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Infections and allergy — helminths, hygiene and host immune regulation

Rick M Maizels

There is increasing evidence that helminth infections can protect the host against Th2-mediated allergic pathologies, even though helminths themselves are strong Th2 inducers. In murine model systems, alleviation of allergy is not achieved through immune deviation to Th1, but is linked to expansion of regulatory T cell activity. Parasite infection does not prevent allergen sensitisation, but restricts the Th2 effector phase responsible for inflammation. Suppression of allergic inflammation can be transferred by Treg phenotype cells from an infected, allergen-naïve animal to an uninfected, sensitized recipient. Patent allergy in humans is also known to be modulated by helminth infections, suggesting that a similar regulatory network may be controlling immunopathologic disease in man.

Addresses
Institute of Immunology and Infection Research, University of Edinburgh, West Mains Road, Edinburgh EH9 3JT, UK

Corresponding author: Maizels, Rick M (rick.maizels@ed.ac.uk)

Current Opinion in Immunology 2005, **17**:656–661

This review comes from a themed issue on
Allergy and hypersensitivity
Edited by Rienk Offringa

Available online 30th September 2005

0952-7915/$ – see front matter

DOI 10.1016/j.coi.2005.09.001

Introduction

The unbounded capacity of our immune system to react to exogenous antigen challenge equips us to recognize all manner of pathogenic agents, but also exposes us to the risk of undesirable pathological reactions to innocuous allergens and autoantigens. Responses to antigenic challenges of different types are by no means autonomous, however, and there are now numerous examples of how the presence of a major infection can greatly influence the manner of immune responsiveness to unrelated antigens, or indeed other infections [1]. The proposition that the character and cadence of infections in humans can critically influence the development of allergies and other immunopathologies — known as the 'hygiene hypothesis' — is one that has attracted much critical comment. Nevertheless, it is increasingly accepted that infection history and status is one of the major factors, against a background of profound changes in environmental conditions and significant genetic diversity, likely to determine whether individuals progress to allergic disease [2].

The original 'hygiene hypothesis' centred around the role of Th1-inducing microbial infections in inhibiting Th2-mediated allergies, and this subject has been well reviewed [3]. In this review, I will focus on a different interplay that has excited much recent interest: that of Th2-driving helminth parasites and their ability to suppress Th2-related allergic pathology. As is now becoming apparent from bacterial and viral systems, the interaction between infection and allergy often involves regulatory T cell (Treg) activity [4,5]. With the emergence of Tregs as a major facet of helminth infections [6], it is timely to summarize the evidence for a regulatory 'hygiene hypothesis' as it relates to the immunology of helminths.

Allergies and immunopathology

Allergies are classically considered to be Th2-mediated inflammatory diseases, involving, in the case of allergic asthma, eosinophil infiltration into the airway epithelium, the release of long-lasting inflammatory mediators (such as arachidonic acid metabolites), the elaboration of goblet cells and their production of secretory mucins, and incremental tissue damage and remodelling which causes longer-term compromise of airway function. Therapies based on switching the allergen-specific response towards a Th1 phenotype have met with some success in murine models [7], but less so in humans [8]. In the same mouse model systems, however, an exuberant Th1 response can also initiate airway inflammation [9], arguing that control of allergy may require not simply a rebalancing of the Th1:Th2 scales, but rather the restraint of inflammatory mechanisms, perhaps by a Treg [10,11].

Interestingly, one established clinical treatment for allergy, known as allergen-specific immunotherapy [SIT], enhances the production of IL-10 and TGF-β, two suppressive cytokines derived from $CD4^+CD25^+$ Tregs which suppress the Th2 effector cytokines IL-5 and IL-13 [12]. In independent studies, Tregs from allergic individuals were less effective in suppressing allergen-specific Th2 cytokine production than comparable cells from nonatopic persons [13], whereas seasonal flare-ups in pollen allergies mapped onto diminished suppressive capacity against Th2 cytokines in allergic individuals [14]. From these data, the scenario emerges that, although there might be an underlying propensity to Th2 responses in all individuals, allergies manifest themselves whenever there is a failure to regulate that response.

Allergy and Tregs

Can allergies be blocked by suppressive Treg cells? In some cases, at least, it appears so. For example, Karlsson *et al.* [15•] studied infants allergic to cow's milk, of whom ~60% became milk tolerant after some months of milk-free diet. Tolerant children had higher numbers of $CD25^+$ Tregs with greater suppressive function than those who remained allergic. In a study of adult atopics reactive to pollen or mite allergens, Akdis *et al.* [16••] reported that the frequency of IL-10-producing Treg cells was greatly diminished in comparison to healthy controls. In addition, symptomatic allergy is associated with reduced regulatory function exerted by each Treg cell [17•], indicating that the quantitative balance between the counteractive Treg and Th2 effector cell populations, together with their relative states of activation, can determine whether a 'regulated' or an 'inflammatory' outcome ensues from allergen encounter.

These human studies are complemented by a series of elegant animal experiments, which were the first to establish that $CD4^+$ T cells expressing the regulatory cytokines IL-10 or TGF-β can control allergic inflammation [18], whereas the neutralisation of the Treg-associated ligand CTLA-4 exacerbates disease [19]. Dendritic cells (DCs) from allergen-exposed mice can, under appropriate conditions, foster the differentiation of Tregs capable of suppressing allergy upon adoptive transfer to a sensitized host [10]. The capacity of Treg cells to repress allergy has been further demonstrated using populations stimulated in two microbial systems: a conventional $CD4^+CD25^+$ Treg subset induced by mycobacterial infection [11], and a novel $CD8^+CD25^-$ Foxp3-expressing Treg arising from immunisation in conjunction with heat-killed *Listeria monocytogenes* [20]. It is arguable, however, that in each instance it has been necessary to provide an exogenous stimulus for Treg activation before *in vivo* efficacy can be demonstrated [21].

Immunology of helminths

Helminths are multicellular worm parasites from two distinct invertebrate phyla (nematodes and flatworms), within which parasitic clades have independently evolved over a long evolutionary time. In general, parasites are well tolerated and infection is highly prevalent in natural populations, indicating that helminths have evolved sophisticated molecular methods of immune evasion and suppression [22]. Equally, helminths have exerted a major influence on the evolution of the vertebrate immune system, perhaps resulting in many of the features of the Th2 response as it now exists. Certainly, immunity to many helminth parasites is Th2 dependent, although paradoxically in the prevalent human infections, dominant Th2 responses co-exist with a persistent parasite burden. The failure of Th2 immunity might be a result of a regulatory T cell response that restrains inflammatory and effector components, in parallel to the 'modified Th2 phenotype' described in allergen-densitized patients [23].

There is indeed evidence that the Th2 response in helminth infections is 'modified': for example, heavily-infected patients have extremely high levels of IgG_4 but relatively little IgE, whereas specific T cell proliferative responses are compromised, and there are poor IL-5 responses despite normal IL-4 release. An association with Treg activity is suggested by the strong IL-10 production in response to parasite antigens *in vitro*, as well as by the restoration of *in vitro* proliferation by antibodies to IL-10 and TGF-β. Recently, the isolation of human Treg clones secreting these cytokines has been reported from a patient with onchocerciasis [24].

Do helminths downmodulate bystander pathologies?

It has been widely noted that the incidence of asthma and other allergic disorders has not risen as sharply in environments with high levels of helminth infections as in more developed countries [25]. Moreover, within the populations of helminth-endemic areas, an inverse association between helminthiasis and allergy has been clearly established [26,27]. The most recent studies, on hookworm-infected children in Ethiopia [28] and *Ascaris*-infected pupils in Ecuador [29], confirm the trend that helminth-infected people are less prone to allergy. These negative associations can be explained either by helminth immune suppression or by a common genetic factor that predisposes to both allergy and resistance to infection.

Evidence from human studies

A key development towards understanding this phenomenon was the demonstration that, in Schistosome-infected Gabonese schoolchildren, protection from allergy is associated with production of IL-10 in response to parasite antigens [30]. Subsequently, Araujo [31•] reported that Schistosome-infected subjects also mount higher allergen-specific IL-10 responses, and following anthelmintic chemotherapy, these responses declined. Thus, the presence or absence of the helminth infection upmodulated or downmodulated, respectively, the level of regulatory cytokine produced in response to the antigenically unrelated allergen.

In a similar manner, treatment studies have permitted the comparison of allergic responses before and after anti-parasite chemotherapy. In seminal work, Lynch [32] reported that allergic symptoms recrudesced in patients given anthelminthic chemotherapy. Not all subsequent studies have reached the same conclusions, but study design has varied greatly with respect to statistical power, choice of drugs and immunological assays. More recently, van den Biggelaar *et al.* [33•] have provided a thorough analysis of house dust mite reactivity in >300 Gabonese children treated with a broad-spectrum anthelminthic

combination and followed-up over 30 months. Their report demonstrates a significantly higher acquisition of atopic reactivity in children following treatment than in children given placebo, consistent with the proposal that helminths actively suppress allergies in humans.

Apart from considerations of drug efficacy, study size and target species, it is also important to note that infection intensity could be a major factor in the outcome of epidemiological studies. As infection is believed to reduce overt reactivity without affecting sensitization, the degree of suppression might be quantitatively proportional to the level of infection. Helminths do not multiply in their definitive host, and there is likely to be a threshold level (or duration) of infection below which no suppressive effect is evident. By contrast, low-level or transient infection could, in fact, exacerbate pathology, as has been indicated in several studies (e.g. [34]).

Animal models of infection and allergy

In animal models, confirmation of the link between helminth infection and reduced allergic responses has been provided by key studies. The nematodes *Strongyloides stercoralis* and *Heligmosomoides polygyrus* depress allergic reactions to airway or food allergies, respectively [35,36]. In a recent report on *Nippostrongylus brasiliensis*, inhibition of airway allergy was also seen in mice, as long as more than two weeks had elapsed since infection [37•], echoing the implication from human studies that infection dynamics are critically important to the outcome of bystander responses. In our own, as yet unpublished, studies (MS Wilson *et al.*, unpublished) we have demonstrated that the interaction between one helminth parasite (*H. polygyrus*) and the airway allergic response is mediated by conventional $CD4^+CD25^+Foxp3^+$ Treg cells, which expand following gastrointestinal infection, and can be transferred to uninfected sensitized animals with resultant suppression of airway allergic inflammation in the recipient mice. The generation of Tregs in helminth infection, which has been substantiated in other experimental systems [38,39], offers a mechanistic explanation for how infected hosts exhibit altered responsiveness to allergens and other bystander antigens.

Control of both Th1 and Th2 pathologies

Allergies and autoimmunities are often considered to have opposing aetiologies (Th1 vs Th2), although epidemiological evidence does not show a clear discordance between the two. For example, the incidence of asthma and diabetes have shown parallel increases over the past half-century [40], and in one of the few studies to report on individual incidence, the risk of autoimmune disease is actually higher in allergic patients not lower [41,42], demonstrating that, even in the single individual, there is not necessarily a Th1 vs Th2 bias.

Consistent with the viewpoint that helminth-associated downregulation can act against both Th1 and Th2 hyperreactivity, there are many published examples of attenuated autoimmune pathology in helminth infections, including intestinal colitis, type I diabetes and experimental allergic encephalomyelitis (reviewed by [43,44]. Protection against pathology is dependent on IL-10 in one case [45], but not in another [46•]; thus, the mechanisms involved in the beneficial effect of helminth infection against non-allergic immune disorders might be heterogeneous in nature.

Tregs, dendritic cells and infectious tolerance

From the human and animal model data, which indicate both that Treg cells are activated in helminth infection and that cells of a similar phenotype can actively suppress airway allergic inflammation, we have proposed that a major component of the immunological interaction between infection and allergy is mediated by Tregs [6,43]. Several key unanswered questions are raised by this model, concerning, for example, the antigen specificity of the helminth-stimulated Treg population, and the possible involvement of allergen-specific Tregs? One possibility is that an initial population of parasite-specific cells is able to convert allergen-reactive T cells into a regulatory phenotype; for example, along the TGF-β-dependent pathway, which facilitates the recruitment of house dust-mite-specific Tregs from $CD25^-$ precursors [47]. This, and other forms of infectious tolerance [48], is consistent with a model in which a widening regulatory network develops, encompassing bystander antigenic specificities, such as allergens, in the host harbouring a chronic helminth infection.

An alternative viewpoint is that successful helminth parasites provide a strong activation stimulus for natural, pre-existing Tregs, which are consequently more effective than in the uninfected host; this might explain why, to date, suppression of airway allergy has only been achieved with Treg populations generated through exogenous stimulation.

In both the initial stimulation of Tregs and in any subsequent conversion of naïve peripheral T cells into a regulatory phenotype the influence of DCs is all important [49]. Within the lung, a crucial distinction has been drawn between the pro-allergic myeloid DC population and a tolerogenic plasmacytoid subset [50]. The factors that lead DCs to favour Th2 development in the proto-allergic individual have yet to be defined, and it will be interesting to discover if these share the 'partially-activated' features so far identified in helminth-stimulated Th2-driving DCs, such as IL-6 production in the absence of IL-12p70 [51]. Perhaps more germane to the question of how helminths block established allergic responses, and whether it might be possible for DCs modified by

exposure to infection to alter the outcome of airway allergen challenge in the sensitized host.

Non-Treg mechanisms

One should also consider other mechanisms by which parasite infection could impede the expression of allergic pathology [52]. One simple explanation for cross-suppression between infection and allergy is that the immune system has a limited capacity for responsiveness and, through competition or division of effort, the anti-allergic response is reduced in the presence of infection. This homeostatic model [53] is consistent with the observed quantitative reduction without a qualitative shift in response phenotype. Challenging the homeostatic model is evidence that allergy can be suppressed by the transfer of a small number of Treg phenotype cells into a sensitized animal (e.g. MS Wilson *et al*., unpublished) and data showing that regulatory cytokine responses to allergens change according to infection status (e.g. [31]).

A second physiological explanation, which does not invoke Tregs or shifts in host cell phenotype, is that infections alter the manner in which allergen-reactive cells migrate and localize to sites such as the bronchial mucosa, which is known to be highly dependent on a suite of chemokines, leukotrienes and prostaglandins [54]. For example, gut parasites might interfere with host T cell localisation, or release specific antagonists of these mediators and/or their receptors. Although this model explains the reduction in inflammation observed in infected hosts, it does not account for the ability of purified Treg cells to suppress allergy on adoptive transfer to an uninfected recipient.

Other regulatory cells, apart from the conventional Treg subset, can play a significant role. One recent demonstration of this point is made by Mangan *et al*., who showed that mice infected with *S. mansoni* are protected from systemic penicillin-induced anaphylaxis by B-cell derived IL-10 [55]. This is consistent with several earlier studies on the expansion of counter-inflammatory B cells in schistosome infection and their importance in preventing fatal pathology in chronic infection [56]. Thus, in further exploring the interplay of infection and allergy, the full range of potential host regulatory populations needs to be investigated.

A remarkable link between helminths and allergies is the stimulation of IgE isotype antibodies; although IgE is not necessary for murine asthma-like symptoms [57], IgE-mediated reactions commonly drive both airway and cutaneous allergic pathologies. A long-held hypothesis is that helminth-driven expansion of polyclonal IgE levels saturates mast cell and basophil FcεR sites, preventing uptake of sufficient allergen-specific IgE molecules for cross-linking and degranulation to occur. Mitre and colleagues [58], however, recently quantified the ratio of polyclonal:parasite-specific IgE in filariasis patients, and found that nonspecific IgE did not functionally block histamine release from basophils in any patient.

The evolutionary balance between allergy and infection

Most recently, the overlap between allergy and helminth infection has become apparent in another arena: that of human polymorphisms governing susceptibility to disease. Examples are now emerging of alleles that were originally described as predisposing towards asthma and are now significantly linked to resistance to helminthiasis. Thus, a polymorphism in the 3′ UTR of STAT-6 is linked to differential resistance to *Ascaris* in a Chinese population as well as to asthma in Japan [59•]. Similarly, an IL-13 promoter allele (1055T) first identified as increasing gene transcription and thereby asthma risk has subsequently been shown to confer greater resistance to schistosome infection in Mali [60••]. These findings are not coincidental: indeed, they argue strongly that immune system polymorphisms are maintained in the population to provide finely graded variations in our response to pathogens, in this case helminths, with balancing selection provided by a range of infection intensities or parasite exposure across the population. In the absence of predominant helminth infection (and in the absence of the modest immune suppression which accompanies such infections), alleles carrying the higher levels of Th2 responsiveness now show a new phenotype, that of susceptibility to allergy and immunopathology.

Conclusions

The past two years have seen accelerating activity on the issue of whether helminth infections impact on the allergic status of the host, and new studies have been published regarding model systems, in which it is possible to dissect the interplay between these separate and complex responses. Although mechanistic explanations have yet to be provided in any detail, there is satisfactory evidence that regulatory T cells play at least some part in the crossover from the 'suppressive' helminth-infected environment to the 'reactive' allergic response. This interaction invites further investigation into a range of important issues, such as the antigen specificity of the regulatory population and whether helminths have evolved to selectively stimulate Treg expansion. Future work should result in the discovery of further new immunological insights and the development of a general perspective on how the immune system as a single unit balances and integrates the very different influences of parasite and allergen.

Update

The work referred to in the text as (MW Wilson *et al*., unpublished) is now in press [61].

Acknowledgements

I would like to warmly thank our colleagues Judith Allen, Adam Balic, Constance Finney, Matt Taylor, Mark Wilson and Maria Yazdanbakhsh

for their many constructive discussions and for sharing unpublished data; and the Wellcome Trust for research grant support.

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