

Review Article

Worms and allergy

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SUMMARY

Worms and asthma are associated with a type 2 immune response, but evidence has accumulated that helminth infection is negatively associated with atopy, prevalence of allergic diseases and severity of asthma. One important difference between these polarized type 2 responses is that in allergy modulation of the immunological response is not appropriate, whereas in infection with helminths, several host mechanisms down-regulate the host immune response. As a result, patients infected with worms have a decrease in both type 1 and type 2 responses. The main mechanism involved in this down-modulation is increased production of IL-10, but expansion of regulatory T cells and NKT cells may also participate. Regarding the interaction between worms and allergy, a few variables need to be taken in account: phase (acute or chronic) of helminth infection, parasite load and species of helminth. In animals and humans, acute helminth infection may increase manifestations of allergy, whereas chronic infection with parasites decreases atopy. The modulation of the immune response by helminths is dependent on having an adequate parasite load. Moreover, although several helminth species have been shown to modulate immune responses, most in vitro and in vivo studies have focused on the importance of Schistosoma mansoni in down-modulating allergic reactions.

Keywords *helminths and asthma, S. mansoni and atopy, worms and asthma, worms and atopy*

INTRODUCTION

Helminth infection and allergy are common diseases. It is estimated that 1 billion individuals in the world are infected by *Ascaris lumbricoides*, 500 million by *Ancylostoma duodenale* and 200 million by *Schistosoma mansoni* (1,2). As the prevalence of asthma and rhinitis, the most common manifestations of allergy, are also high in countries where helminths are endemic (3), studies evaluating the immunological and clinical consequence of this association have been performed.

Asthma is a complex disease influenced by genetic factors, immunological response and environmental conditions. Vasodilatation, oedema and bronchial constriction secondary to mediators released by mast cells after interaction with IgE-linked allergen compose the early events of immediate hypersensitivity. This reaction is followed by an inflammatory response leading to changes in the bronchial structure and airway hyper-responsiveness. The airways are infiltrated by mononuclear cells, mainly CD4⁺ T cells in addition to eosinophils, macrophages and neutrophils. Th2 cytokines (IL-4 and IL-13) participate in the production of mast cells and IgE synthesis, as well as IL-5 in the differentiation, proliferation and activation of eosinophils. The Th2 cytokines IL-4, IL-5, IL-9, IL-11 and IL-13 account directly or indirectly for the great majority of pathophysiological manifestations of allergic diseases. IL-4 is able to induce rolling and adhesion of circulating eosinophils to endothelial cells (4), which can then be attracted into target tissue by both IL-5 and chemokines such as eotaxin and monocyte chemotactic proteins, CCL7 and CCL13 (5). Eotaxin (CCL11) is also produced by epithelial cells, endothelial cells, and fibroblasts upon IL-4 and IL-13 activation (6). Finally, IL-13 is responsible for mucus hyper-secretion, and IL-4 and IL-13 stimulate fibroblast growth and chemotaxis as well as the synthesis of extracellular matrix proteins (7). Transforming growth factor (TGF)- β produced by Th2 cells eosinophils and fibroblasts induces subepithelial fibrosis. This sequence

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Received: 23 December 2005

Accepted for publication: 27 March 2006

of events indicates that Th2 cells play a central role in the allergic inflammatory reaction, including the airway remodelling that is observed in asthma. Asthma may occur even in mice deficient for B cells, immunoglobulin E or mast cells; however, asthma is not observed in animals deficient in CD4⁺ T cells, IL-4 and IL-5 (8).

Helminths, similarly to allergens, also induce a type 2 immune response. Although pathology can be documented in some patients infected with worms, the majority of helminth-infected individuals have an asymptomatic form of infection or present mild clinical manifestations. This host–parasite relationship appears to be determined by adaptive mechanisms developed by the worms to escape the host immune defence and by the host to prevent an exacerbated inflammatory response leading to tissue damage. Worms are in fact able to down-modulate the type 1 inflammatory response and attenuate auto-immune disease in experimental models (9,10). In humans it is known that *Schistosoma* infection is inversely associated with a positive skin test response to aeroallergens (11,12) and that worms may attenuate clinical manifestations of asthma (13). This review describes epidemiological, immunological and clinical aspects of the interaction between allergy and helminth infections.

HELMINTH INFECTION AND ALLERGIC DISEASES

It is estimated that 130 million people worldwide suffer from asthma and the prevalence is increasing mainly in developed countries (14,15). The International Study of Asthma and Allergies in Childhood (ISAAC) through a questionnaire validated in a population study of prevalence of allergic diseases, demonstrated that the prevalence of wheezing in the last 12 months in children between 13 and 14 years old was quite variable, ranging from 2.1% in Indonesia to 32.2% in England (3). In Brazil the prevalence of asthma was 23.3%. This study demonstrated that asthma is more prevalent in industrialized countries with western culture, whose first language is English, such as the UK, New Zealand, Austria, the USA and Canada. In another study, the European Community Respiratory Health Survey (ECRHS), performed in 13 countries in Europe, evaluated the prevalence of asthma and other respiratory disease in individuals from 20 to 44 years of age. In agreement with the ISAAC study, it found that in countries where English is spoken the prevalence of asthma was higher than in other countries such as Italy and Greece (16). In this study they showed that the prevalence of asthma was generally low in China and Taiwan, while in more affluent Asian countries, i.e. Singapore, Japan and Hong Kong they found a relatively high prevalence of asthma.

Genetic factors could explain the difference in prevalence of asthma and other allergic diseases among countries; however, some studies have shown strong evidence that environmental factors also influence the development of allergic diseases. The prevalence of asthma among a population sharing the same ethnic group was higher in Hong Kong, an affluent city, than in Guangzhou, a less affluent city which is geographically close to Hong Kong (16).

Coincident with an improvement in lifestyle, the prevalence of asthma increased in Sweden from 1979 to 1991 (17) and atopy and allergic rhinitis also increased in prevalence in East Germany after the unification with West Germany (18). Even within a country, the prevalence of allergic diseases varies among rural and urban areas, being less prevalent in rural areas (19). In the state of Bahia in North-eastern Brazil the industries are localized around Salvador, the state capital, while agriculture is the main economic activity in rural areas. The prevalence of asthma in Salvador determined by the ISAAC questionnaire was 27% (3), while in the village of Conde, a rural area endemic for helminth infections located 200 km from Salvador, the prevalence of asthma was 14.4% (20).

The influence of infections on the prevalence and severity of allergic diseases is a topic of great interest, because of the possible development of strategies to better control these diseases. There are many published studies indicating that infections protect against atopy. The first studies in this field suggested that children exposed to environmentally driven Th1 responses, such as viral infections, would be protected against atopy, whereas those living in industrialized countries in which vaccination and use of antibiotics is frequent had a higher prevalence of allergic diseases. This is the so-called 'Hygiene Hypothesis' (21).

Initial data indicating that helminth infections were inversely associated with atopy were published in the early seventies and since then a large number of studies have shown that helminths can protect against allergy (11,22–26).

Studies performed in Venezuela not only showed a low prevalence of positive skin test (SPT) to aeroallergens in individuals living in an endemic area of *Ascaris lumbricoides* infection (27), but also that after antihelminthic treatment there was an increase in the prevalence of positive SPT responses (24). The authors of these studies also demonstrated an increase in the prevalence of wheezing after antihelminthic treatment. Evaluating 2865 school age children ranging from 5 to 19 years in Ecuador, Cooper *et al.* (28) demonstrated that infection with geohelminths was negatively associated with skin test reactivity to allergens. A very low frequency of positive SPT response to dust mites was also documented among school age children living in Gabon, Africa (29).

Although the majority of the studies in this field have shown an inverse association between helminth infection

and atopy, there are a few reports associating geohelminths with an increased risk of asthma crisis (30–32). Possible explanation for these conflicting data includes age of the population, the parasite burden, the time of exposure to the worm (if acute or chronic), and also the species of helminth. We demonstrated, for instance, that in individuals infected with a low parasite burden of *Ascaris lumbricoides* living in an urban area, the frequency of positive SPT to dust mite did not differ from those without infection living at the same area (33). Lynch *et al.* (34) had demonstrated that the prevalence of positive SPT to allergens was lower in individuals with high parasite burden of geohelminths compared to those with low parasite burden. Furthermore, we also demonstrated lower prevalence of SPT response to aeroallergens in individuals infected with a high parasite burden of *Schistosoma mansoni* living in a rural area, when compared to uninfected individuals living in the same area (11). Another factor that could explain the conflicting results regarding the role of helminth infections on the development of allergies, is that most of the published data did not take into account the fact that exposure to allergens is required to develop a SPT response. We evaluated if those individuals with negative SPT to aeroallergens living in rural areas endemic for *S. mansoni* were exposed to allergens, and demonstrated that they were exposed to sensitizing levels of house dust mites, which are the most important allergens in Brazil (13).

IMMUNOLOGICAL RESPONSES AND HELMINTH INFECTION

For many years helminth infection was known to be associated with eosinophil and IgE production. IL-4 and IL-13 are recognized as important cytokines able to stimulate B cells to secrete IgE, and IL-5 is known to influence eosinophil differentiation, proliferation and activation. Upon lymphocyte stimulation with *Strongyloides stercoralis* antigen, patients with strongyloidiasis produce predominantly IL-4, IL-5, IL-10 and low levels of IFN- γ . There is evidence that this type of immune response may protect hosts against helminths. Despite the inherent difficulties in documenting *in vivo* that worms are killed by components of the type 2 immune response, there is evidence from experimental models that IL-4 and IL-13, by stimulating peristalsis and increasing intestinal fluid, contribute to parasite elimination in stool (35). This defence mechanism is extremely important in *S. stercoralis* infection because persistence of parasite infection and development of disseminated strongyloidiasis is dependent on autoinfection that occurs after the transformation of rhabditiform larvae into the infective filariform larvae in the intestinal lumen. In experimental models, killing of *S. mansoni* may occur after mast cell degranulation (36), and *in vitro*,

eosinophils can kill parasites by the mechanisms of antibody-dependent cellular cytotoxicity (37). In humans, resistance to re-infection with *S. mansoni* is an age-dependent phenomenon also related to anti-schistosomal IgE antibody or the anti-schistosomal IgE/IgG ratio (38). Together these data clearly show that, whereas in allergy the Th2 immune response is only associated with pathology, this type of response in helminth infection is also associated with protection.

Pathology related to helminths may also be caused by the type 2 immune response. In *S. mansoni* infection granulomas around dead eggs may result in liver fibrosis, the main pathological feature of schistosomiasis. Although development of liver fibrosis is dependent on multiple factors, the role of eosinophils and cytokines in granuloma formation and consequently hepatic fibrosis has been documented. Animal studies have shown that IL-4 and predominantly IL-13 are the major stimuli for the development of egg-induced liver fibrosis, possibly for direct stimulation of collagen deposition by fibroblasts (39). Neutralization of IL-4 reduces granuloma formation and mice lacking IL-4 α and β receptors that bind to IL-4 and IL-13, abrogate granuloma formation (40). In humans, a positive association was found between the levels of IL-5 and IL-13 in supernatants of lymphocyte cultures stimulated with *S. mansoni* antigen and a more severe degree of liver fibrosis detected by ultrasonography. Moreover, progression of liver fibrosis detected by ultrasound was associated with an increase in IL-5 and IL-13 levels (41). Liver fibrosis leads to the hepatosplenic form of disease that results in oesophageal and gastric varices and gastro-intestinal bleeding. IL-10, a potent anti-inflammatory cytokine, plays an important role in decreasing pathology in schistosomiasis. IL-10 decreases lymphoproliferative response to *S. mansoni* antigens (42), modulates granulomatous response *in vitro* (43,44) and induces apoptosis in T cells (45). Compared to patients with intestinal schistosomiasis, those who develop hepatosplenic disease produce less IL-10 (42,46). The ability of IL-10 to down-modulate the type 1 inflammatory response is well documented. It has been shown that neutralization of IL-10 increased IFN- γ production in patients with schistosomiasis (47). Moreover, after vaccination with tetanus, patients with schistosomiasis have a significant decrease in IFN- γ production after mononuclear cell stimulation *in vitro* with tetanus toxoid (10). The Human T Lymphocytotropic Virus type 1 (HTLV-1) is associated with a strong type 1 immune response with high levels of endogenous IFN- γ and TNF- α production. Compared with HTLV-1 carriers without helminth infection, HTLV-1 carriers co-infected with *S. mansoni* produce less IFN- γ and TNF- α , have decreased IFN- γ -producing CD4 $^{+}$ T cells and an increased number of T cells producing IL-10 (48). Modulation of the type 2 immune response has also been observed in *S. mansoni*

infection. Asthmatics infected with *S. mansoni* produce lower levels of IL-4 and IL-5 than uninfected asthmatics and exogenous addition of IL-10 decreases *in vitro* levels of IL-5 (20).

Taken together these data emphasize that in contrast to allergies, the Th2 immune response in helminth infection can be modulated. Dendritic cells, regulatory T cells and IL-10 may play an important role in this modulation. Whereas in asthma and schistosomiasis there is a decreased ability of dendritic cells to produce IL-12, allowing development of the type 2 immune response (49), in schistosomiasis interaction of dendritic cells with *S. mansoni* antigen induces IL-10 production (50), a cytokine able to down-modulate both type 1 and type 2 immune responses (51).

TH2 POLARIZATION IN HELMINTH INFECTION AND ASTHMA

The primary function of the immune system is a defence against pathogens. However, expansion or development of auto-reactive T and B cells and an exacerbated and inappropriately modulated immune response lead to the appearance of autoimmune and chronic inflammatory disorders. The description in 1986 of CD4 T cells that were heterogeneous and could be divided in Th1 and Th2 subtypes was an important observation for understanding the heterogeneity of the immune system regarding the effectors and regulatory functions (52). Th1 cells secrete IFN- γ and TNF- α , whereas Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. Th1 cells activate macrophages to kill intracellular pathogens, support CD8+ antiviral effector cells and induce IgG antibodies important in the opsonization and phagocytosis of extracellular microorganisms. In contrast, Th2 cells stimulate differentiation of B lymphocytes to IgE-producing cells and stimulate the growth, differentiation and activation of eosinophils and mast cells. Therefore both Th1 and Th2 cells participate in the host defence. Moreover, these phenotypes regulate each other, since IFN- γ down-regulates the type 2 immune response and IL-4 and IL-10 down-modulate the type 1 immune response. These counter-regulatory mechanisms are important for the regulation of the inflammatory reaction, preventing the occurrence of tissue damage.

Both worms and allergy are associated with Th2 polarization. However, in allergy, expression of Th2 cells may be due to a loss of immune regulatory mechanisms (53) and have as a consequence the development of disease. Whereas in helminth infection the type 2 immune response is primarily a host defence mechanism against worms, and it is further down-modulated to prevent pathology.

In the first 5 weeks following *S. mansoni* infection in mice, the host immune response to worm antigens is weak and primarily Th1 in nature (54). In humans living outside an endemic area, the immune response in the first 8 weeks after

first exposure to *S. mansoni* is characterized by an intense production of pro-inflammatory cytokines, such as TNF- α , IL-1 and IL-6, and a predominant production of IFN- γ over IL-4 and IL-5 (55). Moreover, in contrast to what is observed in endemic areas where no clinical manifestations follow acute infection, acute schistosomiasis in subjects living outside endemic areas is a severe disease characterized by fever, chills, asthenia, weight loss and respiratory and gastrointestinal symptoms, including abdominal pain and diarrhoea. After egg deposition the immune response changes and a highly polarized Th2 response is established (47,56,57). This response is characterized by high levels of total and parasite-specific IgE, as well as eosinophilia. Changes in the immune response are also observed in the chronic phase of other helminth infections such as *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Wuchereria bancrofti* and *Ancylostoma duodenale* (35).

IL-4 has been identified as the major cytokine inducing a type 2 immune response. The major sources of IL-4 are CD4+ T cells, mast cells, eosinophils and NK T cells. Multiple sources of IL-4 may play redundant roles in Th2 polarization. However, in some models of helminth infection and allergy, IL-4 seems not to play a central role in inducing the Th2 response. For instance, the primary Th2 immune response during *Nippostrongylus braziliensis* infection is IL-4 independent (58), and some models of allergen-induced airway hyper-reactivity are IL-4 independent (59).

One of the strongest examples of the role of IL-4 in inducing Th2 polarization and the ability of the type 1 immune response in preventing Th2 polarization is the experimental model of leishmaniasis. After infection with *Leishmania major*, BALB/c mice develop a severe form of leishmaniasis, whereas C57BL/6 mice control *Leishmania* growth and develop only mild disease (60). Whereas neutralization of IL-4 in BALB/c promotes a type 1 immune response and control of the infection (61), neutralization of IL-12 or IFN- γ in *L. major*-infected C57BL/6 resulted in dissemination of infection (62). Besides the type 1 immune response, IL-12-producing dendritic cells also play a role in down-modulating IL-4 production. Administration of exogenous IL-12 together with *S. mansoni* eggs completely blocks Th2 development and induces a typical Th1 type response (63). The role of IL-12, the main cytokine involved in differentiation of Th1 cells, in down-regulating IL-4 production is also well documented in other models. Although dendritic cells play a key role in the production of IL-12, there is no evidence that they produce IL-4. However, evidence has accumulated for the role of dendritic cells in inducing a type 2 immune response independent of IL-4. These studies show that down-regulation of dendritic cell function is critical for Th2 cell development. Evidence for the role of dendritic cells in allergy has also been documented. For instance, Th2

polarization to *Dermatophagoides pteronyssinus* antigen (Der p1), the major house dust mite allergen, is associated with a decreased state of dendritic cell activation (64). Moreover, pollen-associated phytoprostane allergens are known to increase Th2 polarization and inhibit IL-12 production by dendritic cells (65).

Dendritic cells recognize infectious agents through a panel of pattern recognition receptors, predominantly toll-like receptors (TLR) (66) and C type lectins (67). Interaction of antigens with TLRs induces dendritic cell maturation and secretion of IL-12. In contrast to TLRs, ligation of C type lectins does not induce dendritic cell maturation and antagonizes TLR-signalling, playing a role in the interaction of schistosome Ag with dendritic cells. For instance, dendritic cells pulsed *in vitro* with schistosome egg antigen (SEA) induced an SEA-specific Th2 response in infected mice (68). One explanation for this result could be that SEA induces Th2 responses simply by default, owing to its failure to elicit IL-12 production. However, a decrease in IL-12 secretion results in a profound suppressive effect on signalling initiated by classical inflammatory TLR ligands. In contrast, SEA augments TLR ligand-induced production of IL-10 (69). These data suggest that *S. mansoni* infection promotes Th2 polarization by preventing maturation of dendritic cells, and consequently decreasing the pro-inflammatory phenotype of dendritic cells. Additionally, the induction of IL-10 helps to prevent TLR ligands from stimulating the production of inhibitory signals that block Th2 cell development (69).

PARASITE ANTIGENS AND ALLERGY

Helminth infections are associated with high levels of IL-4, IL-5, IL-13, eosinophils and production of high IgE levels. This would suggest that worm infection predisposes individuals to allergic reactions. Supporting this is evidence that helminth proteases exhibit significant homology with known allergens and that, during acute helminth infection, allergic manifestations in the skin and respiratory tract can be documented (70).

The model of *Strongyloides venezuelensis* in rodents clearly shows that lung larvae migration increase IgE levels, induces leucocyte infiltration with increasing number of mononuclear cells and eosinophilic inflammation with thickening of the bronchial epithelial layer and airway hyper-responsiveness (71). In contrast with the airway hyper-responsiveness observed with the passage of larvae through the lungs, chronic helminth infections have been inversely associated with allergy (72).

Helminths are large parasites that have the ability to survive in humans for a long period of time and a large amount of antigens are present in the larvae, adult worms and eggs. Helminths synthesize protease molecules that provoke

allergic responses and excretory/secretory products of helminths can induce Th2 responses (73). Other studies have documented that parasite antigens cross-react with allergens (74), which could increase allergic reaction in atopic individuals and initiate allergic diseases in non-atopic individuals. However, in contrast to allergens that induce IL-4, IL-5, IL-13 and low IL-10 levels (75), the type 2 immune responses in helminth infection is associated with high levels of IL-10, a known regulatory cytokine that inhibits both type 1 (10) and type 2 immune responses (20). The anti-inflammatory cytokines, such as IL-10 and TGF- β , are produced in response to continual stimulation of the immune system by parasite antigens to protect the host from tissue damage by helminths, and may also have a bystander protective effect against allergic reactions.

The ability of helminths and their antigens to down-modulate allergic responses has been documented. *Ascaris lumbricoides* extract decreases eosinophil infiltration and airway hyper-responsiveness in the allergic response induced by ova (76), and there is an inverse association between helminth infection and atopy (11,42,77,78). The ability of helminths to down-modulate the allergic reaction is correlated with parasite load. In a *S. mansoni*-endemic area, patients with a low degree of *S. mansoni* parasite ova in the stool were compared to patients with high parasite ova load; the rate of positive skin tests to aeroallergens was significantly reduced in the latter group (11). *In vitro*, parasite antigens may also change the immune response to an allergen, as has been observed in patients who have allergy and *S. mansoni* infection. Compared to patients who have asthma without helminth infection, individuals who have asthma plus *S. mansoni* infection produce higher levels of IL-10, and there is a positive correlation between IL-10 production in response to Der p1 antigen and the parasite load, determined by the number of eggs per gram of stool (20). Several *S. mansoni* antigens are known to induce IL-10 production. It has been shown that the oligosaccharide produced by *S. mansoni*, lacto-N-fucopentose not only induces a type 2 immune response in mice (79), but is capable of inducing IL-10 production *in vitro* in human cells (80). Studies performed with a protein obtained from *S. mansoni* adult worms (SWAP) by HPLC, the PIII antigen, have shown that this protein is able to down-modulate granuloma formation around *S. mansoni* eggs (43). Moreover P24, an antigen from PIII, induces IL-10 and inhibits T cell proliferation and cytokine syntheses (43).

WORMS AND CLINICAL MANIFESTATION OF ATOPY

The negative association between infection with helminths and allergic reactions to a common allergen has been widely

observed. Many of these studies describe a protective effect of intestinal helminths, such as *Ascaris lumbricoides*, *Trichura trichiuris*, Hookworm and *Schistosoma*. In humans, epidemiological, immunological and clinical studies have also shown the ability of helminths to decrease allergic reactions. These studies have been performed in patients infected with geohelminths, in particular with *A. lumbricoides* and *Schistosoma* spp. (11,28,29,78). The role of worms in decreasing atopy has been further documented by the demonstration that treatment of helminth infection is associated with increased skin test response and aeroallergen-specific IgE levels (24,81). Helminths by themselves induce B cells to differentiate into IgE-producing cells, and total IgE levels are usually very high in patients infected with helminths. The decrease in atopy mediated by helminths has not been associated to a decrease in the total of allergen-specific IgE in patients infected with worms (13). In contrast, there is strong evidence that protection against allergy in helminth infection is mediated by IL-10. First, IL-10 is one of the most anti-inflammatory cytokines, and it is increased in helminth infections (42,47,82). Second, IL-10 decreases Th2 cytokine production (20), induces regulatory T cells (83) and also suppress mast cell degranulation (84).

While the increased incidence of allergic diseases over the past 30 years has been associated with environmental changes and increased exposure to pollutants, very few studies have closely evaluated the exposure to allergens of individuals living in rural areas, where helminths are highly prevalent. Comparing the concentration of mites in the dust of houses from individuals with similar socio-economic levels but living in urban or rural areas, we observed that concentration of mite antigen was similar in individuals living in rural villages to that observed in individuals living in slums of a large city (85). Whereas in a rural area endemic for *S. mansoni* the prevalence of helminth infection and specifically of *S. mansoni* was very high, patients living in the slum had a low prevalence of helminths. In contrast, the rate of positive skin prick tests to aeroallergen was lower (19%) in the population infected with helminths than in patients (76%) from the urban area. As a few studies have not observed an inverse association between worm infection and allergy, it is possible that parasite burden and the type of helminths may influence the down-modulation of the allergic reaction. *Schistosoma mansoni* has been one of the most important helminths that decrease allergy. However, if studies are performed in patients infected by *S. mansoni* who have lived outside the endemic areas for many years, this inverse association may not occur. In fact, parasite load is an important variable in the immune response observed during *S. mansoni* infection, and it influences the magnitude of the modulation of the immune response. Evaluating patients with asthma living in an area endemic for

schistosomiasis in Brazil, it was observed that reduced skin test response was lower in those who had a high parasitic load of infection (more than 200 eggs per gram of stool) than in those with low levels of infection (11). The type of helminth may also influence the ability to down-modulate allergic responses. Studies performed in two villages, one endemic for *S. mansoni* (Caatinga do Moura) and the other without *S. mansoni* but endemic for other helminths (Lage do Batata), showed that a decrease in atopy was more evident in the *S. mansoni*-endemic area (only 19% of the individuals with asthma had a positive skin test) than in the villages where helminths other than *S. mansoni* infected the population (46%). Although there is a consensus that helminth infection decreases skin reactivity to aeroallergens and reduces the risk of asthma, there are only a few controlled studies evaluating the influence of helminths in the clinical course of asthma. Most epidemiological studies use the ISAAC questionnaire, and very few studies have taken into account the data from clinical examination, pulmonary function tests and the effect of anti-helminthic treatment on asthma severity. As the pathogenesis of asthma is complex and disease expression results from many factors, the clinical manifestations of asthma are quite variable.

To test the hypothesis that infection with *S. mansoni* interferes with asthma severity, Medeiros *et al.* (13) performed a case-control study in a rural area endemic for schistosomiasis in Brazil. An ISAAC-based questionnaire was used to identify individuals with a history of asthma in the endemic area. Age- and sex-matched asthmatic controls from an urban area non-endemic for schistosomiasis but endemic for other helminths were also selected using the same questionnaire. As a cross-sectional evaluation did not show differences in the two groups of patients, a cohort study was performed and the patients were evaluated every 3 months for 1 year. It was demonstrated that people from the *S. mansoni* area had less severe asthma as assessed by: (a) a questionnaire that included questions about presence of asthmatic symptoms, such as, cough, wheezing, and dyspnoea; (b) use of anti-asthmatic drugs and (c) physical examination. This study showed that individuals from a *S. mansoni*-endemic area, who were equally exposed to aeroallergens, home pollutants, climate conditions and of the same socioeconomic status had a milder course of asthma in a 1-year follow-up, compared to asthmatics not living in a *S. mansoni* endemic area, but infected with other helminths.

HOW DOES HELMINTH INFECTION PROTECT AGAINST ALLERGY?

Chronic infection with a high burden of helminths is thought to induce regulatory networks that can alter immune response to both parasite and harmless antigens.

Four mechanisms that could be involved in the regulation of the immune response and protection against allergy in patients infected with helminths have been studied: (a) competition between helminth-induced polyclonal or specific IgE and aeroallergen-specific IgE for the high affinity IgE receptor present on mast cells; (b) production of helminth-specific IgG4 antibodies that could cross-react and compete with antigen-specific IgE and therefore inhibit the IgE-mediated response; (c) development of regulatory T cells that could decrease type 2 response against allergens and (d) high levels of regulatory cytokines such as IL-10 and TGF- β that could suppress immune response to non-related antigens. It is known that helminth infection increases IgE levels, but there is no strong evidence that high levels of IgE decrease atopy or prevent allergen-specific IgE binding to mast cells. Evaluating patients infected with different degrees of *S. mansoni* parasite load in Brazil, we did not find an association between a decrease in atopy and IgE levels (11).

High IgG4 antibody titres are associated with decreased atopy and have been found at increased levels upon allergen immunotherapy (86,87). IgG4 protects from IgE-mediated allergic responses by competing for allergen binding with IgE. Evaluating school age children in Ecuador, Cooper *et al.* showed that children with IgG4 to *A. lumbricoides* had a lower frequency of atopy than those who were IgG4-negative (28). Other studies showed that the negative skin prick test response in subjects infected with helminths in Africa was not associated with a high production of IgG4 (88).

Regulatory T cells (Treg cells) reduce the magnitude of the immune response by suppressing either or both Th1 and Th2 cell function as well as other immune cells. Based on origin and mechanisms of action, at least three phenotypes of regulatory cells have been described. CD4⁺, CD25⁺ Treg cells that express Foxp3 acquire their phenotype before leaving the thymus and regulate auto-immune reactions. Others Treg populations can arise from non-regulatory peripheral T cells. Treg 1 (Tr1) are activated in the presence of IL-10 (89) and by IL-10-treated dendritic cells in the presence of antigen. Th3 regulatory cells predominantly secrete TGF- β and are found in gut-associated lymphocyte tissues (90).

Evidence that regulatory T cells can control allergy comes from studies showing that T cell lines expressing TGF- β (91) or IL-10 (92) protect OVA-sensitive recipient mice from airway inflammation. In humans, successful immunotherapy with high doses of the house dust mite allergen Der p1 was followed by secretion of IL-10 and TGF- β by CD4⁺, CD25⁺ T cells (93). Attention has also been given to the role of regulatory T cells from atopic and non-atopic individuals in down-regulating the immune response. Whereas Tregs from allergic individuals suppress only the allergen-specific Th1 response and not the Th2-derived IL-4 and IL-5, Tregs

from non-atopic individuals suppress both types of immune responses (94). Regulatory T cells have been documented in schistosomal, filarial and other helminth infections (95–97). In schistosomiasis, regulatory T cells down-modulate the type 1 immune response (97), and it has been shown that *Heligmosomoides polygyrus* inhibits colitis in IL-10-deficient mice (98). It has also been shown in animals infected with *Nippostrongylus braziliensis* that CD4⁺ CD25⁺ IL-10⁺ T cells modulate allergen-induced airway inflammation (99). There are other regulatory cells, such as Natural Killer T cells (NKT), which are CD1-restricted cells expressing NK cell markers and T cell receptors. NKT cells are part of the innate immune system and play a critical role in the control of the adaptive immune response. Importantly, according to the conditions of stimulation, they can either enhance or suppress immune response in a Th1 or Th2 direction. The role of the NKT cell in allergy has pointed out the importance of this cell's participation in Th2 polarization (100). In helminths, NKT cells were found to play a role in preventing NOD mice infected with *S. mansoni* eggs from developing diabetes (101). However, the role of NKT cells in down-modulating the allergic immune response still needs to be determined.

Although regulatory T cells and increasing levels of allergen-specific IgG4 that compete with IgE for antigen binding may contribute to amelioration of allergic diseases, in helminth infections most evidence indicates a central role of IL-10 in this immunoregulation. IL-10 inhibits antigen-presenting cells and their effector function (102), down-modulates Th2 cytokine production (20) and prevents the release of inflammatory mediators by mast cells (84). Together these effects of IL-10 are sufficient to prevent the development of the allergic response and asthma.

CONCLUSION

The effector mechanisms in asthma involve mast cell degranulation in the early phase and the inflammatory response mediated by eosinophils and cytokines, such as IL-4, IL-5 and IL-13, that participate in fibrosis. High levels of IL-10 are produced during helminth infection and the ability of IL-10 to down-modulate the allergic response is well documented. However, both allergy and helminth infection produce complex changes in the immune system, and it is likely that other mediators participate in the different steps leading to a down-regulation of the immune response caused by helminth infection. There is a consensus that allergen sensitization occurs normally and high level of allergen-specific IgE are found in patients infected with helminths. However, there is clear evidence for a reduced allergen type 2 immune response and suppression of the effector functions in atopic patients infected with helminths.

This suppression results in decreased pathology and attenuation of the clinical manifestations of asthma.

ACKNOWLEDGEMENTS

We thank Daniel Morgan for reviewing the manuscript and Elbe M. Silva for secretarial assistance. We also thank the NIH for grant no. D43 TW06216 and NIH/FIC grant no. D43 TW00919 for financial support.

REFERENCES

- Chitsulo L, Loverde P & Engels D. Schistosomiasis. *Nat Rev Microbiol* 2004; **2**: 12–13.
- Iarotski LS & Davis A. The schistosomiasis problem in the world: results of a WHO questionnaire survey. *Bull World Health Organ* 1981; **59**: 115–127.
- Asher MI & Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. *Clin Exp Allergy* 1998; **28** (Suppl. 5): 52–66; discussion 90–91.
- Bochner BS, Udem BJ & Lichtenstein LM. Immunological aspects of allergic asthma. *Annu Rev Immunol* 1994; **12**: 295–335.
- Teran LM. Chemokines and IL-5: major players of eosinophil recruitment in asthma. *Clin Exp Allergy* 1999; **29**: 287–290.
- Doucet C, Brouty-Boye D, Pottin-Clemenceau C, Canonica GW, Jasmin C & Azzarone B. Interleukin (IL) 4 and IL-13 act on human lung fibroblasts. Implication in asthma. *J Clin Invest* 1998; **101**: 2129–2139.
- Postlethwaite AE, Holness MA, Katai H & Raghov R. Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin 4. *J Clin Invest* 1992; **90**: 1479–1485.
- Kay AB. T lymphocytes and their products in atopic allergy and asthma. *Int Arch Allergy Appl Immunol* 1991; **94**: 189–193.
- La Flamme AC, Ruddenklau K & Backstrom BT. Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. *Infect Immun* 2003; **71**: 4996–5004.
- Sabin EA, Araujo MI, Carvalho EM & Pearce EJ. Impairment of tetanus toxoid-specific Th1-like immune responses in humans infected with *Schistosoma mansoni*. *J Infect Dis* 1996; **173**: 269–272.
- Araujo MI, Lopes AA, Medeiros M *et al.* Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. *Int Arch Allergy Immunol* 2000; **123**: 145–148.
- van den Biggelaar AH, van Ree R, Rodrigues LC *et al.* Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000; **356**: 1723–1727.
- Medeiros M Jr, Figueiredo JP, Almeida MC *et al.* *Schistosoma mansoni* infection is associated with a reduced course of asthma. *J Allergy Clin Immunol* 2003; **111**: 947–951.
- Sears MR. Descriptive epidemiology of asthma. *Lancet* 1997; **350** (Suppl. 2): SIII-4.
- Sears MR. Evolution of asthma through childhood. *Clin Exp Allergy* 1998; **28** (Suppl. 5): 82–89; discussion 90–91.
- Pearce N, Sunyer J, Cheng S *et al.* Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. *Eur Respir J* 2000; **16**: 420–426.
- Aberg N, Hesselmar B, Aberg B & Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995; **25**: 815–819.
- von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998; **28** (Suppl. 5): 45–49; discussion 50–51.
- Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E & Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *Lancet* 1997; **350**: 85–90.
- Araujo MI, Hoppe B, Medeiros M Jr *et al.* Impaired T helper 2 response to aeroallergen in helminth-infected patients with asthma. *J Infect Dis* 2004; **190**: 1797–1803.
- Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–1260.
- Jarrett EE & Kerr JW. Threadworms and IgE in allergic asthma. *Clin Allergy* 1973; **3**: 203–207.
- Carswell F, Meakins RH & Harland PS. Parasites and asthma in Tanzanian children. *Lancet* 1976; **2**: 706–707.
- Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R & Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. *J Allergy Clin Immunol* 1993; **92**: 404–411.
- van den Biggelaar AH, Borrmann S, Kremsner P & Yazdanbakhsh M. Immune responses induced by repeated treatment do not result in protective immunity to *Schistosoma haematobium*: interleukin (IL)-5 and IL-10 responses. *J Infect Dis* 2002; **186**: 1474–1482.
- Cooper PJ, Chico ME, Rodrigues LC *et al.* Risk factors for atopy among school children in a rural area of Latin America. *Clin Exp Allergy* 2004; **34**: 845–852.
- Hagel I, Lynch NR, DiPrisco MC, Lopez RI & Garcia NM. Allergic reactivity of children of different socioeconomic levels in tropical populations. *Int Arch Allergy Immunol* 1993; **101**: 209–214.
- Cooper PJ, Chico ME, Rodrigues LC *et al.* Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol* 2003; **111**: 995–1000.
- van den Biggelaar AH, Lopuhaa C, van Ree R *et al.* The prevalence of parasite infestation and house dust mite sensitization in Gabonese schoolchildren. *Int Arch Allergy Immunol* 2001; **126**: 231–238.
- Kayhan B, Telatar H & Karacadag S. Bronchial asthma associated with intestinal parasites. *Am J Gastroent* 1978; **69**: 605–606.
- Gument JM. [Bronchial asthma, spasmodic coryza and parasitic diseases]. *Nouv Presse Med* 1973; **2**: 2125.
- Palmer LJ, Celedon JC, Weiss ST, Wang B, Fang Z & Xu X. *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. *Am J Respir Crit Care Med* 2002; **165**: 1489–1493.
- Ponte E, Lima F, Araujo MI, Oliveira RR, Cardoso LS & Cruz AA. Skin test reactivity and Der p1-induced IL-10 production in patients with asthma or rhinitis infected with *Ascaris*. *Ann Allergy Asthma Immunol* 2006; **96**: 713–718.
- Lynch NR, Lopez RI, Di Prisco-Fuenmayor MC *et al.* Allergic reactivity and socio-economic level in a tropical environment. *Clin Allergy* 1987; **17**: 199–207.
- Finkelman FD, Shea-Donohue T, Goldhill J *et al.* Cytokine regulation of host defense against parasitic gastrointestinal

- nematodes: lessons from studies with rodent models. *Annu Rev Immunol* 1997; **15**: 505–533.
- 36 Mota-Santos TA, Oliveira AF, Gerken SE & Vaz NM. Anaphylaxis with *Schistosoma mansoni* extracts in normal and infected mice. *Rev Inst Med Trop Sao Paulo* 1985; **27**: 179–185.
 - 37 Pincus SH, Butterworth AE, David JR, Robbins M & Vadas MA. Antibody-dependent eosinophil-mediated damage to schistosome of *Schistosoma mansoni*: lack of requirement for oxidative metabolism. *J Immunol* 1981; **126**: 1794–1799.
 - 38 Demeure CE, Rihet P, Abel L, Ouattara M, Bourgois A & Dessein AJ. Resistance to *Schistosoma mansoni* in humans: influence of the IgE/IgG4 balance and IgG2 in immunity to reinfection after chemotherapy. *J Infect Dis* 1993; **168**: 1000–1008.
 - 39 Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat Rev Immunol* 2004; **4**: 583–594.
 - 40 Chiamonte MG, Cheever AW, Malley JD, Donaldson DD & Wynn TA. Studies of murine schistosomiasis reveal interleukin-13 blockade as a treatment for established and progressive liver fibrosis. *Hepatology* 2001; **34**: 273–282.
 - 41 de Jesus AR, Magalhaes A, Miranda DG *et al.* Association of type 2 cytokines with hepatic fibrosis in human *Schistosoma mansoni* infection. *Infect Immun* 2004; **72**: 3391–3397.
 - 42 Correa-Oliveira R, Malaquias LC, Falcao PL *et al.* Cytokines as determinants of resistance and pathology in human *Schistosoma mansoni* infection. *Braz J Med Biol Res* 1998; **31**: 171–177.
 - 43 Zouain CS, Falcao PL, Goes TS, Leite MF & Goes AM. *Schistosoma mansoni* PIII antigen modulates *in vitro* granuloma formation by regulating CD28, CTLA-4, and CD86 expression in humans. *Immunol Lett* 2004; **91**: 113–118.
 - 44 Falcao PL, Malaquias LC, Martins-Filho OA *et al.* Human Schistosomiasis mansoni: IL-10 modulates the *in vitro* granuloma formation. *Parasite Immunol* 1998; **20**: 447–454.
 - 45 Carneiro-Santos P, Martins-Filho O, Alves-Oliveira LF *et al.* Apoptosis: a mechanism of immunoregulation during human *Schistosomiasis mansoni*. *Parasite Immunol* 2000; **22**: 267–277.
 - 46 Booth M, Mwatha JK, Joseph S *et al.* Periportal fibrosis in human *Schistosoma mansoni* infection is associated with low IL-10, low IFN- γ , high TNF- α , or low RANTES, depending on age and gender. *J Immunol* 2004; **172**: 1295–1303.
 - 47 Araujo MI, de Jesus AR, Bacellar O, Sabin E, Pearce E & Carvalho EM. Evidence of a T helper type 2 activation in human schistosomiasis. *Eur J Immunol* 1996; **26**: 1399–1403.
 - 48 Porto AF, Santos SB, Alcantara L *et al.* HTLV-1 modifies the clinical and immunological response to schistosomiasis. *Clin Exp Immunol* 2004; **137**: 424–429.
 - 49 Chung F. Anti-inflammatory cytokines in asthma and allergy: interleukin-10, interleukin-12, interferon- γ . *Med Inflamm* 2001; **10**: 51–59.
 - 50 Ramalingam TR, Reiman RM & Wynn TA. Exploiting worm and allergy models to understand Th2 cytokine biology. *Curr Opin Allergy Clin Immunol* 2005; **5**: 392–398.
 - 51 Del Prete G, De Carli M, Almerigogna F, Giudizi MG, Biagiotti R & Romagnani S. Human IL-10 is produced by both type 1 helper (Th1) and type 2 helper (Th2) T cell clones and inhibits their antigen-specific proliferation and cytokine production. *J Immunol* 1993; **150**: 353–360.
 - 52 Mosmann TR, Cherwinski H, Bond MW, Giedlin MA & Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986; **136**: 2348–2357.
 - 53 Grindebacke H, Wing K, Andersson AC, Suri-Payer E, Rak S & Rudin A. Defective suppression of Th2 cytokines by CD4CD25 regulatory T cells in birch allergics during birch pollen season. *Clin Exp Allergy* 2004; **34**: 1364–1372.
 - 54 Pearce EJ & MacDonald AS. The immunobiology of schistosomiasis. *Nat Rev Immunol* 2002; **2**: 499–511.
 - 55 de Jesus AR, Silva A, Santana LB *et al.* Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. *J Infect Dis* 2002; **185**: 98–105.
 - 56 Montenegro SM, Miranda P, Mahanty S *et al.* Cytokine production in acute versus chronic human Schistosomiasis mansoni: the cross-regulatory role of interferon- γ and interleukin-10 in the responses of peripheral blood mononuclear cells and splenocytes to parasite antigens. *J Infect Dis* 1999; **179**: 1502–1514.
 - 57 Pearce EJ, Caspar P, Grzych JM, Lewis FA & Sher A. Down-regulation of Th1 cytokine production accompanies induction of Th2 responses by a parasitic helminth, *Schistosoma mansoni*. *J Exp Med* 1991; **173**: 159–166.
 - 58 Schmitz J, Thiel A, Kuhn R *et al.* Induction of interleukin 4 (IL-4) expression in T helper (Th) cells is not dependent on IL-4 from non-Th cells. *J Exp Med* 1994; **179**: 1349–1353.
 - 59 Hogan SP, Matthei KI, Young JM, Koskinen A, Young IG & Foster PS. A novel T cell-regulated mechanism modulating allergen-induced airways hyperreactivity in BALB/c mice independently of IL-4 and IL-5. *J Immunol* 1998; **161**: 1501–1509.
 - 60 Li J, Scott P & Farrell JP. *In vivo* alterations in cytokine production following interleukin-12 (IL-12) and anti-IL-4 antibody treatment of CB6F1 mice with chronic cutaneous leishmaniasis. *Infect Immun* 1996; **64**: 5248–5254.
 - 61 Sadick MD, Heinzel FP, Holaday BJ, Pu RT, Dawkins RS & Locksley RM. Cure of murine leishmaniasis with anti-interleukin 4 monoclonal antibody. Evidence for a T cell-dependent, interferon gamma-independent mechanism. *J Exp Med* 1990; **171**: 115–127.
 - 62 Scharton-Kersten T, Afonso LC, Wysocka M, Trinchieri G & Scott P. IL-12 is required for natural killer cell activation and subsequent T helper 1 cell development in experimental leishmaniasis. *J Immunol* 1995; **154**: 5320–5330.
 - 63 Patton EA, Brunet LR, La Flamme AC, Pedras-Vasconcelos J, Kopf M & Pearce EJ. Severe schistosomiasis in the absence of interleukin-4 (IL-4) is IL-12 independent. *Infect Immun* 2001; **69**: 589–592.
 - 64 Ghaemmaghami AM, Gough L, Sewell HF & Shakib F. The proteolytic activity of the major dust mite allergen Der p 1 conditions dendritic cells to produce less interleukin-12: allergen-induced Th2 bias determined at the dendritic cell level. *Clin Exp Allergy* 2002; **32**: 1468–1475.
 - 65 Traidl-Hoffmann C, Mariani V, Hochrein H *et al.* Pollen-associated phytoestrogens inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. *J Exp Med* 2005; **201**: 627–636.
 - 66 Barton GM & Medzhitov R. Toll-like receptor signaling pathways. *Science* 2003; **300**: 1524–1525.
 - 67 McGreal EP, Miller JL & Gordon S. Ligand recognition by antigen-presenting cell C-type lectin receptors. *Curr Opin Immunol* 2005; **17**: 18–24.
 - 68 MacDonald AS, Straw AD, Bauman B & Pearce EJ. CD8–dendritic cell activation status plays an integral role in influencing Th2 response development. *J Immunol* 2001; **167**: 1982–1988.
 - 69 Kane CM, Cervi L, Sun J *et al.* Helminth antigens modulate

- TLR-initiated dendritic cell activation. *J Immunol* 2004; **173**: 7454–7461.
- 70 Donnelly S, Dalton JP & Loukas A. Proteases in helminth- and allergen-induced inflammatory responses. *Chem Immunol Allergy* 2006; **90**: 45–64.
 - 71 Silveira MR, Nunes KP, Cara DC *et al.* Infection with *Strongyloides venezuelensis* induces transient airway eosinophilic inflammation, an increase in immunoglobulin E, and hyperresponsiveness in rats. *Infect Immun* 2002; **70**: 6263–6272.
 - 72 Dagoye D, Bekele Z, Woldemichael K *et al.* Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. *Am J Respir Crit Care Med* 2003; **167**: 1369–1373.
 - 73 Yazdanbakhsh M, Kreamsner PG & van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 2002; **296**: 490–494.
 - 74 Arruda LK & Santos AB. Immunologic responses to common antigens in helminthic infections and allergic disease. *Curr Opin Allergy Clin Immunol* 2005; **5**: 399–402.
 - 75 Borish L, Aarons A, Rumblyrt J, Cvietusa P, Negri J & Wenzel S. Interleukin-10 regulation in normal subjects and patients with asthma. *J Allergy Clin Immunol* 1996; **97**: 1288–1296.
 - 76 Macedo MS, Faquim-Mauro E, Ferreira AP & Abrahamsen IA. Immunomodulation induced by *Ascaris suum* extract in mice: effect of anti-interleukin-4 and anti-interleukin-10 antibodies. *Scand J Immunol* 1998; **47**: 10–18.
 - 77 Cooper PJ. Can intestinal helminth infections (geohelminths) affect the development and expression of asthma and allergic disease? *Clin Exp Immunol* 2002; **128**: 398–404.
 - 78 Lynch NR, Hagel IA, Palenque ME *et al.* Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. *J Allergy Clin Immunol* 1998; **101**: 217–221.
 - 79 Terrazas LI, Walsh KL, Piskorska D, McGuire E & Harn DA Jr. The schistosome oligosaccharide lacto-N-neotetraose expands Gr1(+) cells that secrete anti-inflammatory cytokines and inhibit proliferation of naive CD4(+) cells: a potential mechanism for immune polarization in helminth infections. *J Immunol* 2001; **167**: 5294–5303.
 - 80 Velupillai P, dos Reis EA, dos Reis MG & Harn DA. Lewis(x)-containing oligosaccharide attenuates schistosome egg antigen-induced immune depression in human schistosomiasis. *Hum Immunol* 2000; **61**: 225–232.
 - 81 van den Biggelaar AH, Rodrigues LC, van Ree R *et al.* Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. *J Infect Dis* 2004; **189**: 892–900.
 - 82 Williams ME, Montenegro S, Domingues AL *et al.* Leukocytes of patients with *Schistosoma mansoni* respond with a Th2 pattern of cytokine production to mitogen or egg antigens but with a Th0 pattern to worm antigens. *J Infect Dis* 1994; **170**: 946–954.
 - 83 Fowler S & Powrie F. Control of immune pathology by IL-10-secreting regulatory T cells. *Springer Semin Immunopathol* 1999; **21**: 287–294.
 - 84 Royer B, Varadarajalou S, Saas P, Guillosson JJ, Kantelip JP & Arock M. Inhibition of IgE-induced activation of human mast cells by IL-10. *Clin Exp Allergy* 2001; **31**: 694–704.
 - 85 Medeiros M Jr, Almeida MC, Figueiredo JP *et al.* Low frequency of positive skin tests in asthmatic patients infected with *Schistosoma mansoni* exposed to high levels of mite allergens. *Pediatr Allergy Immunol* 2004; **15**: 142–147.
 - 86 Lu FM, Chou CC, Chiang BL & Hsieh KH. Immunologic changes during immunotherapy in asthmatic children: increased IL-13 and allergen-specific IgG4 antibody levels. *Ann Allergy Asthma Immunol* 1998; **80**: 419–423.
 - 87 Akdis M, Blaser K & Akdis CA. T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. *J Allergy Clin Immunol* 2005; **116**: 961–968; quiz 9.
 - 88 Scrivener S, Yemaneberhan H, Zebeignus M *et al.* Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet* 2001; **358**: 1493–1499.
 - 89 Groux H, O'Garra A, Bigler M *et al.* A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; **389**: 737–742.
 - 90 Inobe JI, Chen Y & Weiner HL. *In vivo* administration of IL-4 induces TGF-beta-producing cells and protects animals from experimental autoimmune encephalomyelitis. *Ann N Y Acad Sci* 1996; **778**: 390–392.
 - 91 Hansen G, McIntire JJ, Yeung VP *et al.* CD4(+) T helper cells engineered to produce latent TGF-beta1 reverse allergen-induced airway hyperreactivity and inflammation. *J Clin Invest* 2000; **105**: 61–70.
 - 92 Oh JW, Seroogy CM, Meyer EH *et al.* CD4 T-helper cells engineered to produce IL-10 prevent allergen-induced airway hyperreactivity and inflammation. *J Allergy Clin Immunol* 2002; **110**: 460–468.
 - 93 Jutel M, Akdis M, Budak F *et al.* IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003; **33**: 1205–1214.
 - 94 Bellinghausen I, Klostermann B, Knop J & Saloga J. Human CD4+CD25+ T cells derived from the majority of atopic donors are able to suppress TH1 and TH2 cytokine production. *J Allergy Clin Immunol* 2003; **111**: 862–868.
 - 95 Elliott DE, Li J, Blum A *et al.* Exposure to schistosome eggs protects mice from TNBS-induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G385–G391.
 - 96 Taylor A, Verhagen J, Akdis CA & Akdis M. T regulatory cells in allergy and health: a question of allergen specificity and balance. *Int Arch Allergy Immunol* 2004; **135**: 73–82.
 - 97 McKee AS & Pearce EJ. CD25+CD4+ cells contribute to Th2 polarization during helminth infection by suppressing Th1 response development. *J Immunol* 2004; **173**: 1224–1231.
 - 98 Elliott DE, Setiawan T, Metwali A, Blum A, Urban JF Jr & Weinstock JV. *Heligmosomoides polygyrus* inhibits established colitis in IL-10-deficient mice. *Eur J Immunol* 2004; **34**: 2690–2698.
 - 99 Wohlleben G, Trujillo C, Muller J *et al.* Helminth infection modulates the development of allergen-induced airway inflammation. *Int Immunol* 2004; **16**: 585–596.
 - 100 Akbari O, Stock P, Meyer E *et al.* Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. *Nat Med* 2003; **9**: 582–588.
 - 101 Zaccane P, Fehervari Z, Jones FM *et al.* *Schistosoma mansoni* antigens modulate the activity of the innate immune response and prevent onset of type 1 diabetes. *Eur J Immunol* 2003; **33**: 1439–1449.
 - 102 Fiorentino DF, Bond MW & Mosmann TR. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *J Exp Med* 1989; **170**: 2081–2095.