

Suppression of T_H2 -type allergic reactions by helminth infection

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Abstract | There is no immunological mechanism to adequately explain the sudden epidemic in allergies noted in the last 30 years in developed countries. The reduction in the development of allergic disorders observed in individuals infected with parasitic helminths, however, supports a possible role for worms in suppressing allergies. Helminths regulate the immunity of the host to ensure a mutually beneficial environment for the survival of both the parasite and the host. This interplay between helminths and allergic responses raises fundamental questions in immunobiology. Harnessing current mechanistic studies for translational research into helminth infections and atopy might have potential for the identification of novel biomarkers, and even therapeutics, in allergic diseases.

Allergen

An antigenic substance that can induce an allergic response.

Atopic disorders comprise a range of allergic diseases including asthma, anaphylaxis, allergic rhinitis and atopic dermatitis. Atopy is the result of systemic inflammatory reactions triggered by aberrant T helper 2 (T_H2)-type cytokine responses to allergens. The stereotypical T_H2 atopic response involves an elevation in the T_H2 -type cytokines interleukin-4 (IL-4), IL-5, IL-9 and IL-13, with increased amounts of allergen-specific and total IgE and eosinophilia. In the past three decades, both the frequency and severity of atopic disorders have been steadily increasing, particularly in developing countries where approximately 15–30% of the population is affected¹. Within this allergy epidemic, asthma prevalence, for example, has increased by about 1% a year since 1980 (REF. 2), with between 200 and 300 million people around the world currently suffering from asthma. Recently, there have been some reports stating that the increase in asthma is stabilizing, although why this might have occurred is not obvious².

One theory to explain the increase in T_H2 -associated allergic diseases is the hygiene hypothesis³. This hypothesis encompasses a dynamic list of causative agents that might account for the dramatic rise in allergies in recent years in industrialized societies. Factors that have been implicated include improved public health, the use of antibiotics or vaccines and the subsequent reduction in childhood infections, the exposure to endotoxins, domestic-animal ownership, farm habitation and alterations in gut flora^{4–7}. Exposure of the innate immune system to such factors, especially *in utero* or during early life, can alter adaptive immune responses to predispose the individual

to develop allergies, however, an underlying universal immunological mechanism is not known⁸.

It is important to emphasize that, independent of the reduction in infectious diseases in industrialized countries, other lifestyle changes in such societies might explain the increase in allergies; this is illustrated by the potential link between obesity and asthma⁹. That a change in environmental conditions might also explain the recent increase in allergies in humans is shown by alterations in the prevalence of asthma in Tokelauan children. Following a hurricane in 1966, approximately half the population of the Tokelau atolls in the South Pacific Ocean were resettled in New Zealand, resulting in a transition from a traditional island lifestyle to that of a modern urban society¹⁰. A particular feature of the difference in such urban versus rural lifestyles is the microbes present in the environment and the levels of exposure of individuals to these microbes¹¹. By the 1980s, atopy and symptoms of asthma were two to three-fold greater in Tokelauan children living in New Zealand than those children still living on Tokelau¹². Potential reasons for the reduced allergies in the environment in Tokelau include the exceptionally low aero-allergen levels and higher endotoxin levels in the houses in Tokelau compared with houses in New Zealand¹².

A study from genetically similar individuals living in East Germany compared with West Germany indicates that environmental factors, rather than solely hereditary factors, influence differences in the levels of atopic diseases and the balance of T_H1 and T_H2 responses¹³. Moreover, the speed of the recent increase in the prevalence of atopy is illustrated by a study of a population in

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Greenland, where the levels of atopy in adults increased by 90% between 1987 and 1998 (REF. 14).

Independent of environmental factors, there is also clear evidence for the genetic influence in the susceptibility of humans to the development of allergies. An analysis of genetic linkage and association studies carried out has so far identified at least 25 candidate genes that have been linked to an asthma or atopy phenotype in six or more published studies, with another 54 genes also showing some evidence of a disease association¹⁵. The complexity of this genetic predisposition is evident by the disparate immunological functions of the various genes associated with allergies, such as the genes

encoding the T_H2 cytokines, which are involved in the induction of allergic asthma, and the pro-inflammatory cytokine tumour-necrosis factor (TNF), which is associated with the pathogenesis of asthma. The impact of environmental factors, such as exposure to helminths or common allergens, however, will also result in a manipulation of gene expression and might collectively influence the development of allergic phenotypes (FIG. 1).

Initial epidemiological studies of the allergy epidemic have proposed that early childhood infections might reduce the risk of developing atopic disorders by deviating the immune response from a T_H2 response to an anti-allergic T_H1 phenotypic response (elevated interferon- γ (IFN γ) and IL-12 production and suppression of T_H2 responses)¹⁶. More recently, in view of the increases in T_H1 -mediated autoimmune diseases that have occurred at the same time as the rise in T_H2 allergic conditions in developed countries, the hygiene hypothesis has been revised to reflect a general deviation in the regulation of both T_H1 and T_H2 responses⁴. The modulation of the immune response observed during parasitic helminth infections is a notable exception to this pathogen-induced T_H2 - T_H1 cytokine-shift paradigm. In this case, individuals with parasitic worm infections characteristically have T_H2 -polarized responses, similar to atopic individuals, but they might also have reduced allergic responses. Therefore, it is possible that the increase in unchecked allergic diseases in the developed world is due to a reduction in infections with microbes or parasites that, if present, might stimulate regulatory cells and cytokines to suppress detrimental allergic T_H2 or autoimmune T_H1 responses^{4,17–19}.

Characteristically, parasitic helminths can infect humans for years or decades. To achieve such chronic infections, the host's immune system is tolerized to the presence of the parasite through the stimulation of selective immune suppression. Some examples of selective mechanisms that helminths use to modulate immunity are outlined in BOX 1. It is this chronic down-regulation of the immune system during worm infection that evokes a regulatory environment that might impart protection from allergies^{17,20}. As the association between helminths and allergies was first shown in various studies in the 1970s (for example, see REF. 21), it therefore was postulated before the emergence of Strachan's hygiene hypothesis³.

Here, we review some of the fundamental principles involved in the immune association between helminth infections and allergies. A number of mechanistic studies are consolidated to explain how the manipulation of the host's immune response by helminths might suppress allergic responses.

Helminths and allergies

Worms and allergies in humans. In 1947 Stoll put forward the term 'this wormy world' to reflect the high prevalence of helminth infections in the then-global population of 2.2 billion people²². Fifty years later there remained a limited reduction in the overall prevalence of people infected with worms²³; today, approximately one-quarter of the world's population is infected with

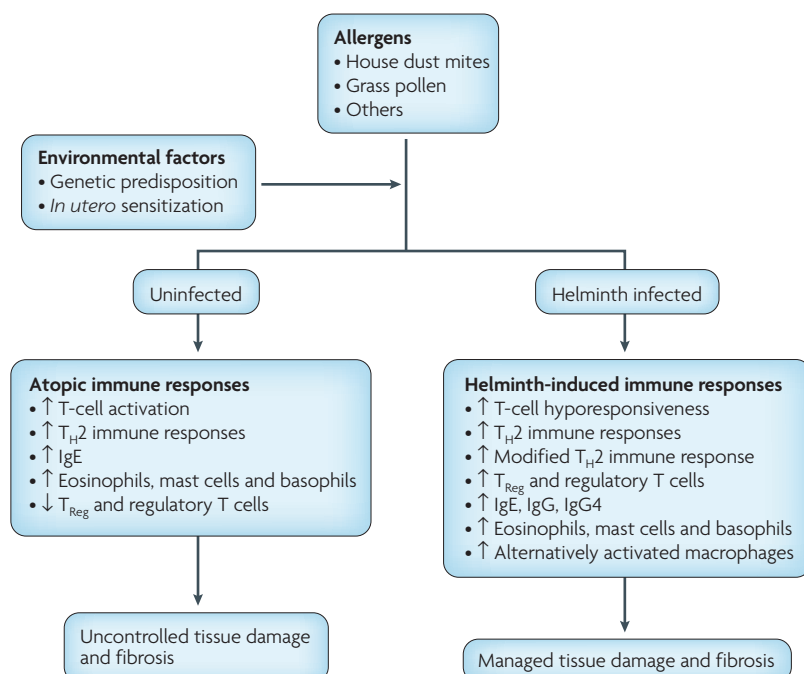


Figure 1 | Influence of helminths on the immune response to allergens. In people not infected with helminths, exposure to common allergens, such as pollen or house dust mites, can induce atopic responses. The immune response will typically be type-2-cytokine-biased, and characterized by a dysregulation in T cells, with increased numbers of activated CD4⁺ T helper 2 (T_H2) cells, fewer T_H1 cells and a crucial reduction in naturally occurring CD4⁺CD25⁺ regulatory T (T_{Reg}) cells and other regulatory T cells, including interleukin-10 (IL-10)-producing cells. The T_H2 cells and other type 2 cells secrete IL-4, IL-5, IL-9 and IL-13. This type-2-cytokine-dominated environment will evoke elevated total and allergen-specific IgE, eosinophilia and increases in mast-cell and basophil numbers, as well as goblet-cell hyperplasia. The resulting allergic inflammation will cause tissue damage and fibrosis that is often localized at the site of allergen challenge; therefore, if the allergic inflammation occurs in the lungs, remodelling of the airways will compromise pulmonary function and lead to asthma. By contrast, infection with helminths evokes a modified type-2 immune response that might not lead to allergic inflammation following exposure to allergens. Features of helminth infection that might suppress allergies are the state of T-cell hyporesponsiveness, including T-cell anergy, increased frequency of T_{Reg} and regulatory T cells and elevated production of IL-10 and transforming growth factor- β (TGF β). These changes in T-cell response, the increase in total and parasite-specific IgG and IgG4 antibody levels, and alterations in the T_H2 -cytokine profile collectively are part of the helminth modified T_H2 response. Although helminth infection will induce cellular inflammation, it is a tightly regulated process with restrained tissue damage and fibrosis. The susceptibility of an individual to developing allergic responses is also controlled by environmental factors, including *in utero* sensitization and genetic predisposition. ↑, increase; ↓, decrease.

Box 1 | Helminth-induced immune modulatory mechanisms

Helminths are potent modulators of immunity, as shown in humans and experimental animal studies⁹³, and have a number of mechanisms at their disposal.

Various helminth parasites have been shown to induce naturally occurring CD4⁺CD25⁺ regulatory T (T_{Reg}) cells and other types of regulatory T cell^{20,93}. In schistosomes, such regulatory T cells control T helper 2 (T_H2) responses and pathology^{94,95}, whereas in nematode infections they might influence helminth survival⁹⁶. The regulatory cytokine interleukin-10 (IL-10) has an important role in preventing immunopathology in the host during schistosome infection^{97,98}, and is produced by T_{Reg} cells and non-T-cell sources⁹⁴, such as B cells^{49,99}, which function in the regulation of pathology during infection¹⁰⁰. Additionally, IL-10-independent functions for forkhead box P3 (FOXP3)⁺ T_{Reg} cells following schistosome infection or egg injection have been described^{101,102}.

Helminths also induce T-cell hyporesponsiveness, which is in part due to modulation of dendritic cells (DCs) and macrophages. Various helminths modulate the activation of DCs^{103–107}; interestingly, schistosomes can do so by involving CD4⁺ invariant natural-killer T cells¹⁰⁸, and a Toll-like-receptor-2-dependent mechanism controls the ability of a glycolipid from schistosomes to modulate human DCs to induce IL-10-producing regulatory T cells⁶³. A schistosome-egg-derived glycan can also induce a macrophage population that can suppress T-cell proliferation¹⁰⁹. Furthermore, schistosome infection modulates macrophages to induce T-cell suppression¹¹⁰.

Mouse studies using filarial parasites have shown helminth induction of alternatively activated macrophages¹¹¹, which suppress CD4⁺ antigen-specific T-cell proliferative responses at the site of infection¹¹². Mechanistically, the induction of alternatively activated macrophages in helminth infections has been proposed to function in repairing tissue damage at the site of infection¹¹³. Consistent with this, alternatively activated macrophage activation is essential for host survival and regulation of pathology during infection with *Schistosoma mansoni*^{114,115}. Furthermore, studies using the helminth *Heligmosomoides polygyrus* showed a role for alternatively activated macrophages in protection of the host from infection¹¹⁶.

various parasitic worms. Nevertheless, in industrialized countries there has been a reduction in the prevalence of helminth infection of humans. With respect to trends in allergies, helminth infections might have been eradicated in developed countries before the increase in allergic responses; it is not known whether the 10–30-year absence of worms in humans living in urbanized environments had an effect on the immune system and altered the demographics of allergies. One approach to determine the relationship between helminth infections and allergies is to study people who are naturally infected with helminths and analyse their allergic disease status and immune responses to parasite-specific antigens or allergens.

Studies of children in various developing countries, such as Venezuela²⁴, Ethiopia²⁵, The Gambia²⁶, Taiwan²⁷ and Ecuador²⁸, who have chronic intestinal helminth infections have been shown to have reduced prevalence of allergic disorders. To test whether the presence of helminths actively suppresses allergic reactions, anthelmintics are given to infected people to remove the worms, and subsequent changes in allergic responses are then monitored. After drug treatment of Venezuelan children who were chronically infected with *Ascaris lumbricoides* and *Trichuris trichiura* there was increased atopic reactivity to mites (from 17% to 68%) within 2 years of treatment²⁹. Similarly, in Israel, a notable increase in skin reactivity to newly acquired allergens and loss of immune suppression was reported following anthelmintic treatment in migrants from Ethiopia with allergic rhinitis³⁰. Chronically infected Gabonese children also

showed increased atopic reactivity to locally relevant airborne allergens during a 30-month follow-up study after anthelmintic treatment to remove geohelminths³¹.

The role of helminths in ameliorating allergies is not universally accepted, as several studies do not show a protective role. In a study in China, infection with *A. lumbricoides* was associated with increased aero-allergen sensitization, airway inflammation and asthma risk in a cross-sectional study of 2,164 children³². Indeed, previous studies in European populations also showed an association between infection with *Ascaris* spp. and an increased incidence of allergies^{33,34}. Furthermore, a recent in-depth study reported that an intensive 12-month anthelmintic treatment programme in Ecuadorian school children reduced helminthiasis without promoting atopic sensitization and allergic symptoms³⁵. Therefore, protection from allergies in humans is not associated with infection by all species of helminths.

A meta-analysis of published data (up to January 2006) on geohelminth infections and allergies did not show a consensus on a role for nematode infection preventing the development of allergies, although hookworm infection did show some beneficial effects³⁶. This might be due to a lack of consistency between human population cohorts (for example, because of genetic and environmental differences), and variations between species of helminths that are endemic or the intensity of infection; therefore, drawing generalized worldwide epidemiological conclusions is difficult. However, the use of population-association studies complemented with experimental studies in animal models will validate whether an individual parasitic helminth can suppress allergic responses, and also facilitate elucidation of the mechanism involved.

Schistosomes — worms implicated in suppression of allergies. In this Review, we use schistosomes (BOX 2) as one example of a parasitic worm that is implicated in the suppression of the development of allergic responses in both infected humans and mouse models. A relationship between allergies and schistosome infection of humans was formally shown by van den Biggelaar and colleagues³⁷. The authors studied immune responses to allergens in 520 school children (aged 5–14 years) in an area of Gabon where *Schistosoma haematobium*, filarial worms and geohelminths were endemic. Skin-prick test (SPT) responses to house dust mites (important perennial allergens) were reduced by 68% in school children who were infected with *S. haematobium*, and also when they were infected with filarial worms, compared with responses in uninfected children. The reduction in SPT responses in children infected with helminths was independent of a range of confounding factors, including sex, age and socio-economic factors³⁷. In Brazil, a study of people from a *Schistosoma mansoni*-endemic area also showed a significant negative association between the SPT responses and helminth infection³⁸. The first comprehensive study on whether infection with *S. mansoni* influenced asthma was carried out by Carvalho and colleagues³⁹. In comparative studies of age- and sex-matched cohorts of people with asthma

Anthelmintic

A drug that is used to kill parasitic helminths.

Geohelminth

A parasitic helminth in which part of the life cycle involves living in the soil.

Nematode

A phylum of worms with elongated bodies that include free-living species (such as *Caenorhabditis elegans*) and parasitic species.

Filarial worm

A parasitic nematode, the life cycle of which involves an invertebrate intermediate host and a vertebrate primary host.

Trematode

A class of parasitic flatworms that is often referred to as the flukes, and includes schistosome species in the blood.

Granuloma

A localized cell infiltration surrounding, in this context, a schistosome egg trapped in various tissues. The schistosome egg granuloma comprises a type 2 infiltrate that is rich in T_H2 cells, eosinophils and macrophages, which progresses to a fibrotic lesion.

Cercariae

Infective free-swimming larvae of trematodes. Humans are infected when the cercariae penetrate the skin while the individual is in contaminated water.

Airway hyperresponsiveness

A hyperactivity of the airways, initiated by exposure to a defined stimulus that is usually tolerated by normal individuals, that causes bronchoconstriction and inflammatory-cell infiltration in allergic individuals.

from a rural *S. mansoni*-endemic area compared with asthmatics from an urban and non-endemic area, a significantly milder form of asthma was found in infected individuals³⁹. Therefore, in schistosome species a universal mechanism might suppress host allergic responses, as seen in two studies on genetically distinct people on separate continents (Africa and South America) who were infected with two different species of schistosome (*S. haematobium* or *S. mansoni*), and who had reduced SPT responses to allergens^{37,38}.

Worms and allergies in animal models. Animal models of parasitic helminth infections have made important contributions to the understanding of the induction of the allergic T_H2 immune response; for example, in elucidating the induction of specific genes associated with alternatively activated macrophages⁴⁰ or eosinophils and basophils⁴¹, and in investigating the functional role of new cytokines, such as IL-25 (REFS 42,43) or the IL-21 receptor⁴⁴. Therefore, helminths are valuable tools for dissecting the functions of new cytokines and processes in immunology research in the twenty-first century, as worm–host co-evolution occurred over thousands of years of immune deviation. For example, the propensity of a helminth infection to induce T_H2 -biased immunity involves suppression of T_H1 cells, which was attributed in part to the blocking of IL-12. The discovery of newer members of the IL-12 family (IL-23 and IL-27) and also T_H17 cells (IL-17-producing T_H cells) has revised our understanding of T_H1 immune responses^{45,46}, but it is clear that helminths encountered these genes before they were identified by modern immunologists, and will have selected mechanisms to coexist with these cytokines. Indeed, the mechanisms of induction and suppression of T_H2 immune responses by helminth infection overlap and contrast with those of allergic inflammation in response to common allergens (FIG. 1).

Box 2 | Schistosomes in mice and humans

Schistosomes are trematode parasites that infect ~200 million people throughout the world, primarily in developing countries in the tropics. Three main species are responsible for most of the infections in humans: *Schistosoma mansoni* (South America and sub-Saharan Africa), *Schistosoma haematobium* (sub-Saharan Africa) and *Schistosoma japonicum* (east Asia). Schistosomes are well adapted to have a balanced relationship with human hosts, with <10% of infected people developing severe disease. Nevertheless, schistosomiasis is the main parasitic worm infection that affects humans in terms of morbidity and mortality¹¹⁷. The pathology of schistosomiasis is primarily attributed to the CD4⁺ T-cell-dependent and eosinophil-rich granulomatous infiltrates evoked around parasite eggs that become trapped in the tissues in various organs, in particular the liver and intestines. In infection of mice and humans with *S. mansoni* there is a crucial requirement for CD4⁺ T-cell-induced granulomatous inflammation to facilitate the passage of eggs through the intestinal wall so that they can be excreted from the infected host^{118,119}. This process of translocating *S. mansoni* eggs through the intestinal wall has to be tightly regulated — if not adequately controlled, the resulting exacerbated intestinal inflammation and endotoxin leakage can cause sepsis and TNF (tumour-necrosis factor)-mediated death of the host. Regulatory cytokines, in particular interleukin-10 (IL-10), have an important role in managing the balance between T helper type 1 or type 2 cytokine responses that can lead to severe disease^{120,121}. The infection of mice with *S. mansoni* is used as a robust experimental model to elucidate various aspects of the immunopathology of schistosome infection¹²².

To validate studies on humans infected with schistosomes, as described above, the mouse model of infection with *S. mansoni* has been used to delineate suppressive mechanisms (BOX 1). In mice, stages of schistosome infection can be experimentally analysed (FIG. 2a,b). Schistosome eggs are potent inducers of T_H2 immune responses when injected into mice⁴⁷ (FIG. 2c). The T_H2 -inducing capacity of injected eggs is illustrated by the fatal anaphylaxis, following secondary challenge with eggs, of transgenic mice that overexpress IL-13 (REF. 48). Surprisingly, when schistosome eggs are produced naturally *in vivo* (that is, when they are laid during infection (FIG. 2a), rather than being injected (FIG. 2c)), they do not induce anaphylaxis in IL-13-transgenic mice⁴⁹. Infection with *S. mansoni* male cercariae only (FIG. 2b) also rendered mice completely refractory to antibiotic-induced anaphylaxis. The propensity for a helminth to prevent anaphylaxis is not unique to *S. mansoni*, as infection of mice with the gastrointestinal nematode *Heligmosomoides polygyrus* also prevented peanut-allergen-induced anaphylaxis⁵⁰. It is intriguing that although these parasites are located at different sites — schistosomes in the mesenteric circulation and *H. polygyrus* in the intestine — they can both modulate host immunity to prevent acute allergic reactions. The prevention of anaphylaxis by infection with both helminths was IL-10-dependent^{49,50}, which indicates potentially common mechanisms.

Helminth infections might use such regulatory mechanisms to suppress the allergenicity of their own molecules, with this activity potentially acting as a bystander suppressor of other common allergens that are implicated in atopy. However, as mentioned above, not all helminth infections suppress the development of allergic reactions. Indeed, infection with *Trichinella spiralis* causes exacerbated anaphylaxis in mice⁵¹. That different parasitic worms can induce opposing effects in a mouse model illustrates the variation in immune-modulating activity between distinct parasite species. Infection of primates with *Ascaris suum* can increase sensitivity to aero-allergens⁵². This primate study is notable because, as stated above, studies in humans also indicate that *A. lumbricoides* might exacerbate allergic responses^{32–34,36}. In addition to *Ascaris* spp., there are examples of other non-helminth pathogens, such as respiratory syncytial virus infection, that might exacerbate rather than suppress allergic responses⁵³.

Regulation of asthma in mice and humans

Asthma in humans is a chronic inflammation of the airways that is associated with airway hyperresponsiveness and a dysregulation in T_H2 -associated immunity⁵. Much work has also been carried out on defining the importance of the specific regulatory networks, which involve transforming growth factor- β (TGF β), IL-10 and both naturally occurring CD4⁺CD25⁺ regulatory T (T_{reg}) cells and inducible regulatory T cells, including forkhead box P3 (FOXP3)⁺ cells⁵⁴, that might counteract T_H2 responses and thereby protect against asthma⁵⁵. Of all these regulatory networks, IL-10 has a potentially significant role in preventing asthma⁵⁶. This is exemplified

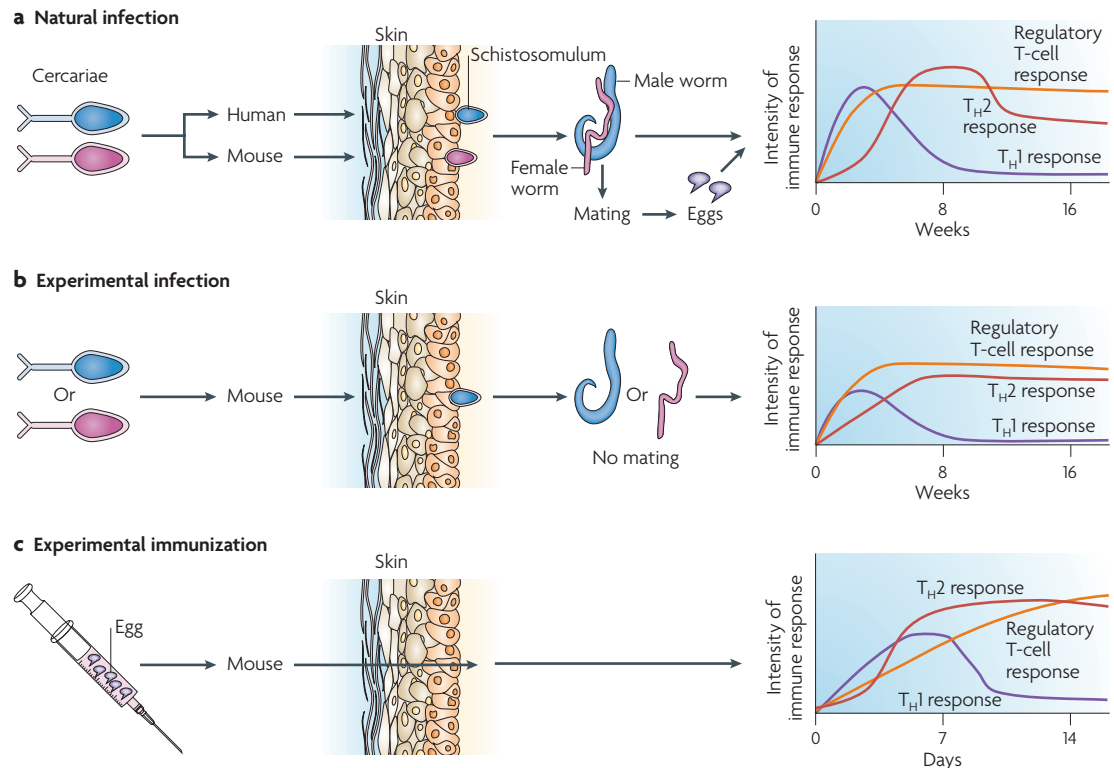


Figure 2 | Kinetics of altered T-cell responses in natural *Schistosoma mansoni* infection of humans or mice and during experimental studies in mice. a | Male and female cercariae penetrate the skin of the host in infection, and adult male and female worms, residing in the mesenteric vasculature, pair to lay eggs after 4–5 weeks. The intensity of the immune response during the course of infection involves an initial T helper 1 (T_H1) response, which is reduced at the same time that a T_H2 response is stimulated by the eggs, and the emergence of a regulatory T-cell environment. After 12–16 weeks a chronic state of immune activation exists with controlled T_H1 and T_H2 responses and a sustained regulatory T-cell response. People can be infected chronically, inducing prolonged immune modulation, as the lifespan of worms in humans is estimated to be 5–10 years. **b** | Experimentally, male or female cercariae can be isolated. Mice can be infected with a single-sex, male- or female-only infection. As no eggs can be produced, in this model the potent T_H2 -inducing properties of the eggs are absent. The mouse will be exposed to worm modulatory mechanisms and develop a worm-induced regulatory environment^{49,68,110}. **c** | Experimental injection of mice with isolated eggs induces an acute and potent T_H2 response within ~7 days⁴⁷, with an initial expansion in T_H1 responses and an emerging regulatory T-cell response. The induction of T_H2 responses by eggs is glycan dependent, and is mediated by a Lewis X-containing oligosaccharide lacto-*N*-fucopentaose III (REF. 123). There might be roles for additional T-cell subsets (such as TGF β (transforming growth factor- β)-producing T_H3 cells, interleukin-17 (IL-17)-producing pro-inflammatory T_H17 cells and IL-25 (also known as IL-17E)-producing effector T cells) in schistosome infection, but these are not yet fully defined.

in allergic individuals with asthma having high levels of IL-4-secreting T_H2 cells, whereas non-allergic individuals have high levels of IL-10-producing regulatory T cells in the bloodstream⁵⁷. Furthermore, studies have shown that the reduction in allergic symptoms in humans after allergen-specific immunotherapy was associated with the emergence of IL-10-producing regulatory T cells^{58,59}. Indeed, the development of methods to selectively induce these IL-10-producing regulatory T cells, such as treatment with vitamin D3, is an active area for the development of new therapies for asthma⁶⁰.

Helminth-infected individuals have elevated levels of IL-10 compared with non-infected controls, which is consistent with a regulatory environment¹⁷. For example, T cells cloned from peripheral-blood mononuclear cells from patients infected with the filarial parasite *Onchocerca volvulus* had cytokine profiles with increased IL-10 and TGF β , which are characteristic of the presence

of regulatory T cells⁶¹. Babu and co-workers also identified that the immune system of patients infected with the parasite *Brugia malayi* showed regulatory-cell networks, including FOXP3⁺CD4⁺ T cells, and also identified distinct roles for cytotoxic T-lymphocyte-associated protein 4 and TGF β that might downregulate both T_H1 and T_H2 pathways during infection⁶². This propensity of helminths to evoke a regulatory environment (BOX 1) might significantly affect the allergy profile of infected individuals. In support of this, the reduction in allergic responses in people infected with schistosomes correlated with an elevated production of IL-10 (REFS 37,39). A potential mechanism for the stimulation of IL-10 secretion by schistosomes in infected individuals was illustrated by the treatment of human dendritic cells (DCs) with schistosome mono-acylated lysophosphatidylserine (lyso-PS), which resulted in the modulation of DCs to prime naive T cells to suppress proliferation

of autologous T cells through the production of IL-10 (REF. 63). Interestingly, DC recognition of lyso-PS is an innate immune response, as it is mediated by Toll-like receptor 2 (REF. 63).

One of the first experimental demonstrations of a role for helminths in the suppression of lung inflammation involved the infection of mice with *Strongyloides stercoralis*⁶⁴, although no mechanism was described. Subsequently, infection with *Nippostrongylus brasiliensis* was also shown to suppress lung inflammation through an IL-10-dependent mechanism⁶⁵. More recently, infection of mice with *H. polygyrus* reduced ovalbumin (OVA)-induced or allergen-induced airway inflammation in part by a T_{Reg}-cell-mediated mechanism, although protection was not exclusively CD4⁺ T-cell-dependent or solely mediated by parasite-induced IL-10 (REF. 66). By contrast, Kitagaki *et al.* reported that *H. polygyrus*-induced protection from lung inflammation involved T_{Reg} cells and IL-10 (REF. 67).

In addition to being refractory to experimental anaphylaxis⁴⁹, schistosome-infected mice are also resistant to OVA-induced airway hyperresponsiveness through an IL-10-dependent but CD4⁺ or CD25⁺ T-cell-independent mechanism⁶⁸. The mechanism whereby schistosomes suppress such allergic responses is independent of TGFβ (REFS 49,68). In schistosome infection, resistance to allergies is B-cell dependent, with these cells being another potential source of IL-10 production^{49,68}. In other systems B cells have been shown to participate in the induction of immune tolerance and the suppression of diseases, which gives rise to the possibility of IL-10-producing B cells⁶⁹. Have helminths in fact evolved mechanisms to manage the growing repertoires of types of regulatory T cell or IL-10-producing B cell, which might potentially influence the balance between the development and suppression of allergic reactions?

The modified anti-allergic T_H2 response

Although asthma covers a range of maladies with compromised pulmonary function, owing to various aetiologies, allergic asthma is caused by an unregulated increase in T_H2 responses to allergens⁵. With respect to the reasons for the development of allergic asthma, one often-discussed factor that might increase allergic sensitization is the effect of domestic-animal ownership and exposure of humans to cat or dog allergens^{70–72}.

Platts-Mills and colleagues have proposed a potential mechanism to explain the reduced levels of asthma in children who are exposed to cat allergens. They have called this the ‘modified T_H2 response’^{72,73}. However, the modification in T_H2 responses is cat-allergen specific, as reactivity to house dust mite exposure shows no such protective effect⁷³. The modified T_H2 response indicates that high exposure to cat allergens induces an IgG antibody response (specifically IgG4) that counteracts allergen-specific IgE antibodies, and thereby promotes tolerance⁷⁴. Therefore, in some people with high-level exposure to cat allergens, a non-allergic IgG4 response is induced, which results in these individuals also having high production of IL-10. So, the modified T_H2 response involves the induction of selective tolerance to environmental allergens (TABLE 1). In further support of a regulatory facet of the modified T_H2 response, studies on the *in vitro* T-cell response to cat-allergen peptides have identified two peptides at the amino terminus of the peptide chains that selectively induce IL-10 (REFS 75,76).

Do helminths also induce a modified T_H2 response in a manner similar to that proposed for cats? Parasitic helminth infections also stimulate IL-10 production, as described above, and in humans can induce elevated amounts of antigen-specific IgG4 (REF. 20), which has a predominant role in blocking IgE-mediated allergic responses to parasite antigens⁷⁷. Therefore, chronic antigen exposure to cats or helminths is associated with a T_H2 modified response that might suppress allergies (TABLE 1).

There are experimental data to support the idea that schistosomes induce such a protective response. *Schistosoma mansoni* worms are refractory to OVA-induced compromised lung function, and inflammation involving pulmonary eosinophil infiltration and mucus hyperplasia is suppressed through a mechanism that we have termed a helminth-modified type 2 pulmonary immune response⁶⁸. The suppression of lung inflammation in schistosome-infected mice after exposure to allergen is characterized by elevated amounts of pulmonary-allergen-specific IL-4 and IL-13, but markedly reduced amounts of IL-5 and elevated amounts of IL-10, in the lungs of the mice. Despite the reduced allergic lung inflammation and modified T_H2 immune responses in the lungs of mice, it is striking that this is

Table 1 | Characteristics of an allergic T_H2 response versus a modified T_H2 response

Immune effectors	T _H 2 allergic response	Modified T _H 2 response	
		Exposure to cats	Helminth infection
T _H 2 cell : regulatory T-cell ratio	T _H 2 cells > regulatory T cells	T _H 2 cells < regulatory T cells	T _H 2 < regulatory T cells
IL-10	+	+++	+++
IL-5	+++	++	+
IL-4	+++	+++	++++
IL-13	+++	+++	++++
IgE	+++	+++	++++
IgG4	+	+++	+++

+ represents an arbitrary scoring system. IL, interleukin; T_H2, T helper 2.

a specifically localized pulmonary effect, with intact or elevated systemic OVA-specific responses (for example, IgE and IgG in sera and IL-4, IL-5 and IL-13 production by spleen cells). Therefore, the helminth-modified type 2 pulmonary immune response involves compartmentalization of immunity, with elevated IL-10 and reduced IL-5 in the lungs, although this is not systemic. An important potential overlap with human asthma is that the suppression of disease in asthmatics infected with *S. mansoni* is also associated with increased production of IL-10 and reciprocal downmodulation of IL-5 (REF. 39).

Why have a modified pulmonary response?

The mechanisms of modulation of immunity by helminths outlined in BOX 1 did not evolve for the sole purpose of suppressing unrelated allergic inflammation, which raises the question: for what reason do schistosomes need to induce a modified pulmonary type 2 immune response? In FIG. 3a a representation of the initial schistosome infection and migration in humans is shown. In reality, humans living in endemic areas are repeatedly exposed to new infections when they come into contact with water containing infective cercariae. If all cercariae successfully infected the host and matured to adult worms, the resulting increasing numbers of worms would eventually kill the host, or crowding effects would reduce the fitness of the worms. As both these scenarios are undesirable to the helminth parasite, it has evolved mechanisms to regulate the number of new infections in the host.

Helminths, including schistosomes, manage their numbers in the host by inducing a state of 'concomitant immunity', whereby the mature worm modulates the host such that new infective larvae are killed without affecting the residing adult worms (FIG. 3b). Concomitant immunity was first shown in a study approximately 40 years ago in which, after the surgical transfer of adult *S. mansoni* worms into uninfected rhesus monkeys, the recipient monkeys tolerated the transplanted adult worms, whereas new infecting larvae were killed⁷⁸. Concomitant immunity is also considered to occur in naturally infected humans⁷⁹. Although concomitant immunity might not be solely immune mediated as it also involves egg-induced tissue pathology⁸⁰, it results in newly invading larvae being trapped after penetrating the skin.

A caveat with concomitant immunity is that the death of new migrating larvae within the host, in particular in the lungs, will evoke inflammation around dead larvae that will lead to a pulmonary pathology that might be detrimental to the host if not regulated. The schistosome-modified type 2 pulmonary immune response might have evolved to potentially suppress the magnitude of pathology induced when new larvae are killed by concomitant immunity (FIG. 3b). As schistosome infection of humans can continue for many years, and there would be a sustained insult to the lungs as new larvae are killed by concomitant immunity, the parasite has evolved mechanisms to limit the magnitude of inflammation and also to repair any consequential damage in the lungs (FIG. 3c). In effect, concomitant immunity to new

larvae would also inadvertently suppress inflammation in the lungs following exposure to allergens, and, furthermore, repair any resulting tissue damage (FIG. 3c). Additionally, the repeated cutaneous exposure to invading larvae might also suppress skin inflammation, such as atopic dermatitis, which has already been shown by the diminished SPT responses to common allergens in people infected with schistosomes^{37,38}. It should be noted that schistosomes have evolved mechanisms to suppress inflammation in the intestines, and to facilitate passage of the egg through the intestinal wall with regulated intestinal inflammation without endotoxaemia (BOX 2) (which will also affect the suppression of intestinal inflammation). The propensity of helminths to evoke alternatively activated macrophages (BOX 1) is relevant in the context of tissue-damage repair in the lung by schistosomes. Helminth induction of DCs that induce T_H2 immune responses (BOX 1) might also be implicated owing to the crucial role of DCs in orchestrating the priming, induction and control of the magnitude of inflammation in the lung⁸¹. Further work is required to determine whether the helminth-modified pulmonary type 2 response has relevance in humans.

Clinical implications

If one accepts the evidence that parasitic helminth infections might suppress the development of allergies, it would indicate that helminths have therapeutic potential. Indeed, infection with helminths might also prevent a range of other diseases¹⁹; this indicates that the mechanism of modulation of immunity by helminths could have broader therapeutic applications. In addition to allergies, the incidence of inflammatory bowel disease (IBD) is also increasing in developed countries⁸². Similar to allergies, the reasons for this increase are complex and multifactorial, but IBD is associated with a breakdown in homeostasis between gut antigens and immunity⁸³. Therefore, one hypothesis to explain the disruption of the balance between the gut and the immune system that might lead to IBD is the reduced presence of parasitic helminth infections in modern societies^{82,84}. In support of this, using mouse models of experimental colitis, it has been shown that infection with a number of helminths can reduce the severity of the disease⁸². Although not fully elucidated, the mechanisms described in FIGS 2,3 could also apply to helminth regulation of inflammation in the colon.

If the helminth-modified type 2 response is the desirable therapeutic mechanism, is the cure for allergies simply to infect allergic people with helminths? Will a worm a day keep asthma at bay? This might seem at first an alarming approach. However, IBD patients have already been deliberately infected with parasitic helminths. The regular administration of larvae of *Trichuris suis*, a whipworm that naturally infects pigs, has been reported to be a safe and effective treatment for IBD^{84,85}. In other studies, infection of IBD patients with the human hookworm *Necator americanus* has also been shown to have therapeutic potential⁸⁶. In addition to its use in IBD, *N. americanus* is being tested in volunteers with asthma or other allergies⁸⁷; the results of these studies might

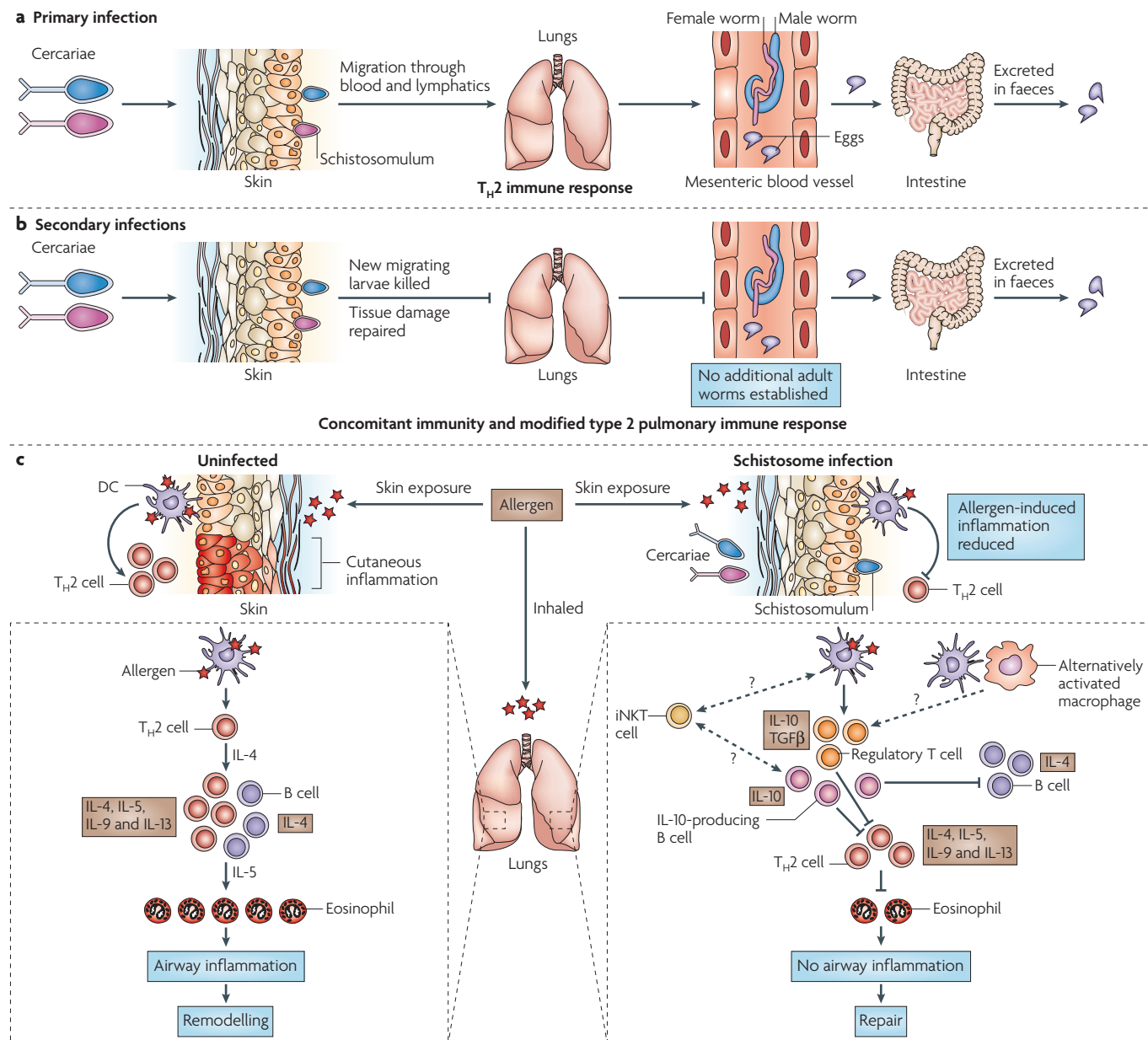


Figure 3 | *Schistosoma mansoni*-infection-induced modulation of the allergic immune response. **a** | The initial primary helminth infection involves infective cercariae penetrating the skin and the developing larvae then migrating through the lungs, by way of the circulation and lymphatics, before maturing in the mesenteric vasculature. The adult worms lay eggs that migrate through the intestinal wall to be excreted in the faeces. The infection induces a regulated T_H2 immune response, with increased levels of interleukin-4 (IL-4), IL-5, IL-9 and IL-13. **b** | On subsequent re-infection, concomitant immunity that is induced by the residing worms kills new migrating larvae, with a modified T_H2 pulmonary response controlling the magnitude of inflammation around dead larvae in host tissue. Any resulting tissue damage is resolved by a worm-induced repair process. **c** | Comparison of allergen-induced responses in individuals with and without schistosome infection. Repeated exposure of the skin to infective cercariae could tolerate the cutaneous environment to suppress the development of allergic skin inflammation by an as-yet-unknown mechanism. Inhaled allergen might induce asthma-like inflammatory responses in the lungs of an uninfected person, which can ultimately result in airway remodelling that compromises lung function. In schistosome-infected individuals, the helminth-modified pulmonary type 2 response (with reduced levels of IL-5, markedly increased IL-10 and possibly transforming growth factor- β (TGF β)) will prevent exacerbated T_H2 -mediated inflammation and also repair any lung tissue damage. The increase in frequency of potential modified regulatory T cells and IL-10-producing B cells that have suppressive activity will counter-regulate the activity of exacerbating T_H2 cells. As helminths induce invariant natural killer T (iNKT) cells, these cells might also have a role in modulating allergic inflammation in the lungs. The effects of helminth modulation on pulmonary dendritic cells (DCs) or alternative activation of macrophages have not yet been confirmed in this model. Additionally, modulation of the intestines (not shown) during schistosome infection (BOX 2) to facilitate excretion of eggs might similarly suppress the development of inflammatory bowel disease^{82,124}.

show that common mechanisms exist whereby an individual helminth influences both allergic and intestinal inflammation in humans.

Rather than infect people directly with pathogens, with the inevitable risk of side effects, a more rational approach to exploit the ability of a pathogen to modulate the immune system as a therapy is to identify the immune-modulating molecules⁸⁸. Such helminth-derived molecules could be used to selectively mimic the desirable regulatory effects of parasitic helminths, without the side-effects of infection, in new therapeutic approaches for immune-mediated diseases. Therefore, are worms the potential 'drug cabinets' that contain molecules for future therapeutics for a range of immune-mediated diseases? There are already examples of helminth molecules with potential anti-inflammatory activity, including ES-62 from *Acanthocheilonema viteae*⁸⁹, schistosome lacto-N-fucopentaose III (REF. 90), schistosome lyso-PS⁶³, an *S. mansoni* chemokine-binding protein⁹¹ and thioredoxin peroxidase from *Fasciola hepatica*⁹². Therefore, the search is now on for the helminth molecules that induce a modified T_H2 response to suppress the development of allergies and asthma.

Concluding remarks

It is significant that infections with certain helminth parasites stimulate regulatory mechanisms that are relatively associated with suppression of allergic responses in humans, and these immune processes are also functional in animal models. It is notable as we look forwards that no universal immunological mechanism has yet been identified in the context of helminth infection and allergy modulation. In the past, the objective of finding an 'ideal' unified mechanism for all helminth modulation of allergies has yielded more conundrums than solutions. This might be the result of attempts to fit mechanisms of helminth immune modulation into existing paradigms in the allergy field. Perhaps a roadmap for the future lies with a lateral approach to generate new paradigms from the perspective of how, and why, the helminths themselves mechanistically suppress allergies.

An immediate objective is the isolation from helminths of specific inducers of regulatory cell(s) and/or cytokines that dampen allergic T_H2 immune responses, or induce repair at the sites of inflammation. A caveat with using these immune-modulating molecules from helminths is that they have evolved to function in a situation in which the helminth infection lasts for years. Therefore, the immune system will be exposed to a trickle of helminth molecules, probably a cocktail of antigens and allergens, that chronically and progressively modulate immunity. Although a helminth molecule might induce a desirable suppressive response on cells *in vitro* or modulate an acute allergic response (lasting days or weeks) in *in vivo* models, it remains to be seen whether a helminth molecule can suppress allergies in reality — that is, in a situation in which allergic disease, like helminth infections, is often a chronic condition. Conversely, if a helminth-modified pulmonary type 2 response is therapeutically stimulated to suppress allergic inflammation, will a side effect be the increased susceptibility to other pathogens or inflammatory diseases? In the context of which individual to treat, although not discussed here, it is important to emphasize that susceptibility to helminth infection and the induction of immune responses in humans has, like atopy, a genetic component.

Apart from the implications of exploiting parasitic helminths or their molecules as future therapies, the analysis of how helminths modulate immune responses will lead to significant advances in the fundamental understanding of the processes involved in immune function in allergy and asthma. It will be important to determine which of these mechanisms of allergy suppression are relevant to atopy in humans.

Exciting times are ahead for investigations into helminth modulation of allergies. Considering the various modulatory mechanisms used by helminths, one interesting question is which of these mechanisms is the best suppressor of allergic responses? The answer, to paraphrase George Orwell's *Animal Farm*, is probably that 'All worms are regulatory, but some worms are more regulatory than others.'

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Competing interests statement

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