outsider with degrees in physics and political philosophy, her theories spurred press attention but little interest from the academic community. Only in 2008 did researchers report that epidemiological data accumulated over decades seem to suggest that allergy sufferers appear to enjoy protection

from certain types of cancer, in line with Profet's theory.

The first experimental confirmation of the toxin hypothesis came in 2013 when two US groups, Stephen Galli's at Stanford University, and Ruslan Medzhitov's at Yale University independently showed that low doses of bee venom, such as those that might induce allergy in humans, can protect mice from a larger dose that would otherwise have been fatal (*Immunity* (2013) 39, 963–975; *ibid.* 976–985).

At the Bruges meeting, Galli discussed further investigations into the toxin response in mice. In experiments aiming to clarify the roles of specific components of the allergic response, including IgE antibodies, mast cells, and basophils, Galli's group studied the effects of Russell's viper snake venom on the immune system of mice. Galli showed that IgE antibodies and the IgE-binding chain of a specific high-affinity receptor are required for mice to develop acquired immunity to this venom, and mentioned preliminary evidence that mast cells, which express this receptor but are also part of the innate immune system in mammals, can contribute to such acquired immunity as well. The most likely explanation is that, upon activation via their receptor by venom-specific IgE antibodies, mast cells secrete proteases which help to degrade the protein agents in the venom.



Fight club: Honey badgers are fierce fighters known to scare off even much bigger predators. Their rich and varied menu includes poisonous snakes, such as the puff adder shown here. It appears that they develop immunity after their first exposure to the venom. A related video can be seen at <https://www.youtube.com/watch?v=z0tycmec1fw> (photo used with permission from Colleen Begg www.honeybadger.com).

As Galli pointed out, snakes have spent around 200 million years co-evolving with their prey and occasional predators — long enough for the more recently arriving mammals to develop defensive mechanisms against their venoms. This has led to remarkable resistance to venoms in certain mammalian species that prey on snakes, such as the honey badger *Mellivora capensis* in Africa and South Asia, which exhibits high resistance to snake and bee venom that, as Galli speculated, may include elements of both innate and adaptive mechanisms.

While these findings have strengthened the toxin hypothesis as an evolutionary explanation for the existence of the whole allergy apparatus, two fundamental questions remain to be answered — namely, why and how nature flicks the switch between a useful protective mode and sensitisation leading to the risk of anaphylaxis and how the latter outcome may be averted.

Airborne allergens

Many of the most widespread allergies are triggered by inhalation of allergens, like pollen or the excretions of house dust mite (*Dermatophagoides pteronyssinus*). In addition, airborne allergens can also trigger asthma, a chronic inflammatory disease of the airways, which has dramatically risen in prevalence in the Western world over the last decades. As this rise has mirrored the decrease of infectious disease, it is often cited in support of the hygiene hypothesis.

A large volume of research into the phenomenon, mainly conducted in mice models and using extracts of house dust mites as an allergen, has shown that the airway epithelia are far more than a passive barrier and play a crucial role both in defence against inhaled substances and in sensitisation to allergens. Moreover, the sensitisation process involves both the adaptive and the innate immune system in complex interactive processes, which Bart Lambrecht and Hamida Hammad from the VIB Ghent, Belgium, reviewed recently (J. Allergy Clin. Immunol. (2014) 134, 499–507).

At the Cell Symposium, Hammad reviewed experiments testing various approaches to protecting mice from asthma and allergies. Farm dust, which contains lipopolysaccharide as an immunologically relevant agent, as

well as certain enterotoxins have been identified as protective environmental influences in the early education of the immune system, but they only work when the genetic disposition is right. There are known mutations that block this protective effect.

As Lambrecht reported at the meeting (which he co-organised), specific studies using purified allergens from house dust mites, classified after the systematic name, *Dermatophagoides pteronyssinus*, as Der-p1, Der-p2, etc, have yielded insights into the mechanisms of sensitisation. (Lambrecht warned that the variability of the widely used house dust mite extracts may be responsible for contradictory and irreproducible results.) Specific populations of dendritic cells and of basophils appear to play well-defined roles in this process. There is hope that a detailed understanding of these mechanisms will help to develop new ways of preventing sensitisation to allergens.

Arthropods like house dust mites, spiders and insects all produce the biopolymer chitin for the rigid parts of their anatomy, so it is no surprise that the defences of mammals include chitinase enzymes. What is surprising and in need of an explanation, however, is the finding that numerous chitinase-like proteins (CLPs), despite having lost the chitinase activity after gene duplication, still appear to play significant roles in adaptive immunity and indeed in allergy.

These proteins are found in abundance during helminth infection and also in allergic inflammatory diseases, such as asthma. Their specific roles have remained elusive, and progress has been slowed down by the fact that the CLP most widely expressed in mice appears to lack a human orthologue and thus failed to attract much attention from medical researchers.

Judith Allen from the University of Edinburgh, UK, reported recent investigations into the activity of mouse CLPs as a group, using a model involving nematode (*Nippostrongylus brasiliensis*) invasion into the lungs. Allen's group found that the proteins triggered a neutrophil response that helped to kill off the parasites, but also contributed to the acute damage to the lungs (Nat. Immunol. (2014) 15, 1116–1127). Both neutrophils and human CLPs play prominent roles in chronic severe asthma, so these



Breathe in: Asthma is increasing in prevalence, and much research effort is being invested into understanding the underlying reasons for its rise. (Image: Wikimedia Commons/Source: <http://www.nhlbi.nih.gov/health/healthtopics/topics/asthma/livingwith.html>.)

findings again link modern disease to mechanisms that evolved for defence against parasites.

Complex challenges

Investigations into how we — and our tireless representatives, the lab mice — interact with our environment at interfaces like skin, lungs and guts, and how we sometimes become allergic to compounds from that environment, have overwhelmingly led to one conclusion: it's complicated.

The phenomena discussed here include both genetic and environmental factors, both innate and adaptive immunity, and a confusing plethora of immune cells and molecules. In our evolution, these responses of the mammalian immune system have been shaped by interactions with organisms from other phyla, ranging from nematodes and arthropods through to poisonous snakes.

Thus, more interdisciplinary work linking immunology to areas like ecology and toxicology may be required to improve our understanding of allergies, and immunologists will have to try to communicate their ideas to colleagues from other departments without the notoriously dense thicket of acronyms that tends to thrive in their publications. Better communication and joined-up thinking may lead us to understand what evolution was thinking when it gave us allergic responses, and from there we could go on to stop them from happening.

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