Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease

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The immune response to helminth infections has long been known to share key features with the allergic response. In particular, both are typified by enhanced T helper 2 (Th2) responses with high levels of interleukin-4 (IL-4), IL-5 and IL-13, accompanied by eosinophilia and abundant IgE production. Paradoxically, the geographical distribution of helminth parasitism and allergic disease is complementary rather than coincident. Thus, the question arises does the Th2 response to parasites protect or pre-empt the host from developing Th2-linked allergic manifestations? It is suggested that downregulatory immune mechanisms, which dampen the anti-parasite response, might benefit the host by blocking progression to atopic reactions. This is of relevance in explaining how the ‘hygiene hypothesis’ might operate immunologically and in the design of therapeutics.

Until the 20th century, helminth infections were universal among the human population, and even today they are highly prevalent in developing countries. Many more people suffer from schistosomiasis (~250 million) than asthma (~155 million), but the realms of parasitism and allergy intersect in more ways than simple numbers. Both sets of diseases are associated with a polarized Th2 helper 2 (Th2)-type immune response, typified by reactive IgE antibodies (Abs) and cell types (eosinophils and mast cells). However, this response leads to starkly contrasting outcomes in the two contexts. How do these two states of the immune response compare and most importantly, how does parasite infection impact on the probability of allergic disease?

There are two dominant features of all helminth infections: first, they are chronic and long-lasting, affording slowly maturing parasites the time to reach target organs and reproduce; second, they are the most efficient known inducers of the Th2 immune response. Controversy continues as to whether the Th2 response to helminths is protective or acts to dampen potentially damaging inflammatory responses against abundant and well-established tissue parasites. We will not address the issue of whether Th2 responses benefit host or parasite, but will concentrate on another intriguing feature of these infections, namely their relationship to atopy. (For a related view in this area see ‘Why is the prevalence of allergy and autoimmunity increasing?’ by P. Black on pp. 354–355 of this issue.)

Atopy and allergy

Atopy and allergy are generic terms that cover a range of aberrant responses to environmental targets, termed allergens. Atopic individuals can be identified by laboratory assays for serum IgE binding to known allergens, or by injection of allergens into the epidermis in a clinical skin test. Atopy is a state that indicates an increased risk of clinical end-point measurements of allergic diseases, such as asthma, eczema, food allergies and rhinitis.

‘...the anti-inflammatory network during chronic helminth infections might be the key to the lower prevalence of allergic disease in Th2-skewed populations.’

The development of allergic disease can be divided into ‘induction’ and ‘effector’ stages (Fig. 1). The induction phase is characterized by the skewing of T-cell responses towards the Th2 phenotype, with accretion of IgE, mast cells and eosinophils. It might be that the immunological environment of organs prone to allergic disease favors Th2 responses, or that allergens cause a dysregulation or aberrant activation of Th2 cells. The outcome is manifested in the effector phase, in which various components of the Th2 response precipitate active inflammation. The inflammatory process itself can be biphasic. First, mast-cell degranulation releases mediators with both a pharmacological effect on surrounding tissues and chemotactic action, which generates secondary inflammation by recruiting eosinophils, monocytes, neutrophils and additional lymphocytes. These recruited cells, in turn, release large quantities of cytokines, which further disrupt tissue homeostasis. This is vividly demonstrated in the bronchial airways, where the interleukin-13 (IL-13)-stimulated production of mucus by goblet cells and the stimulation of smooth muscle cell contraction by tumor necrosis factor α (TNF-α) can culminate in a full-blown asthmatic attack.

The doubling of the incidence of atopy and allergic diseases in just 20 years is a major concern of the
The mechanisms proposed to characterize the progression from sensitization to airway hyperresponsiveness. This process is divided into (a) ‘induction’ and (b) ‘effector’ phases, which encompass allergen processing, T helper 2 (Th2)-response expansion and mast-cell sensitization, followed by mast-cell degranulation, chemotract, the release of inflammatory mediators and pathophysiological changes in the lung target tissue. Abbreviations: APC, antigen-presenting cell; cAMP, cyclic adenosine monophosphate; IL, interleukin.

Fig. 1. The lower prevalence of allergies in helminth-infected populations

Are there in fact fewer allergies in people with helminth infections? This has been the outcome of many – but not all – studies. Direct measurements of intestinal helminths, such as Ascaris, Trichuris and hookworm, in South America have shown that despite high levels of IgE against house dust mite allergen (HDM) and other environmental allergens in children heavily infected with helminths, their skin reactivity...
The immunological mechanisms underlying the negative relationship between atopy and infections

A central hypothesis to explain the reduced allergic manifestations in helminth-infected subjects has been exposed by Hagel, Lynch and coworkers23,24. Because high levels of polyclonal (i.e. nonantigen-specific) IgE occur in most worm infections, these investigators have suggested that few of the FcεRI receptors (FεRIs) on mast cells are occupied by IgE molecules to any one allergen. The mast-cell degranulation response requires crosslinking between two molecules of IgE–FεRI binding to a single allergen, hence the production of many irrelevant specificities of IgE will block the allergic response to HDM. Support for this hypothesis comes from studies involving the anti-helminthic treatment of children, whose gain in skin reactivity paralleled significant reductions in total IgE levels25. However, not all investigators accept this model, citing for example, the elasticity of FεRI expression and the difficulties of saturating mast-cell capacity for IgE in vitro26,27.

More recent human studies also cast doubt on an explanation involving nonspecific IgE. In studies of schoolchildren exposed to tissue helminths (schistosomiasis and filariasis), a high degree of sensitization to HDM was also reported (32% of the children studied had IgE anti-HDM Ab levels of >11U ml⁻¹)28. However, far fewer children manifested any physical sign of allergy (11% were reactive in the skin-prick test and only 3% showed bronchial hyperresponsiveness). Infected children showed a significantly lower reactivity to HDM than children free of infections (8% compared with 17%). In this study, which took into account a number of socioeconomic, nutritional as well as immunological parameters, the level of total IgE, which was highly elevated, did not show any significant influence on the skin reactivity to HDM (Ref. 21).

Could anti-inflammatory cytokines be responsible for the lower incidence of allergies in highly infected populations?

Inflammation is often categorized as a function of Th1 responses, but it is important to note that allergies are essentially inflammatory diseases dependent on Th2 activation (Fig. 1). Moreover, the timely resolution of an inflammatory reaction is as important to a healthy outcome as is the selection of the appropriate response in the first place. Thus, even the most pro-inflammatory stimuli, such as lipopolysaccharide (LPS), also trigger the production of anti-inflammatory cytokines, such as IL-10, allowing a negative feedback loop to forestall excessive inflammation. Helminth infections have the added dimension of chronic antigen challenge, and downregulation might be the immune system’s natural response to continuous antigen exposure. An interesting parallel might perhaps be found with food antigens, which induce regulatory responses initiated in the mucosal-associated lymphoid tissue27 (Fig. 2).
antigens released by metabolically active worms. Continuous challenge of the immune system by foreign antigens can lead to chronic helminth infections, where individuals develop prominent cytokine responses.

Children were categorized into high or low producers of interleukin-5 (IL-5) (high: IL-5 > 140 pg ml$^{-1}$, IL-10: high: >12.5 pg ml$^{-1}$, IL-13: high: >154 pg ml$^{-1}$) and interferon-γ (IFN-γ) (high: >140 pg ml$^{-1}$). The proportion of children with a positive skin-prick test (SPT) to house dust mite allergen (HDM) (Dermatophagoides pteronyssinus, found abundantly in dust samples from Gabonese houses) is shown in children with high or low cytokine responses. Only high parasite-induced IL-10 production was associated with a decreased skin reactivity to HDM, despite equivalent levels of anti-HDM IgE antibodies.

The two most prominent anti-inflammatory cytokines are IL-10 and transforming growth factor β (TGF-β). It has already been reported that allergic individuals express lower levels of IL-10 in affected sites. For example, the bronchoalveolar lavage (BAL) fluid and cells of asthmatic patients produced three to ten times less IL-10 than corresponding samples from nonasthmatics\(^\text{26}\). In addition, the size of the skin reaction (wheel) to HDM is negatively associated with the level of allergen-induced IL-10 (Ref. 27). TGF-β is a major counter-inflammatory product which, when transfected into T cells, is capable of downregulating not only Th1- but also Th2-mediated inflammation\(^\text{26}\).

Is the production of IL-10 and TGF-β a major feature of chronic helminth infection? We believe so. Several patients with filariasis and schistosomiasis have revealed that IL-10 production is upregulated in PBMCs (Refs 29–31). Peripheral T-cell populations from these patients have depressed proliferative responses to helminth antigens, often accompanied by a degree of “spill-over” suppression to unrelated antigens\(^\text{32,33}\). This defect in proliferative responses has been attributed to IL-10 and TGF-β, because neutralizing Abs to these cytokines rescue reactivity\(^\text{30,34}\). These studies suggest that individuals with chronic helminth infections develop prominent anti-inflammatory networks. These operate to restrict the tissue damage that might otherwise result from the continuous challenge of the immune system by foreign antigens released by metabolically active worms.

We suggest therefore that the presence of the anti-inflammatory network during chronic helminth infections might be the key to the lower prevalence of allergic disease in Th2-skewed populations. Recent results on schistosomiasis and atopy in Gabon support this view. By multiple logistic regression analysis, it was shown that, of all the immunological parameters measured, parasite-induced IL-10 significantly reduced (by 53%) the probability of skin reactivity to HDM (Ref. 21). Fig. 3 shows the proportion of children that are atopic to HDM in groups with high or low parasite-induced cytokine responses, highlighting the influence of IL-10 on atopy.

The case for regulatory T cells in infection and allergy

The combination of IL-10 and TGF-β production is encountered in another context, which we suggest is highly relevant to both infection and allergy. Immunological tolerance to certain autoantigens is maintained not by thymic deletion or peripheral T-cell anergy, but by a specialized population of regulatory T cells (Treg, also termed Th3 or Tr1), which suppress T-cell responses by the production of IL-10 and TGF-β. These T cells are activated to express pro-inflammatory mediators. Regulatory T cells, when expanded in numbers, could influence allergic reactivity either nonspecifically, by creating an anti-inflammatory milieu, or specifically, by responding to epitopes crossreactive between allergens and helminths.

How the anti-inflammatory network might protect against allergy

The primary effect of the immuno-regulatory response to helminth infections is not likely to be at the level of induction of Th2 responses to allergens as there are high levels of IgE in helminth-infected subjects. However, the higher prevailing levels of IL-10 and TGF-β might limit the extent to which cells are activated to express pro-inflammatory mediators. Moreover, IL-10 can block key components of the effector phase, such as mast-cell degranulation, and might impair amplification of the response, which is dependent upon the recruitment of other cells. However, a particular effect of the anti-inflammatory network might be in blocking reactions in nonhematopoietic tissues, greatly generalizing its influence.
The downregulatory effects of IL-10 and TGF-β on T cells and antigen-presenting cells (APCs) are well documented, but in addition a wide variety of cells in other tissues express receptors for these cytokines. The type 1 and type 2 serine and/or threonine kinase receptors that are directly involved in TGF-β signal transduction have been well characterized and, along with other accessory receptors, have a widespread tissue distribution, including the airways37. More recently, the molecular structure of the receptor for IL-10 (IL-10R) has been defined and shown to comprise two subunits: IL-10R1, which is the ligand-binding subunit with weak signaling capacity38, and IL-10R2, originally referred to as CRF2–4 (also a coreceptor for IL-22), which is the signaling subunit38. The expression pattern of these receptors is interesting in that IL-10R1 is expressed in most hematopoietic cells, whereas IL-10R2 is constitutively expressed by a wide range of cells and tissues39. It is important to note that the expression of IL-10R1 can be upregulated by nonhematopoietic cells, such as fibroblasts and epithelial cells, following activation by for example, LPS (Ref. 40). Therefore, it is possible that in tissues from subjects facing repeated inflammatory insult, constitutive IL-10R2 expression is supplemented by induced IL-10R1, allowing the suppressive influence of IL-10 to expand into nonhematopoietic compartments.

Theoretically, the downregulation of target tissue responses might be effected quite simply by raising the threshold at which cells respond to pro-inflammatory stimuli. Pro-inflammatory responses, for example mediated by LPS or TNF-α, are driven largely by the transcription factor nuclear factor κB (NF-κB), which coordinates the activation of numerous genes41. IL-10 signaling has been shown to decrease the binding of NF-κB to DNA, either directly or by decreasing the degradation of the inhibitor of κB (IkB)42. Thus, IL-10 signaling can attenuate the responses in target cells involved in an inflammatory insult (Fig. 2). In the light of this, it should be noted that hematopoietic cell populations in subjects with chronic helminth infections appear to show defective signaling responses. PBMCs from infected Ethiopians showed poor signaling, as measured by the decreased phosphorylation of mitogen-activated protein kinases (MAPKs) or the deficient degradation of phosphorylated IkBα (Ref. 43). It is interesting to note that anti-inflammatory corticosteroids, which are the most effective drugs for the treatment of allergic diseases, act mainly by the inhibition of NF-κB (Ref. 44).

Whether the decreased signaling in subjects with chronic helminthiasis also applies to nonhematopoietic cells, such as smooth muscle cells or epithelial and/or parenchymal cells, has yet to be established. It is also unclear whether the defective signaling is mediated by the anti-inflammatory cytokines or represents yet another additional physiological pathway that might help to explain the negative association between chronic infections and atopy.

**New strategies for therapy?**

The existing interpretation of the hygiene hypothesis in terms of Th1 versus Th2 responses has led to therapeutic strategies that aim to bias anti-allergen responses towards Th1-type responses17,45. We argue that in the light of the present review, it would be more appropriate to induce allergen-specific Th3/Th1 cells capable of releasing anti-inflammatory cytokines such as IL-10 and/or TGF-β. Experimental models of allergy have allowed the detailed dissection of the role that Th1 and Th2 cells play in the pathophysiology of airway responses. By localizing ovalbumin (OVA)-specific Th1 or Th2 cells and challenging with OVA, it has been clearly shown that not only Th2, but also Th1, cells can induce airway inflammation and lung injury46,47, although bronchial hyperresponsiveness is mediated by Th2 cells only48. More importantly, Th1 cells were not capable of reducing Th2-mediated airway hyperreactivity, although there was some reduction in mucus production, which has been attributed to signaling through IL-4Rα (Ref. 48). In humans, there is evidence that not only Th2 cytokines, but also IFN-γ and TNF-α, are strongly upregulated in lungs from asthmatic patients49. Therefore, the present collective efforts to prevent atopy by stimulating allergen-specific Th1 cells might be futile and even hazardous in the absence of a strong anti-inflammatory network in children born in the West. Perhaps, now is the time to design new strategies, mimicking chronic infections that result in the development of strong anti-inflammatory networks and stimulating T cells with anti-inflammatory potential50.


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