Schistosoma mansoni Infection Modulates the Immune Response against Allergic and Auto-immune Diseases

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Chronic Schistosoma mansoni *infection leads to a type 2-immune response with increased production of interleukin (IL-10). Evidence indicates chronic exposure to* S. mansoni *down regulates the type 1 immune response and prevents the onset of Th1-mediated diseases such as multiple sclerosis, diabetes mellitus and Cronh's disease. Furthermore, our own studies have revealed that chronic exposure to* S. mansoni *also down regulates atopic disease, Th2-mediated diseases. Our studies show an inverse association between the skin prick test reactivity and infection with* S. mansoni *and show the severity of asthma is reduced in subjects living in an endemic area of* S. mansoni. *Moreover, we hypothesize the mechanisms involved in the modulation of inflammatory response in atopic individuals, is likely dependent on IL-10 production, an anti-inflammatory cytokine elevated during helminth infections. Patients with asthma and helminth infections produced less IL-5 than patients with asthma without helminth infections, and this down regulation could, in part, be mediated by IL-10. In conclusion, helminthic infections, through induction of regulatory mechanisms, such as IL-10 production, are able to modulate the inflammatory immune response involved in the pathology of auto-immune and allergic disease.*

Key words: *Schistosoma mansoni* - alergic disease - asthma - auto-immune diseases

Strong support exists, that the development of allergies and auto-immunity are influenced by both genetic background and environment/lifestyle (Herz et al. 2000, Weinstock et al. 2002). Among the environmental factors, low socio-economic status (Patterson et al. 1996, von Mutius et al. 1994, Staines et al. 1997a, Blanchard et al. 2001), and the presence of infections have been implicated in protecting people against allergic (Lynch et al. 1993, Araujo et al. 2000, Cooper et al. 2003, Medeiros et al. 2003) and autoimmune diseases (Cooke et al. 1999, Kurtzke 2000, La Flamme et al. 2003). Recently, there has been growing interest in the hypothesis that infections might play a role in preventing or suppressing auto-immune and allergic disorders as studies have revealed that the prevalence of allergies and auto-immune diseases are increasing in developed countries, in conjunction with improved hygienic conditions. Examples of this can be seen in studies on multiple sclerosis, Crohn's disease, atopic diseases, and type I diabetes.

There is a lower prevalence of multiple sclerosis in tropical areas compared to subtropical developed regions (Sanchez et al. 2000, Callegaro et al. 2001). In Brazil, the incidence of multiple sclerosis is low, however within the country, São Paulo – a big city, in which the socio-economic status has been improved, the incidence of the disease increased three time from 1990 to 1997 (Callegaro et al. 2001). In addition, in South Lower Saxony, Germany the incidence of multiple sclerosis doubled from 1969 to 1986 (Poser et al. 1989), and increased four-fold in Japan over the last two decades (Itoh et al. 2003). As well, Crohn's disease is more common in highly industrialized countries and less prevalent in Asia, Africa and South America (Elliott et al. 2000). The incidence of the disease tripled in Europe from 1950 to 1990 (Farrokhyar et al. 2001), appearing to correlate with decreasing prevalence of helminthic infections (Elliott et al. 2000). The incidence of type I diabetes among Pakistanis who migrated to the United States is the same as the rate among Americans and ten times higher than the incidence of the disease in Pakistan (Bodansky et al. 1992, Staines et al. 1997b, Bach 2002). Although better ascertainment of data could have artificially affected the prevalence of these immune-based diseases, there is a concomitant decrease in prevalence of infectious disease in developed countries. The prevalence of rheumatic fever, measles, mumps and tuberculosis decreased from 1950 to 2000, while there was an increase in prevalence of allergic and auto-immune diseases (Bach 2002). In fact, the prevalence of asthma, allergic rhinitis and eczema doubled in Swedish schoolchildren between 1979 and 1991 (Aberg et al. 1995).

Of recent interest are studies looking at the association of helminths with other diseases in order to evaluate if the pathology of many chronic infections and autoimmune diseases, could be regulated by the type 2 immune response induced by helminth infections.

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THE IMMUNE RESPONSE TO PARASITE INFECTIONS

The immune response to intestinal helminths is characterized by a polarized Th2 response with an elevated production of interleukin (IL-4, IL-5, IL-13, IL-10). The role of these cytokines in protecting humans against parasite infections is still not well understood. High levels of *Schistosoma mansoni*-specific IgE correlated with protection against re-infection in subjects living in an endemic area of *S. mansoni* (Demeure et al. 1993). Studies performed in mice or rats infected with geo-helminths suggest that besides the induction of IgE synthesis, IL-4, in association with other cytokine such as IL-3, IL-9, and IL-13, stimulates the production of mast cells (Comoy et al. 1998, Else & Finkelman 1998, Keane-Myers et al. 1998, Urban et al. 1998). Once stimulated, these cells release inflammatory mediators capable of damaging the parasite membrane, stimulating secretion of mucus and enhancing the intestinal contractility in order to expulse the parasite. Considering the high prevalence of parasite infections, we conclude that they are so well adapted to the host that the immune response is not able to destroy them.

S. mansoni infection in mice models lead to an initial Th1 response with production of interferon-γ (IFN-γ), that is followed by a Th2 response induced by the parasite eggs' antigens, that stimulates IL-10 production (Grzych et al. 1991, Pearce et al. 1991). In humans the immune response in the acute phase is also associated with Th1 response with increased production of tumor necrosis factor (TNF-α) and IFN-γ (de Jesus et al. 2002), while in the chronic phase the immune response is the Th2 type, with elevated levels of IL-4, IL-5, and IL-10 and decreased levels of IFN-γ (Araujo et al. 1994, Malaquias et al. 1997, Joseph et al. 2004).

THE ROLE OF PARASITE INFECTION ON THE SUSCEPTIBILITY OF AUTO-IMMUNE DISEASES

While the pathogenesis of auto-immune diseases mediated by T cells involve the type I immune response with production of IFN-γ and TNF-α, chronic *S. mansoni* infection induces a strong type 2 immune response with increased production of IL-10. IL-10, described in 1989, by Fiorentino et al., is a cytokine produced primarily by monocytes/macrophages in the natural immune response, by Th2 type cells in the mice model, and by both Th1 and Th2 type cells in humans. It possesses the ability to inhibit both, the cellular proliferation and synthesis of cytokines by Th1 and Th2 cells (Del Prete et al. 1993). IL-10 is able to inhibit the production of pro-inflammatory mediators such as IFN-γ, TNF-α and NO (Royer et al. 2001). Studying the role of IL-10 in the immune response of *S. mansoni* chronically infected subjects, we demonstrated that in peripheral blood mononuclear cells (PBMC) cultures stimulated in vitro with *S. mansoni* antigens, neutralization of endogenous IL-10 with the monoclonal Ab anti-IL-10, restored IFN-γ production (Araujo et al. 1996).

In recent years, due to the immuno-modulatory properties of IL-10 and its induction by helminthic infections, researchers have evaluated the influence of *S. mansoni* infection on the immune response and development of a number of infections and autoimmune diseases. Previously, our group showed that infection with *S. mansoni* affects the immune response to vaccine antigen. Individuals vaccinated with tetanus toxoid antigen and who were infected with *S. mansoni* produced the type 2 cytokine, IL-4, rather than IFN-γ in response to restimulation in vitro, while uninfected vaccinated individuals in vitro, produced type 1 cytokine, IFN-γ (Sabin et al. 1996). The down-regulation of the type 1 response by *S. mansoni* infection was further supported by an experimental study, which showed that infection with this parasite prevented the development of the insulin dependent diabetes mellitus in genetically susceptible non-obese diabetic (NOD) mice (Cooke et al. 1999). In this study injection of *S. mansoni* eggs into 5 week-old NOD mice totally inhibited the development of the disease, and latter it was demonstrated that soluble extract of *S. mansoni* worm or egg completely prevented the onset of type 1 diabetes in NOD mice (Zaccone et al. 2002). Since insulin dependent diabetes mellitus is mediated by a Th1 response against beta cell antigens, it is probable that the parasite antigens induce IL-10 production and prevent the disease by switching the immune response toward the Th2 type. Indeed, T cells from diabetes-protected mice make IL-10 after re-stimulation in vitro with *S. mansoni* antigen (Zaccone et al. 2002).

S. mansoni infection also decreased tissue damage and clinical manifestation of others Th1-mediated autoimmune diseases such as multiple sclerosis and Crohn's disease. In a mice model to study experimental autoimmune encephalite (EAE), a multiple sclerosis like disease, it was demonstrated that infection with *S. mansoni* delays the onset of the disease and prevents inflammation in the central nervous system (La Flamme et al. 2003, Sewell et al. 2003). Attenuation of the clinical course of EAE was followed by a reduction in the synthesis of pro-inflammatory mediators, such as IFN-γ, TNF-α and NO, by spleen and central nervous cells in vitro, while the levels of IL-4 and IL-5 in plasma were, as predicted, higher in the parasite-infected group (La Flamme et al. 2003). Although the production of IL-10 did not differ between mice that were infected or not with *S. mansoni* in this study, in the EAE *S. mansoni* ova immunization lead to production of IL-10 and TGF-β, in addition to IL-4, by spleen cells in vitro, and decreased IFN-γ synthesis (Sewell et al. 2003).

IFN-γ has been shown to exacerbate multiple sclerosis (Panitch et al. 1987, Panitch 1992), and in mice model, the schistosome ova-induced Th2 response and consequent inhibition of IFN-γ production was, likely, responsible for the amelioration of EAE (Sewell et al. 2003). Moreover, the direct association between Th2 cytokines and helminth ova-induced protection from EAE was further suggested by the absence of any *S. mansoni* ova-induced protection from EAE in STAT6-deficient animals, which experience a more severe clinical course of EAE (Chitnis et al. 2001). Signal transducer and activator of transcription (STAT)-6 is a important protein in the development of Th2 cells (Hou et al. 1994, Schindler et al. 1994).

Crohn's desease is also mediated by an overly active Th1 inflammatory response and it is characterized by dysmotility of the gut as a result of chronic intestinal inflammation. In the trinitrobenzesulfonic acid (TNBS) murine and rat model of colitis the colonic inflammation is

due to an infiltration of over-IFN-γ-producing CD4+ T cells (Neurath et al. 1995). Concurrent infection with *S. mansoni* has been shown to significantly attenuate TNBS induced colitis in rats (Moreels et al. 2004) and that exposure to eggs of *S. mansoni* protects mice from developing TNBS colitis (Elliott et al. 2003). In humans with Crohn's disease and ulcerative colitis, induction of a Th2 immune response by administration of eggs from the porcine whipworm, *Trichuris suis*, lead to remission in 86% (Summers et al. 2003).

INFLUENCE OF PARASITE INFECTION ON THE DEVELOPMENT OF ALLERGIC DISEASES

In addition to the down regulation of the type 1 immune response involved in the pathogenesis of auto-immune diseases, parasites have also been shown to influence the type 2-mediated allergic diseases development. Studies performed by Lynch and collaborators have both demonstrated that people living in an endemic area for *Ascaris lumbricoides* have a decreased reactivity to the immediate hypersensitivity skin prick tests, and that treatment with anti-helminthic drugs resulted in increased frequency of positive skin prick tests and aeroallergen-specific IgE production (Lynch et al. 1993, 1998). Supporting this idea, we evaluated whether immediate hypersensitivity reaction and aeroallergen specific IgE levels are influenced by the presence of *S. mansoni*, taking into account the potential influences of age and gender on this association. We showed that the proportion of patients with a positive skin test for at least one of 7 antigens tested was approximately 5 times greater in the uninfected group (24.3%) than in the group with more than 200 eggs of *S. mansoni* per gram of feces (4.8%). There were no statistically significant differences in the total and *Dermatophagoides pteronyssinus*-specific IgE levels between the two groups. In the unadjusted analysis of the odds of atopy (defined as a positive test for at least one of the antigens), the odds were 6.3 (95% confidence interval = 1.4-27.6; p = 0.01) times greater for the uninfected group compared to the group with a parasite load > 200 eggs/g of feces (Table I). This association did not change significantly after adjusting for the potential effects of age and gender (Odds ratio = 7.0; 95% confidential interval = 1.6-31.1; p = 0.01) (Araujo et. 2000).

Epidemiological, clinical and immunological studies have been performed in the village of Caatinga do Moura, an endemic area of schistosomiasis in NE Brazil, for the last 15 years. Despite continuous programs of mass therapy against schistosomiasis, the prevalence of *S. mansoni* in individuals age ranged from 5 to 30 years is 48%. Due to the treatment, the morbidity has decreased and most of the individuals infected have a light intestinal *S. mansoni* infection (less than 200 eggs/g of feces). Other helminthic infection, such as *A. lumbricoides, Ancilostoma duodenale,* and *Strongiloides stercoralis* are found in less than 5% of this population.

To evaluate if people from the *S. mansoni* endemic area are exposed to dust mite, a case-control study was performed analyzing asthmatic patients living in Caatinga do Moura and in Lages do Batata, a village located close to Caatinga do Moura, in which there is no transmission of *S. mansoni*. High prevalences of dust mites were seen in both areas, and the levels of mite antigen was above that required to sensitize (2 µg/ml). *D. pteronyssinus* was the more prevalent mite specie (above 70% of the houses in both areas) followed by *D. farinae* and *Blomia tropicalis.* Although with increased exposure to mite antigens, only 19% (4/21) of asthmatic patients from Caatinga do Moura had a positive skin prick test to aeroallergens, while the prevalence of positive skin test to aeroallergens was 76.2% (16/21) in age- and sex-matched asthmatic patients living in Lages do Batata. Therefore, despite exposure to mite allergens, there were significantly fewer positive skin prick tests in asthmatics from the endemic area of *S. mansoni* than in those from a rural non-endemic area.

Although there is a consensus that helminthic infections decrease skin reactivity to aeroallergens, there was no well-controlled study showing that helminthic infections interfere with the frequency or severity of asthma (Araujo et al. 2000, Lynch et al. 1993, 1998). In the epidemiological studies above, the prevalence of asthma has only been evaluated through a questionnaire with no clinical examination or pulmonary function tests that could support the data. We tested our hypothesis that infection by *S. mansoni* interferes with asthma severity through a study in the endemic area of Caatinga do Moura. Using the ISAAC questionnaire we identify individuals with history of asthma in the endemic area and an age-and sex-matched asthmatic controls from an urban non-endemic area, all of them with the same socio-economic status. We demonstrated that people from the endemic area had a

TABLE I

Characteristics of individuals living in the *Schistosoma mansoni* endemic area, Caatinga do Moura, BA, Brazil, according to parasitic load

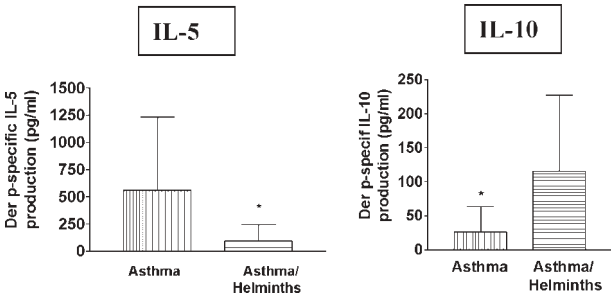
Subjects	Uninfected (n = 133)	> 200 eggs/g stool (n = 42)	p value
Age (Mean ± SD)	20.2 ± 11.9	18.0 ± 9.7	0.60
Gender (% male)	46.6	52.4	0.64
Symptoms of asthma or rhinitis (% positive)	44.4	38.1	0.59
Skin Test (% positive)	24.1	4.8	0.01
Total IgE (IU)			
(Mean±SD)	964 ± 1392	1252 ± 1318	0.34
Median	265	699	
Aeroallergen-specific IgE (% positive)	41.4	14.3	0.10

more severe asthma as assed by: (a) a questionnaire that include questions about presence of asthmatic symptoms, such as, cough, wheezing, and dyspnea, as well as, use of anti-asthmatic drugs, (b) physical examination, and (c) pulmonary function tests (Table II).

Although high levels of type 2 cytokines, such as IL-10, are found in *S. mansoni* infection, little to no IFN-γ is produced (Araujo et al. 1996). It is well known that type 2 cytokines regulate the production of IFN-γ (Fiorentino et al. 1989). Recent studies have shown that during helminthiasis, Lacto N tetrose (LTNT), a sugar present in many kinds of helminths, and lacto N fucopentose (LNFP III), found in *S. mansoni*, act as inducing factors of both the type 2 response and production of IL-10 (Velupillai et al. 2000). The ability of IL-10 to then inhibit the release of histamine and other mediators by cord blood mast cells (Royer et al. 2001) could therefore be the mechanism behind the inhibition of the skin prick test reaction in schistosomiasis. A study evaluating children living in an endemic area of *S. haematobium* in Africa showed high levels of IL-10 and a decreased skin prick tests response suggesting that IL-10 may be involved in that process (van den Biggelaar et al. 2000). Therefore, we hypothesised that IL-10, produced during *S. mansoni* infection, down regulates the immediate immune response in atopic individuals by inhibiting IL-4 and IL-5 production.

The inhibition of the cutaneous response to aeroallergens and the decrease in asthma severity observed in individuals from *S. mansoni* endemic areas could be explained by: (1) competition between *S. mansoni*-induced polyclonal IgE, and aeroallergen specific IgE for the high affinity receptors present on mast cells; (2) the inhibition of aeroallergen specific IgE synthesis by elevated levels of polyclonal IgE; and (3) high levels of regulatory cytokines produced during helminthic infections, such as IL-10, that could suppress the immune response to non-related antigens. Our data (Araujo et al. 2000) shows that there is no significant difference in total and Der p 1-specific IgE production between *S. mansoni* infected subjects with low or high parasite load, which does not support the first two hypothesis. Therefore, we have tested the third theory.

Evaluating the immune response of asthmatic individuals infected with helminths, including *S. mansoni*, living in an endemic area, compared to uninfected asthmatic subjects, we observed that PBMC of asthmatic individuals infected with helminths, after re-stimulation in vitro with *D. pteronyssinus* antigen, produced lower levels of the Th2-cytokine, IL-5, and higher levels of IL-10 in comparison with asthmatic uninfected individuals (Figure). This data could indicate that the influence of helminth infections and, in particularly, *S. mansoni*, to decrease atopy and diminish manifestation of asthma is due to the down regulation of type 2 immune response mediated predominantly by IL-10.



Interleukin (IL) – IL-5 and IL-10 levels (pg/ml) in *Dermatophagoiodes pteronyssinus*-stimulated peripheral blood mononuclear cells cultures of asthmatic patients infected or not with helminths, including *Schistosoma mansoni* (n = 10); * $p < 0.05$

CONCLUSION

In light of the data presented and in accordance with the literature, we found a negative association between allergic diseases and helminthic infection. Helminthic infections are highly prevalent in the world and many infected people are additionally, exposed to other infections and diseases, which leads to the question: Does the highly polarized type 2 immune response, due to chronic *S. mansoni* infections, interfere with the immune response and clinical course of other concomitant diseases such as auto-immune and allergic diseases, which, respectively, induce the type 1 and type 2 response? Observations from our group, demonstrate that individuals living in an endemic areas for *S. mansoni* do not develop severe asthma. A controlled study of the mechanism by which atopic patients, living in endemic areas of helminthic infections do not respond to the skin prick test to aeroallergens and have less severe symptoms of asthma, could lead to the development of new perspectives of prevention and therapy for asthma.

It seems that *S. mansoni* infection could mediate protection against allergic and auto-immune disorders. Iden-

TABLE II

Evaluation of asthma severity during a one-year follow-up study in asthmatic subjects, from two different low socioeconomic status areas (Group I = rural *Schistosoma mansoni* endemic area; Group II = urban, non-endemic area) in state of Bahia, Brazil

Clinical manifestation	Group I (n = 75)	Group II (n = 80)	p
Bronchial asthma symptoms (%/n)	16.6/14	84.0/47	0.0001
Anti-asthmatic drugs use (%/n)	16/12	72.2/58	0.0001
Physical exam abnormal findings (%/n)	10.6/8	38.8/31	0.0001

n: total of evaluations in 21 subjects in each group

tification of parasite molecules that might induce protection against auto-immune and allergic diseases is and will be a challenge to researchers who work in this field.

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