Out of Africa: What is an allergen?

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A macroscopic view of the portal vein of an experimental mouse host. The blood vessel contains a coiled Schistosoma mansoni worm pair. Credit: Wellcome Library, London.

Some fundamental questions in allergy remain unanswered. Among them are ‘What exactly is an allergen?’ and ‘Why is the immune response so similar to that against parasitic worms?’ Researchers are examining the problems through an evolutionary lens.

Film lovers will be familiar with Hitchcock's 'MacGuffin' - the term he used to describe 'the thing that everybody's chasing'. Science, too, can lay claim to some arresting terminology. The word for allergy research, for example: allergology - a tongue-twister hazily redolent of fable and myth.

The MacGuffin for allergologists is the definitive answer to a deceptively simple question: why do some proteins cause allergy and not

others?

What precise property of an intrinsically harmless protein induces our immune system to overreact to it, triggering an allergic response? And why do these allergy-causing proteins (allergens) seem to come from such bewilderingly diverse sources, such as a birch tree, a lobster, a deep pile carpet, a dose of penicillin, a pet dog or a pair of latex gloves?

Part of the answer lies in the immune system itself. Its ingenious armoury includes five different classes of antibodies, known as immunoglobulin A, D, E, G and M (IgA, IgD, IgE, IgG and IgM). These Y-shaped proteins bind to noxious foreign proteins (antigens) - such as bacteria, viruses, toxins or parasites - and signal to other elements of the immune system to destroy them.

Only one of these five classes of antibody - IgE - instigates the hypersensitive, allergic reaction to foreign proteins that are otherwise benign. Again, it does so by binding to the protein, inducing cells in the blood stream and tissues to release histamine and other toxins to disable it. The release of these chemicals creates the symptoms of allergy.

Because the binding of IgE to the allergen is so integral to the allergic response, much of allergology has focused on that interaction. Of particular interest in recent years has been the structure of the receptor (epitope) on the surface of the allergen that binds the IgE. What is it about that structure that the IgE recognises and binds to?

In pursuit of that MacGuffin, allergologists have constructed the allergome (another resonant word for biology). The allergome is a vast, constantly updated league table or database of the 1000 or so proteins researchers have identified as allergens. These have been sorted into around 100 structurally related families and their features described in detail.

The sorting into families yielded a surprising result: less than one per cent of these 100 or so structural families are actually clinical allergens capable of causing severe disease. So although their sources appear to be startlingly eclectic, in reality allergens belong to a very few restricted groups of proteins.

These include the prolamin super family (found in plant sap and mould, accounting for latex and penicillin allergies); profilins (pollen and nuts); tropomyosins (muscle proteins in shellfish and tiny insects like dust mites); and lipocalins (in cat and dog dander).

Why these restricted groups are the only proteins that produce an allergic response is one of the biggest conundrums facing allergology.

Out of Africa

For some years, researchers in a completely different field - parasitic worm infections - have believed they may have part of the answer.

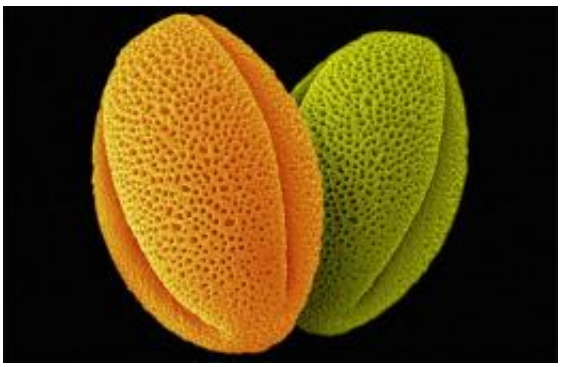
Professor David Dunne at the University of Cambridge has spent the past 25 years travelling between Africa and Cambridge, studying the trematode worm (Schistosoma mansoni), and other neglected parasitic diseases, working closely with African scientists in Kenya, Uganda and Malawi. In the course of that work, he came across IgE in a radically different context to that of allergy.

"Around 20 years ago we and other researchers observed that adults gradually became relatively immune to schistosomiasis reinfection after treatment, whereas children are still very susceptible. And this correlated with the increasing levels of IgE against certain worm proteins in the adults. That led us to believe that IgE is a late evolutionary adaption by mammals to protect against metazoan parasites - worms and insects. It instigates a particularly vigorous and dangerous attack on these

multicellular parasites," he says.

His colleague Professor Rick Maizels at Edinburgh believes that today IgE may be protecting us against many parasites that we never become aware of. "There are many other organisms out there that can't infect humans very well, maybe because IgE is eliminating them before they can take hold."

Since allergy is the only other disease known to be mediated by IgE, it seemed reasonable to assume the two were somehow connected. But how - and why - remained elusive. "There was clearly some common denominator. But exactly what that was has eluded everybody, because there's no obvious link between a worm and a tree pollen," says Professor Maizels.



Two grains of pollen from a peony. Credit: Annie Cavanagh, Wellcome Images.

Advances in structural biology have supported the possibility of a link between worm infection and allergy. Professor Dunne, Professor Maizels and colleagues have spent the last two decades isolating and characterizing target proteins of IgE in a range of different parasitic worms. It became increasingly clear that these worm proteins were

structurally similar to the clinically significant allergens in the allergome.

So it’s not just the IgE-mediated immune mechanisms of allergy and the defence against parasitic worms that are closely related; so are the worm and allergen proteins that induce them.

The bigger picture

To explain this striking coincidence, Professor Dunne believes we need to look at the bigger picture. "Rather than starting with the observation that IgE causes disease and trying to understand its mechanism from that basis - what is it about these structures that make them induce an IgE response - we need to ask a more fundamental question: why do we have IgE in the first place? What is it for?"

He believes we'll only be able to answer that question by stepping back and looking look at the evolutionary relationships between all of us - humans, plants, animals, parasites - in their original contexts, outside the western situation of a modern disease.

"Everything's related to everything else in the biosphere. We're all made out of the same things." As species diversify, they make their own versions of different proteins but continue to retain many of the same proteins they had originally. The amount of proteins species share will depend on their evolutionary closeness. Because worms, like humans, are metazoans (multi-cellular organisms), we have more proteins in common with worms than we do with single-celled organisms such as bacteria.

That poses a challenge for our immune system, which has to distinguish self from non-self and only attack proteins that are sufficiently different from our own versions. If it targeted proteins that were too closely related to us, it might start to mistake our own healthy body proteins for those of a parasitic worm, leading to autoimmune diseases such as

multiple sclerosis, type 1 diabetes and Crohn's disease.

From this perspective it seems that human IgE has evolved as a specialized arm of the immune system: one that is able to recognise a few restricted proteins in parasite worms that differ enough from our own to make the aggressive IgE response against them safe. This may explain why bacteria and viruses - whose proteins differ more radically from our own - are dealt with by the other four groups of antibodies.

By-product

It may also explain the existence of allergy - and its curious similarities with parasitic worm infections. Professor Dunne and colleagues believe that some of those few worm proteins recognised by IgE continue to exist in other living things - grains, pollens, moulds and shellfish - that don't themselves do us any harm or warrant an immune response.

"If the immune system was mistakenly taking the shellfish or the pollen protein as being a sign that a worm or parasite was present, that may be why it's making IgE to that particular target," says Professor Maizels. If so, allergy could be explained as an accidental evolutionary by-product of the IgE response to parasites.

If this were the case, every protein or product we are now allergic to should correspond to a molecular structure inside one of these parasites - a hypothesis Professor Dunne and his colleague Dr Colin Fitzsimmons set out in
a 2009 paper.

Thanks to the increasing availability of genomic data and the increasing sophistication of protein structural analysis, the Cambridge and Edinburgh team have now reached the stage where they believe they can test and prove that hypothesis.

With Wellcome Trust funding they plan to demonstrate that the top ten structural protein families in the allergome league table are also targets for naturally occurring IgE in human worm infections.

"At this stage we know that three of those groups are allergens in some parasite or another," adds Professor Maizels. "We've found possible structural matches for another five. And we haven't yet established parallels in worm parasites for the other two groups." They'll be working with the European Bioinformatics Institute at Sanger, harnessing their huge experience of structural analysis of proteins and protein surface features. "We're taking a very reductionist approach. We're saying let's look at the exact molecular structures, and can we one by one find a correspondence between a real-life allergen and something in a parasite."

Neglected diseases

Proving the hypothesis may shed light on the mechanisms by which the host decides that it can safely switch on an IgE response against a few specific parasite antigens, but not against the others. "That would be a new mechanism, as far as I'm aware," says Professor Dunne. "I don't think we could explain that at the moment in terms of what we know about the regulation of immune responses."

Identifying whether a particular allergen is also an IgE target in worms is also likely to be an important new feature to add to the characteristics of each protein in the allergome. This may help scientists make stronger, more reliable predictions about which proteins will cause allergy.

Crucially, Professor Dunne hopes that the project will bring the fields of allergy and parasitology more closely together - and in doing so help to elucidate some of the conundrums of immunology and basic biology. That's his own personal MacGuffin, and he's passionate about it.

"Here we are spending all this money in western science, looking at modern diseases like autoimmune diseases and allergy. But their basis, and the understanding of them, lies in the countries where you still have the natural relationships between host populations, parasites and infectious diseases.

"We need to look at these chronic neglected diseases, not just because they're incredibly important diseases and millions of people have got them, but also because if we don't look at all the evolutionary relationships in natural populations, we're missing a huge amount of biology. And then not properly understanding the diseases, which are next to come along, like allergy and diseases of modern day living."

More information: Fitzsimmons CM and Dunne DW. Survival of the fittest: allergology or parasitology? *Trends Parasitol* 2011:25(10);447-51.

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