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# Regulation of Allergy and Autoimmunity in Helminth Infection

***Mark S. Wilson and Rick M. Maizels****

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*Institute of Cell, Animal and Population Biology, University of Edinburgh, Edinburgh, UK*

Abstract

Abstract starts here...

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*Author to whom all correspondence and reprint requests should be addressed. E-mail: rick.maizels@ed.ac.uk

## Introduction: Helminths

Helminths are long-lived, multicellular parasites, which induce strong and characteristically trammelled immune responses in their hosts. The common features of helminth infections are the slow accumulation of parasite burdens, the prevalence of chronic infection, and the primary role of the immune response in pathology. The parasite-specific immune response is well-described as being overwhelmingly polarized towards the Th2 phenotype *(1–3)*, and there is increasing evidence of a T regulatory component *(4–6)*. Although the forces which generate Th2 and regulatory T cells ($T_{regs}$) have yet to be defined, it is clear that the immunological environment created by helminth infections has a major impact on concurrent responses to third-party antigens, whether from other pathogens, allergens, or autoantigens.

The Th2 response is often quoted as being protective against helminth parasites, but the evidence is only convincing in the case of gastrointenstinal nematodes *(7,8)*. Within the tissues, protection may require a more complex battery of both type-1 and type-2 cell-mediated mechanisms, such as activated macrophages and granulocytes *(9,10)*, with the canonical Th2 response playing an essential role in restraining immunopathology *(11,12)*. The ubiquity of Th2 responses to helminths suggests that an innate recognition system exists to detect these parasites and initiate the type-2 pathway; however, no helminth-specific molecular patterns have yet been identified. Alternatively, it is possible that Th2 responses actually benefit certain helminth parasites, particularly in the tissues, and that some species have evolved the capacity to enhance this arm of the immune response.

In this review, we will not discuss whether Th2 reactions are protective against or actively elicited by helminths, but focus on the broader implications for immune function of the Th2-dominated regulatory environment. Can helminth infection shift the whole foundation of the immune response towards a Th2 or a $T_{reg}$ mode, to establish an altered immunological state? If so, can such an altered state lead to lower susceptibility to allergies, autoimmunity, and other immunopathologies? And finally, what can we learn of the control processes inherent to the immune system from these observations? These questions are discussed in the context of both human studies and experimental animal systems.

## The Hygiene Hypothesis

There is no doubt that allergies and autoimmune diseases are rising rapidly in prevalence in parallel with economic development. Allergic syndromes such as asthma and allergic rhinitis have reached epidemic levels in industrialized countries since the 1960s, a time frame too short to be attributable to any changes in the human gene pool. Allergic symptoms are rising approx 50% every decade *(13)* with up to 1 in 5 million now affected *(14–16)*. It is hard to resist the inference that environmental or nutritional factors are exacerbating the risk of disease *(18)*.

Most notable among potential environmental factors has been the decline in common infectious diseases, highlighted by the inverse relationship between the prevalence of infectious pathogens and that of allergic disease *(19–21)*. This gave rise, almost 15 yr ago, to the "hygiene hypothesis," when Strachan drew attention to the effect of household size on the incidence of allergic rhinitis *(22)*. This hypothesis later developed within an immunological framework, suggesting that a reduced childhood exposure to bacterial and viral infections would impair the development of a Th1 response, thus allowing an exaggerated Th2 response to be mounted against aeroallergens *(21)*.

Although stimulating much new thinking on allergy, this position did not account for the parallel increase in Th1-mediated autoimmune

diseases during a similar time frame *(23,24)* and even within the same individuals *(25,26)*. Moreover, in developed countries, Th2-inducing helminth infections (such as *Ascaris* and the once-ubiquitous pinworm) diminished in prevalence alongside *Mycobacterium tuberculosis* and other Th1-driving pathogens *(27)*. Most importantly, the paradox emerged that allergies are less prevalent in helminth-infected populations, who show strong Th2 responses. Newer studies described later began to imply that ongoing, chronic infections may be as important as early-life experience in determining the mode of an immune response to allergenic substances. In these ways, the hygiene hypothesis has evolved and is often discussed in the context of disordered immunoregulation, rather than a dysfunctional Th1/Th2 balance *(28–32)*.

Whether the hygiene hypothesis is posed in its original (imprinting) or later (regulatory) context, it has provoked a barrage of fascinating epidemiological studies. For example, allergies are found to be less common in rural children compared to urban populations in countries as diverse as Germany *(33,34)* and Ethiopia *(35)*. Within developed countries, allergies are less prevalent in those experiencing group childcare in early months of life *(36,37)*, as well as those who are exposed to the common pinworm *Enterobius vermicularis (30)*. In the tropical setting, lower levels of overt skin allergy are found in schistosome-infected children, despite the strong Th2-stimulation induced by the presence of the helminth *(38)*. Thus, the spotlight is moving more firmly into infection *per se*, rather than the Th1- or Th2-stimulating nature of different microbes, and the questions now center more on the generic response to infection rather than the consequence of any one pathogen.

## Impact of Helminth Infection on Immune Responses

Many chronic infections, both microbial and parasitic, induce forms of immune suppression or downmodulation *(39,40)*. Helminth infections strongly modulate immune responses to parasite antigens, with substantial evidence of T-cell hyporesponsiveness in helminth-infected individuals (reviewed in ref. *[2]*). Immunosuppression is likely to play a major part in parasite strategies for survival in a sensitized host, event acting to benefit the host in minimizing immunopathogenic responses to infection. Is such suppression strictly antigen-specific, or is there a systemic effect, downmodulating the response to bystander antigens or other infectious episodes? Regulation of nonantigen-specific responses has indeed been reported in both protozoal parasite infections *(41)* and, as detailed later, in a number of different helminth parasitisms.

AU: What is "event acting" here?

Earlier studies identified instances in which helminths either alleviate or aggravate the consequences of bystander infections. In 1977, Murray et al. reported on two neighboring Comorron Islands, one of which had high *Ascaris* infections and little cerebral malaria in comparison with the other *(42)*. Remarkably, half of the asymptomatic group infected with *Ascaris* suffered clinical malaria attacks following anthelmintic treatment *(43)*. More recent studies have strengthened this association between gastrointestinal nematode infection and protection from cerebral malaria *(44,45)*. Protection from pathology occurrs without any diminution in parasitaemia, suggesting that effector stages, rather than sensitization events, are most affected.

Parallel evidence stems from the response of infected individuals to antigen challenge during routine vaccination. One example is the ablated response to tetanus toxoid (TT) immunization in *Schistosoma- (46)* and *Onchocerca- (47)* infected patients. In the former case, the interferon-γ (IFN-γ) response to TT was

inversely correlated with infection intensity, although Th2-type responses remained intact. Onchocerciasis patients were likewise depressed in their IFN-γ response to the antigen, but significantly mounted an IL-10 response not seen in uninfected individuals.

The impact of HIV infection on helminth-infected individuals has been a focal interest. In Ethiopian subjects migrating to Israel, HIV plasma viral load correlated with helminth burden, and impaired cellular immune responses to HIV and a Purified Protein Derivative (PPD) of tuberculin *(48)*. As cellular immunity was recovered after anthelmintic treatment, parasite infection, rather than HIV itself, appeared to be responsible for the depressed immune function, which arguably disabled defenses against HIV in the same individuals.

AU: "for control **of...**" **here?**

Experimental studies in rodents abound with examples of profound immune dysfunction in helminth infections. A systemic Th2 bias is often found, as demonstrated with model antigens such as myoglobin in *S. mansoni*-infected mice *(49)*. Functionally, *S. mansoni*-infected mice are impaired in vaccinia virus clearance, with poorer cytotoxic T-lymphocyte (CTL) responses and type-1 cytokine production *(50)*, whereas *Nippostrongylus brasiliensis* infection delays the rejection (averaging 32 d vs 10 d in controls) of allogeneic kidney grafts *(51)*. Similarly, *N. brasiliensis* drives Th2 differentiation of DO11.10 transgenic TCR-bearing, ovalbumin-specific T cells in infected mice *(52)*, and can also provoke tolerant T cells into interleukin-4 (IL-4) responsiveness to Staphylococcal enterotoxin *(53)*. Particularly profound antigen-nonspecific immunosuppression is associated with the murine intestinal nematode *Heligmosomoides polygyrus* (previously known as *Nematospiroides dubius*); for example, it depresses antibody responses to sheep red blood cells compared with uninfected littermates *(54)*.

A key finding has been that nonliving parasite extracts or secreted products can induce similar switches in the immune system *(51,55-58)*. This strongly suggests that active immunomodulators are being produced, either to generate a less damaging Th2 response, or as illustrated by the action of *Ascaris* pseudocoelomic body fluid (ABF), to induce production of IL-10 *(57)*. The elucidation of the molecular nature of these modulators, and the pathways by which they effect their functions, will provide exciting new leads for understanding parasite immunology, perhaps offering new immunomodulators for therapeutic use.

## Do Helminth Infections Modulate Allergies in Humans?

There is now sufficient evidence, both observational and post-therapy, to support an inverse association between chronic helminth infection and overt allergic responsiveness in humans (reviewed in ref. *[29]*). Further, the available data favor an effect mediated by regulation of effector-phase mechanisms, with the proto-allergic IgE response remaining intact in infected patients. Some of the key findings in recent studies are discussed here.

Seminal work by Van den Biggelaar *(38)* compared 520 Gabonese schoolchildren (5-14 yr) for skin-prick test (SPT) responses to standard allergens, in relation to parasitological data for *S. haematobium* and filarial nematode infection. Children with urinary schistosomiasis had a lower prevalence of skin reactivity to house dust mite compared to those free of infection. A critical point is that infected children were strongly sensitized to house dust-mite allergen (judged by specific IgE) but had lower overt skin reactivity. The proposition that helminths downregulate the effector phase is supported by the negative correlation between SPT scores and the parasite-specific IL-10 response in infected children. Following this study group further *(59)*, Van den Biggelaar discovered that older age-groups who had higher levels of schistosome and filarial infec-

tions, as well as increased mite sensitization, were in fact lowest in terms of skin-test reactivity. Again this study suggests an immunomodulatory mechanism, possibly mediated via IL-10, aimed at the effector stages of an allergic reaction.

Selassie and co-workers studied 153 Ethiopians from 17-67 yr of age, measuring specific IgE for *Necator*, *Ascaris*, and Der p 1, as well as parasite loads, total IgE, and bronchial hyperreactivity. They found asthma correlated positively with levels of Der p 1-specific IgE, but inversely to infection with *Ascaris* and/or *Necator (60)*. As with other studies, the presence of Der p 1-specific IgE was not affected by infection status, again implying helminth infection does not alter the generation of atopy but rather its translation into asthma.

Araujo et al. *(61)* studied Brazilian patients with chronic, heavy *S. mansoni* infections as judged by egg excretion (> 200 eggs/gram of feces). Although 24% of uninfected controls were skin-test positive to house dust mite allergen, this figure was below 5% in chronically infected individuals, demonstrating again a strong inverse association between infection and atopy. In this study, however, uninfected individuals mounted a greater allergen-specific IgE response, indicating that both sensitization (allergen-specific IgE production), and reactivity can be compromised in infection.

In Venezuela, Lynch and co-workers reported a higher incidence of allergic reactivity in residents of low helminth-transmission areas than in those exposed to high-transmission intensities. When children were anthelmintic-treated, they showed increased allergen-specific IgE and SPT-manifested skin allergy *(62)*. Thus, not only does infection repress atopy, but removal of helminth infection results in the reappearance or introduction of allergic reactivity. These studies are some of the most influential, examining helminth-allergy interactions and confirming the inverse association between helminth infection and allergy. Thus, it is clear that despite IgE sensitization to aeroallergens, helminth-infected individuals are somehow protected from mast cell degranulation and inflammation.

The majority of other studies support these general conclusions. For example, Nyan *(63)* reported, from a large study (693 adults) in rural and urban areas of Gambia, an inverse association between skin-test reactivity and the presence of intestinal helminth (*Ascaris* or hookworm) infection. They correctly pointed out that this finding would also result if atopic individuals had a higher level of antiparasite immunity. Thus, the comparison of sensitization vs allergic symptoms is needed to discriminate, because if atopy is protective against parasites, sensitization rates would be higher in uninfected individuals. Scrivener's work in rural Ethiopians argues indeed that in high-intensity infections, Der p 1 sensitization rates remain high among nonatopics, again suggesting only effector phases are downmodulated by parasitism *(64)*. These authors propose that higher allergy incidence in urban Ethiopians (measured as wheeze) is owing at least in part to the loss of the protective effect of hookworm infection.

However, not all studies of helminth-allergy interactions have concluded with an inverse association. Lynch and co-workers reported in a separate study that clinical improvement of asthma could be achieved with anthelmintic (albendazole) treatment for a year, compared with untreated controls *(65)*. Thus, there are contexts in which helminth infection can actually exacerbate allergic symptoms. This may be owing to their migratory pathway, many traveling through the pulmonary system, with consequent local inflammation and airway trauma, or indirectly via potentiation of allergic reactivity to allergens. Quite possibly, as suggested previously *(66,67)*, occasional or short-lived infections may be more pro-allergic, whereas frequent or chronic infection may build up sufficiently to generate a suppressive effect.

In summary, the wealth of data from human studies sets out an enticing scenario in which helminth infections keep allergies at bay. However, as with many epidemiologically based systems, experimental models must be tested if we are to distinguish cause from consequence in these two complex immunological responses.

## Experimental Studies of Helminth-Allergy Interactions

Model systems offer great opportunities to dissect the interplay between pathogens and allergic disease. Although the suppressive influence of mycobacteria, for example, has been well-established in animal models of Th2-type allergic lung inflammation *(40,68-72)*, studies on helminth parasites at this level have only recently been initiated. Nevertheless, very recent data now provide experimental evidence for mitigation of allergic outcomes by helminth infections.

Among the first reports, Wang et al. *(73)* infected mice with two doses of the human parasite *Strongyloides stercoralis*, which produces a short-lived tissue infection. Mice sensitized to ovalbumin (OVA) shortly after the second infection showed greatly reduced allergen-specific IgE production. At the effector level, asthma-like responses can be measured in terms of cytokine secretion and leukocyte exodus into the bronchio-alveolar lavage fluid (BALF) following intratracheal challenge with specific allergen. *S. stercoralis*-infected mice showed reduced eotaxin secretion, but no overall change in pulmonary eosinophilia or the local recruitment of other lymphocytes in the BAL fluid. Because *S. stercoralis* introduces an abortive and highly immunogenic infective episode, its effects may be less far-reaching than a long-lived chronic infection; nevertheless, these data show significant inhibition on components of both the sensitization (IgE) and effector (eotaxin) phases.

Bashir et al. *(74)* showed that allergic responses to a food allergen (from peanut) is downmodulated by infection with the gastrointestinal nematode *H. polygyrus*; both allergen-specific IgE and IL-13 were inhibited, but the whole effect was reversed in animals given anti-IL-10. This implicates a suppressive mechanism involving an immunoregulatory pathway. These results indicate ablation of both sensitization and effector mechanisms. As will be discussed later, IL-13 is a crucial initiator of allergic responses in mice including airway mucus production, and IL-10 is pivotal in its inhibitory effects in experimental allergy.

In our own recent studies, yet to be published, we have found that a chronic *H. polygyrus* infection will significantly reduce airway allergic responses in two systems: Der p 1 in C57BL/6 mice, and OVA in BALB/c mice. Measurements of leukocyte infiltration of the BALF show sharp reduction in inflammatory responses in infected animals, particularly marked in the case of eosinophils (Wilson, M.S., Lamb, J.R., and Maizels, R.M., manuscript in preparation). Other markers of allergic outcome, such as goblet-cell numbers, are also reduced in these experiments. Infected animals show similar levels of allergen-specific IgE responses, and indeed suppression of allergy can be effected in animals sensitized to allergen prior to infection. Thus, sensitization need not be diminished for allergic symptoms to be downregulated by parasites. Because the suppression of allergy can be transferred to naïve, uninfected animals by mesenteric lymph node cells from *H. polygyrus*-infected mice, the cellular basis for the protective effect can now be dissected at the experimental level.

One study has gone so far as to demonstrate that helminth products can modulate allergic disease, without the presence of live infection. Inhibition of lung inflammation and hyper-responsiveness was observed following *Ascaris suum* extract implants *(75)*. Suppressed IL-4, IL-5, and Eotaxin in the BALF may help to explain such an inhibitory effect; however, IgE and IgG levels were also significantly decreased in both serum and BALF. Such

experiments promise to quickly elucidate candidate modulators with potential to dampen allergies in vivo.

Importantly, not all experimental helminth infections modulate allergic disease. Under conditions of existing elevated IL-4 and IL-5 and consequent IgE and localized eosinophilia, an incoming wave of helminth larvae migrating through the respiratory system may exacerbate airway hyperresponsiveness *(76,77)*. As with the human situation, a key distinction may lie between acute and chronic helminth infections, and the extent to which the allergic state pre-exists at the time of parasite invasion.

## Control of Autoimmunity in Helminth Infection

### *Autoimmunity in Humans*

Most major autoimmune diseases arise from activation of type 1 immune responses. A prediction from the original hygiene hypothesis is that the rise of Th2 allergic diseases would be mirrored by a complementary reduction in Th1 activity and therefore of the incidence of Th1-associated diseases. However, this is not the case. In fact, autoimmunity, such as type 1 diabetes (IDDM) *(78)*, multiple sclerosis (MS) *(79)*, and celiac disease (CD) *(80)* are increasing in a manner similar to allergic disorders *(23)*. Most significantly, allergy and autoimmunity can coincide in the same individual and indeed children with CD or RA have a higher incidence of asthma *(25, 26)*.

AU: RA = Rhematoid Arthritis?

Allergic and autoimmune diseases can both be considered as immune disorders or dysregulated diseases. A common risk factor—in which environmental factors including the changing force of infections—could be at play. Such views have helped develop the hygiene hypothesis into a more regulatory model (see below). This model is in some ways counter to the prevailing paradigm of autoimmune disease being precipitated by infectious agents, although specific instances of molecular mimicry between host and parasite are well-established *(81-83)*. However, there are also reports of reduced exposure to mycobacteria and measles correlating with a higher incidence of MS *(84)* with day care centers providing suitable environments for "protective" infections *(37)*. Perhaps, as with allergies, acute "hit-and-run" episodes may be pro-inflammatory, whereas chronic infections (even if asymptomatic) are pro-regulatory and antiinflammatory.

### *Animal Studies of Autoimmunity*

Animal models of autoimmune diseases are among the most defined and instructive in medical science: they have led to clear identification of target epitopes, reactive populations, and pathogenic mechanisms. These models are ideal settings in which to study the impact of infection, with a spectrum of possible outcomes, recently depending on infectious agent and disease model used. Several key studies have highlighted the suppression of autoimmune disease in helminth infection systems.

In experimental autoimmune encephalomyelitis (EAE), the subcutaneous (sc) injection of central nervous system (CNS) antigens leads to localized CNS inflammation, demyelination, and progressive paralysis, modeling human MS. The disease is strikingly modified in the presence of helminth infections *(85)*. In the most detailed study thus far, Sewell and co-workers elegantly showed that treatment of mice, either before or after induction of EAE with *S. mansoni* ova, reduces the degree of muscle paralysis and inflammatory cell infiltration into CNS tissue, while switching the cytokine profile from predominant IFN-γ to IL-4 *(86)*.

The principal model for diabetes is the nonobese diabetic (NOD) mouse, which is reported to show lower frequencies of diabetes in "dirty" animal houses *(24)*. Infection of NOD mice with *S. mansoni* reduces incidence of autoimmune disease by approx 50%. This may be attributed to a systemic shift towards Th2 responses, because the same effect can be

achieved by injection of the strongly Th2-inducing schistosome eggs *(87)*, or even non-living parasite extract *(88)*.

Inflammatory bowel disease or colitis, such as human Crohn's disease, is an interesting syndrome that sits at the cusp of autoimmunity and allergy: essentially this is an inflammatory reaction to harmless commensal gut flora, with all the consequences of an autoimmune disease, although in fact the antigenic target is an extraneous organism. In a trinitrobenzesulphonic acid (TNBS) model of Crohn's disease, administration of 10,000 dead *S. mansoni* ova deviated the cytokine response of splenic and mesenteric lymph node cells, with impeded IFN-γ production and enhanced IL-4, while reducing mortality from 68% to 28% *(89)*. In essentially the same model, DNBS-induced colitis, evidenced by macroscopic and microscopic changes to colonic architecture and cell infiltration or loss, was significantly reduced in mice previously infected with the intestinal nematode *Trichinella spiralis (90)*, In this system, modulation of immunopathology coincided with increased polyclonal IL-4 and IL-13, and decreased IFN-γ. It may be significant that in this system, parasite infestation in the gut is relatively short-term, so that protection against pathology may outlive the infection itself.

AU: DNBS or TNBS?

A similar case of exogenously induced autoimmune type pathology is found in mice infected with *Helicobacter* that develop Th-1 mediated gastritis and gastric atrophy. In this model for gastric ulcer and carcinoma formation in humans, mice concurrently infected with the enteric nematode *H. polygyrus* display a protective immune deviation with enhanced type 2 cytokines and lower gastric levels of mRNA for the inflammatory cytokines IFN-γ, TNF-α, and IL-1β *(91)*. Moreover, immune deviation in this model is accompanied by elevation of the immunomodulatory cytokines IL-10 and TGF-β.

Interestingly, uninfected IL-10 knockout (KO) mice spontaneously develop severe colitis owing to failure to suppress bacterial-reactive T cells, with fatal consequences *(92)*. However, it has been reported that such animals can be rescued by infection with the gastrointestinal nematodes *H. polygyrus* or *T. muris*, indicating that parasites can induce an IL-10-independent route to block immunopathology in vivo *(93)*.

Is there a common theme to these protective effects of helminths against auto-immunity? One probable mechanism could be a simple Th2 polarization *(89)*, supported by the finding that *S. mansoni* egg-induced-protection of EAE was dependent on STAT-6 *(86)*. Perhaps, however, the link to IL-10 and TGF-β most evident in the *H. polygyrus* system *(91)* hints at activation of the $T_{reg}$ pathway. It would be instructive to test the impact of such parasites on Th2-associated autoimmune disease models, because exacerbation of autoimmunity would indicate amplification of Th2 polarization, whereas a protective effect would argue for expansion of regulatory mechanisms in a manner possibly analogous to protection against allergy.

As with allergy models, there are few reports of isolated parasite antigens exerting any effect on the regulation of autoimmunity. One such example is a product from the filarial parasite *Dirofilaria immitis*, described as rDiAg *(94)* and a homolog of the nematode polyprotein allergen family *(95)*. Administration of this protein, expressed in bacteria, elicits nonspecific IgE production and, when given to 6–wk-old NOD mice, completely prevented the onset of insulitis and diabetes *(94)*. Further testing of this product in other autoimmunity models, and comparison with control proteins expressed in similar vectors, would confirm the significance of this finding.

## Mechanisms for Crossregulation

Several contending hypotheses are available to explain how infections in general, or helminth infections in particular, could downregulate allergies and autoimmunity. Before discussing specific alternative postu-

lates, one should consider whether a simple homeostatic model *(96)* could account for the observed features of helminth modulation. This supposes that if the immune system has a predetermined capacity for responsiveness, then infection would distract from a proto-allergic (or autoimmune) pathway, restraining it below the threshold of pathology. Mechanistically, this could operate quite simply at the level of competition between two simultaneous responses (one to pathogen, one to allergen) for cytokines, growth factors, or simply suitable niches within lymphoid tissue, of antigen-specific peripheral T-cell populations *(97)*. Future experimental work will need to address this issue.

A second generic model for downregulation in infection arises from the sustained high antigen levels associated with chronic parasitism. With repeated transmission of infective stages and long-lived adult worm populations, humans in endemic areas suffer a scenario of continuous antigen exposure. One outcome may be repeated generation of pro-inflammatory signals, perhaps leading to chronic pathology such as elephantiasis or hepatosplenic schistosomiasis. Conversely, continuous stimulation may create counter-regulatory conditions, such as simple receptor downmodulation on individual cells, or more overt suppression through regulatory T-cell populations. In these ways, the host immune system could reach a compromise to minimize pathological damage at the cost of accepting long-term parasitism. Any such regulatory mechanism must be able to intercede against both antigen-specific and nonspecific inflammatory responses, to explain the anti-allergic and –autoimmune effects described above.

AU: Do you mean Anti-Autoimmune here?

## IgE Hypothesis

One of the most direct models to explain helminth downregulation of allergic responses is that infection results in both parasite antigen-specific IgE, and very high levels of polyclonal IgE. The resulting elevation in total serum IgE would either or both dilute out allergen-specific IgE and saturate the FcεRI receptors on mast cells and basophils *(98)*. For example, nonallergic children in Venezuela with high rates of helminth infection showed the highest levels of polyclonal IgE and relatively low levels of either parasite- or environmental allergen-specific IgE *(62,66)*. Many other studies, however, do not reproduce these findings; for example, in Gabonese schoolchildren, there were no differences in polyclonal IgE levels between atopic and nonatopic Schistosome-infected individuals *(38)*. An important caveat is that the regulation of FcεRI receptor expression, and the absolute number of mast cells, are both influenced by IgE concentration *(99)*, calling into question whether mast cell FcεRI receptors on a systemic level can reach saturation even in individuals producing high levels of IgE. Furthermore, allergic airway hyperreactivity is intact in mice carrying a null mutation of Cε and are thus unable to produce IgE *(100)*. A more general reservation is that regulation via saturation of FcεRI would operate only in allergy and could not explain how, for example, autoimmune reactivities are also downregulated in parasite infection.

## Deactivating Immune Effector Cells

Mast cells are well-recognized as playing a principal role in acute and systemic allergic responses such as atopic asthma, allergic rhinitis, and anaphylaxis *(101,102)*. Helminths clearly do activate these cells, although generally in the context of the intestinal epithelium during acute, high-dose infection regimes. Thus, in *N. brasiliensis* and *T. spiralis* infections, IL-3, IL-4, and IgE synergize to enhance mast-cell hyperplasia and also increase FcεRI expression on mast cells and basophils *(103,104)*, a phenotype associated with parasite expulsion *(105,106)*. In contrast, chronic infections of mice with *H. polygyrus* display a reduced mast-cell accumulation in the intestinal epithelium and lamina propria, and this depression pertains even in animals co-infected with *N. brasiliensis* or *T.*

*spiralis*, which individually stimulate mastocytosis *(103)*. If chronic nematode infections can downregulate mast-cells, this would provide a satisfactory model for amelioration of allergy, but less so for autoimmunity although examples of involvement in the latter arena can be found *(107)*. In vitro mast-cell degranulation, measured by histamine, IL-5, TNF-α, and IL-8, can be significantly inhibited with exogenous IL-10 *(108)*, indicating a possible mechanism controlling allergic and autoimmune inflammation.

The other effector cell with prominence in allergy is the eosinophil *(109)*, strongly associated with asthma in humans. Eosinophil-deficient mice (lacking IL-5) do not develop airway hypersensitivity following standard sensitization protocols *(110)*. Helminths have long been known to elicit peripheral eosinophilia *(111)*, and eosinophils are able to kill migrating larvae of many helminth species, particularly in a non-natural host *(112)*. Indeed, the human filarial nematode *Brugia malayi* induces eosinophil-dependent airway allergy in mice *(113)*. Why then do helminth infections not exacerbate allergies by activating eosinophils in the human population? Perhaps in the natural host, helminths have evolved specific mechanisms to defuse innate immune attack from cells such as the eosinophil, and such deactivation may spill over to minimize allergic outcomes. For example, hookworms secrete metalloproteases, which cleave eotaxin, a key chemokine for eosinophil activation *(114)*. In *S. mansoni* infection, lung-stage schistosomula produce prostaglandin E2, which stimulates IL-6 production from lung epithelial cells, in turn downmodulating eosinophilia and other leukocyte recruitment *(115)*. On a general note, not all eosinophils are pro-inflammatory, and it is possible that, in an environment rich in downmodulating cytokines, these cells will be switched into a counter-inflammatory role.

## Immune Deviation: Th1, Th2, and the "Modified Th2"

The hygiene hypothesis has developed from its original formulation that a dearth of Th1-associated infections led to exaggerated Th-2 immune responses to aeroallergens. Nevertheless, the control of many allergic disorders appears to be tightly linked to the balance between Th1 and Th2 responses. In humans, influential data included the finding that T cells from nonallergic individuals produce type 1 cytokines in response to allergic epitopes *(116)*, whereas murine experiments of note include the inhibition of airway eosinophilia and suppression of local Th2 cytokine production with previous *Chlamydia trachomatis* infection *(117)* and the reduction of airway hyperresponsiveness by the administration of IL-12 alongside allergens *(118)*. However, in other settings, both Th1 and Th2 clones can cause airway inflammation when transferred into recipient animals *(119)*. Thus, as with many other immunological systems, a simple Th1/Th2 divide is too simplistic *(120)*. Indeed, it can be argued that the whole concept of immune deviation (the alleviation of pathology by diversion to/from Th1 or Th2) falls because of the contrasting phenotypes mediating allergy and autoimmunity. It is not easy to posit a mechanism by which Th1/Th2 switching can be stimulated by similar infections to create opposite outcomes in terms of the Th1/Th2 balance.

More recently, Platts-Mills has put forward the concept of a "modified Th2" response based on observations that, in individuals exposed to cat dander but without allergic disposition, IgG4 levels are high, but IgE remains low *(121)*. This "modified" Th-2 response, suggests Platts-Mills, should be regarded as a form of tolerance *(122)*. This is highly reminiscent of the situation in chronic parasite diseases such as Bancroftian *(123)* and Brugian *(124)* filariasis. In these infections, extremely high levels of IgG4 predominate, a curious feature as this

isotype of antibody is poorly cytophilic and is not associated with any effector responses. Moreover, filarial antigen-specific IgG4 has been shown to block IgE reactivity in vitro *(123)*. An understanding of how the "modified Th2" response may arise can be gained from data demonstrating the differential stimulation of IgG4 by IL-10, which reduces ε transcript expression while upregulating IL-4-induced γ4 transcriptions in vitro *(125)*.

This new IL-10-regulated dichotomy between IgE and IgG4 production, would, if replicated in a helminth infection, provide a link between the cellular and humoral mechanisms involved in chronic infection and allergy. Evidence that this may indeed be the case comes from recent studies in Ecuador in which children with IgG4 to Ascaris had a lower frequency of atopy to common test allergens than those who were IgG4-negative *(126)*. Interestingly, in this study high total IgE was independently associated with protection from allergy, emphasizing that multiple mechanisms of mitigating atopy may be at play.

## Cytokine Regulation

Cytokine modulation is involved in all models of cross-regulation, and a very wide range of additional cytokines, chemokines, receptors, and antagonists are intimately involved in the generation and regulation of allergies *(127,128)*. Much of the anti-allergic phenomenon can, however, be explained by shifts in the expression of a few pivotal cytokines such as IL-10, and consequent changes to other cytokines (e.g., IL-5), cytokine receptors, and cell-activation states in general. It is important to note that IL-10 has proved to be essential for host survival of parasite infection, owing to its ability to restrain both Th1 and Th2 overreactions in pathology. Thus, double-knockout mice, in which IL-10 deficiency is coupled to either IL-4 (Th2) or IL-12 (Th1) gene deletions show that excessive type 1 responses in IL-4 and IL-10 double knockouts result in uncontrolled pro-inflammatory reactions, whereas excessive type 2 responses, in IL-10/IL-12 double-knockout animals, result in significant mortality during the chronic stages of infection with hepatic fibrosis and the formation of large eosinophil-rich granulomas *(12,129)*. One may conceive, therefore, that if IL-10 is necessary in infected mice to minimize parasite-induced pathology, that it might at the same time exert a dampening effect on both Th1 and Th2 responses to concurrent challenge with allergens or other antigens.

In the context of allergy, IL-13 is a remarkably important cytokine *(130,131)*. As well as essential functions in Th2 induction *(132)*, fibrogenesis *(133)*, and airway hyperreactivity *(134)*, IL-13 is a necessary component in the development of acute and chronic allergic asthma *(135,136)*. Whereas IL-13 and IL-4 ligate to receptors with an identical subunit (IL-4Rα), IL-13 is uniquely regulated by a soluble receptor analog, IL-13Rα2. This is secreted into the fluid phase, effectively competing with cell-surface IL-13 receptors and acting in a blocking capacity. The importance of IL-13Rα2 in controlling immunopathology is witnessed by severe hepatic fibrosis, which follows schistosome infection in IL-13Rα2-deficient mice, and the fact that pathology can be prevented with exogenous sIL-13Rα2 *(137)*. Because IL-13Rα2 is upregulated by IL-10 as well as by IL-13 itself *(137)*, this elegant feedback mechanism to prevent over-reactions leading to pathology could very well be responsible for the suppression of allergic effector mechanisms associated with the Th2-inducing parasitic helminths.

## An Antiinflammatory Network: IL-10 and Regulatory T Cells?

Several investigators have recently proposed that an immuno-regulatory network develops during chronic helminth infections, downmodulating allergic reactivity *(29)*. The general antiinflammatory character of the immuno-regulatory network may also restore order to autoimmune and other immunopathological dysfunctions where deficient immuno-

regulation is thought to play a role in pathogenesis. There is growing support in the literature for regulatory models of allergy, in which some form of suppressor or regulatory T cell ($T_{reg}$) population is at the center of an antiinflammatory network *(24,28,31,72,138,139)*. These models have been strongly influenced by the emergence of $T_{reg}$ modulation of autoimmunity and immune homeostasis in a range of systems *(140-142)*, with IL-10 and TGF-β as two of the major functional mediators of regulation.

$T_{reg}$ cells have been described with a variety of phenotypes with respect to surface receptor expression, cytokine secretion, and antigen specificity. In one form, they are induced before leaving the thymus, and mature as essential components of the peripheral immune response without which various spontaneous organ-specific autoimmune diseases ensue *(143)*. In other guises, they mediate tolerance to extraneous specificities derived from commensal gut flora as well as food antigens. Most recently, evidence has mounted that infections can induce the peripheral development of cells with the properties similar to those of the thymic emigrant $T_{reg}$ cells *(144-146)*. In all these forms, $T_{reg}$ function is associated with IL-10, TGF-β, and CTLA-4; additional markers such as the surface receptors CD25 (IL-2Rα) and GITR, as well as the transcription factor Foxp3 *(147, 148)* are now available to chart the development and activity of this cell population.

Evidence for $T_{reg}$ cell generation during helminth infection is now emerging. Human studies have consistently shown peripheral T-cell nonresponsiveness to antigens from the infecting parasites, which can be reversed with antibodies to IL-10 and TGF-β *(149-152)*. More recently, in studies of the antigen-specific T-cell hyporesponsiveness *Onchocerca*-infected individuals, high levels of antigen-specific IL-10 production have been linked to suppression of proliferation and the release of TGF-β characteristic of regulatory T-cells *(153)*. It is not necessary to postulate that a filarial parasite, or any other helminth, has specific means of inducing $T_{reg}$ cells, although this is entirely possible. It would be sufficient, for example, if persistent high antigen load contributed to the development of downregulatory mechanisms in the host.

Significantly, there is a parallel case building for $T_{reg}$ cells controlling allergic airway inflammation *(72,118,154-156)*, with particularly strong evidence that T cells transfected with IL-10 or TGF-β to confer regulatory function *(157,158)* can prevent allergic airway inflammation or autoimmune disease models *(159)*. Therefore, the emergence of pathogen-induced T-cell regulation, together with new concepts of allergy control by T cells, provides a feasible model for helminth suppression of allergy, as outlined in the following section.

## The Regulatory Environment Model

A model has been proposed that the increasing level of overt allergy is linked to underdevelopment of general downregulatory controls of the immune system, such as the regulatory T-cell population *(28,29,139)*. This revised hygiene hypothesis postulates that the protective effect observed with chronic helminth infections may be attributed to appropriate development or education of the immune system, arguably under the conditions for which it has optimally evolved. This hypothesis would not exclude the promotion of a regulatory population from sources other than chronic helminth infections, such as viral, bacterial, and fungal pathogens, and also takes into account the parallel increase in autoimmune diseases, as a common consequence of an ill-balanced immune system and deficient regulatory population.

How would a regulatory network be stimulated in infection? One pathway would be via dendritic cells (DCs), which conventionally recognize micro-organisms by toll-like receptor (tlr) interaction with conserved molecular signatures of different classes of infectious organism, thus initiating a vigorous pro-

inflammatory response. In some circumstances, however, the DCs are induced to promote regulatory cell differentiation. In one example, the filamentous haemagglutinin of *Bordetella pertussis* induces IL-10 production by DCs, leading to $T_{reg}$ development *(146)*.

Likewise, among the helminth parasites, lysophosphatidylserine from *S. mansoni*, drives human DCs to evoke regulatory activities from T cells *(5)*. This active induction by a defined pathogen moiety implies that an initial encounter could be sufficient to drive regulatory responses, and that it is not necessary to postulate a chronic infection with high antigen loads. If so, the possibility of therapeutic intervention with signature molecules remains open as a means of alleviating immunopathological responses.

An underlying assumption in this discussion is that live infections modulate the contemporary responses of the infected individual. However, there are instances of regulatory induction by nonliving parasite-derived substances *(71,72)*, and we have still to weigh up the relative importance of imprinting, in which early exposure to pathogens or vaccine immunogens casts a long-term or permanent bias onto future immune responses *(160,161)*. It may be that irrespective of the Th-1/Th-2 polarizing nature of an immunogen, the prompt "education" or stimulus of the immune system in early life, leading to the generation of a strong regulatory population, may protect from subsequent immunopathologies, such as allergy or autoimmune disease.

## Conclusions

One of the striking features of helminth infections is the preponderance of asymptomatic infections; in which either parasite immune suppression or host feedback inhibition regulate the degree of inflammatory immunopathology, which results from infection *(6)*. It is therefore not surprising that helminths can modulate immunopathology, whether in the context of allergic inflammation or autoimmune disease, either directly or indirectly. Perhaps parasites simply take advantage of a suppressive mechanism already in the repertoire of host immune functions. Understanding immuno-regulatory mechanisms, in particular their induction by helminths, may lead to new therapeutic avenues for immune disorders and also bring some clarification to why inflammatory reactions occur in autoimmunity and allergy.

Perhaps one danger of this scenario, in which the regulatory T cell is cast as a beneficial force preventing pathology, is to ignore the other side of the coin: the regulatory environment may hamper essential responses to other antigens, to vaccinations, and to life-threatening pathogens. Among the panoply of infectious agents, there are likely to be many that can induce or direct the generation of a regulatory mechanism, although in the first instance the purpose will be to modulate immune responses directed at itself. As chronic infections establish and (in the example of helminths) accumulate, the suppression may become more generalized. As a consequence, some circumstances could render the host more susceptible to secondary infections, whereas others might prevent disease otherwise generated by immunopathology. Few direct examples can be offered, but Borkow *(48)* argues that helminth-induced hypo-responsiveness reduces resistance to HIV and tuberculosis infection with fatal outcomes. At this stage of our understanding, we can at least begin to identify both beneficial and deleterious consequences of helminth infections, with the prospect of influencing future strategies to control both infection and immunopathology.

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