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Schistosoma mansoni antigen-driven interleukin-10 production in infected asthmatic individuals

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ABSTRACT

Asthmatics infected with *Schistosoma mansoni* have a less severe course of asthma and an inhibition of the Th2 inflammatory response that seems to be mediated by interleukin (IL-10). The objective of this study was to evaluate the capacity of some *S. mansoni* antigens to stimulate IL-10 production in vitro by cells of asthmatic infected individuals. Peripheral bloods mononuclear cells were stimulated with the *S. mansoni* recombinant antigens Sm22.6, Sm14, P24, and PIII antigen. IL-10 was measured in the supernatants of cultures. As the recombinant antigens were cloned in *Escherichia coli*, we blocked contaminant endotoxin with polymyxin B added to the cultures. We demonstrated that all antigens used drove high production of IL-10 in *S. mansoni* infected individuals (n = 13, 408 ± 514 and 401 ± 383 pg/ml, 484 ± 245 pg/ml, 579 ± 468 pg/ml, respectively). In asthmatics infected with *S. mansoni* (n = 21) rP24 induced higher levels of IL-10 (565 ± 377 pg/ml) when compared to PIII, rSm14 and rSm22.6 (184 ± 209 pg/ml; 292 ± 243 pg/ml; 156 ± 247 pg/ml, respectively). Conclusion: the *S. mansoni* antigens evaluated in this study stimulated IL-10 production by cells from infected individuals and therefore they have the potential to be used as a modulator of the inflammatory response in asthma.

Key words: *Schistosoma mansoni* recombinant proteins - *S. mansoni* antigens - interleukin-10

Evidences has accumulated that helminth infections protect against the development of allergy. For instance Lynch et al. (1993) demonstrated an inhibition of the skin prick test response to aeroallergens in individuals infected with *Ascaris lumbricoides,* and that the anti-helminthic treatment resulted in an increase in the prevalence of positive skin tests. These findings were supported by others authors (van den Biggelaar et al. 2000) and in the last few years some studies have demonstrated that *Schistosoma mansoni* infection not only suppresses the skin prick test response, but modulates asthma severity (Araujo et al. 2000, van den Biggelaar et al. 2000, 2001, 2004, Medeiros et al. 2003).

Asthma is a multifatorial disease that results from genetic predisposition, exposure to allergens and

environmental factors. While some environmental factors precipitate the development of asthma, others seem to be protective. This is the case of helminth infections, particularly *S. mansoni*, which through the modulation of the inflammatory response prevent asthma (Medeiros et al. 2003, Araujo et al. 2004). Studying the mechanisms behind the protection against allergy, Araujo et al. (2004) found that interleukin (IL-10) seems to play an important role in modulating the Th2 inflammatory response involved in the pathology of allergic diseases. Supporting this idea, Bigellar et al. showed high levels of this cytokine in individuals infected with *S. haematobium* who did not respond to skin test to aeroallergens (van den Biggelaar et al. 2000).

It is well known that the acute phase of *S. mansoni* infection is characterized by a strong Th1 inflammatory response that evolues to a parasite antigen-driven Th2 response cronically (Grzych et al. 1991, Pearce et al. 1991). It is also known that this down modulation is mediated by *S. mansoni* antigen-driven IL-10 production (Sher et al. 1991). IL-10 is an anti-inflammatory cytokine produced by a variety of cells such as macrophages, T $CD4^+$, T $CD8^+$ and T $CD4^+$ $CD25^+$ Cells. While in the chronic phase of *S. mansoni* infection IL-10 is produced in high levels (Gazzinelli & Colley 1992, Williams et al. 1994, Araujo et al. 1996), in asthma, despite the immune response being the Th2 type, the production of IL-10 is impaired. Studies have shown that IL-10 is protective against asthma, and increases in levels during immunotherapy (Akdis et al. 1998). The protective role of IL-10 in asthma include the induction of IgG4 (Jeannin et al. 1998), down-modulation of Th2 cytokine production (Araujo et al. 2004) and the inhibition of histamine and other inflammatory mediators by mast cells (Royer et al. 2001).

Considering the potential of *S. mansoni* antigens in protecting against allergic diseases, this study aimed to evaluate some parasite antigens regarding their ability to induce IL-10 production. The *S. mansoni* antigens evaluated were Sm22.6, a soluble protein from the tegument, present in all life cycle of the worm with the exception of egg (Jeffs et al. 1991). Sm14 is a fatty-acid binding protein from the adult worm (Moser et al. 1991). PIII is a fraction of *S. mansoni* soluble adult worm antigen (SWAP) (Hirsch & Goes 1996). This antigen is associated with down-regulation of granuloma formation in vitro (Oliveira et al. 1999) and P24, fraction of PIII that also modulates granuloma size in murine models (Zouain et al. 2000, 2002).

MATERIALS AND METHODS

This study evaluated the ability of some *S. mansoni* antigens in inducing IL-10 production by peripheral blood mononuclear cells (PBMC) of individuals chronically infected with *S. mansoni* living in an endemic area in Bahia Brazil. It was included 34 individuals from 6 to 40 years of age infected with *S. mansoni* and other helminths, such as *A. lumbricoides*, *Trichuris trichiura,* and hookworm. From these individuals 21 had asthma. The Table shows demographic data and *S. mansoni* parasite burden in the two groups.

TABLE

Demographic data from individuals infected with *Schistosoma mansoni* asthmatics and nonasthmatics

Subjects	Infected subjects (n = 13)	Asthmatic infected subjects (n = 21)	p value
Median age (y)	13 (6-40)	11 (6-40)	> 0,05
Gender (% of male)	58%	46.1%	> 0,05
S. mansoni (egg/g feces)	330 ± 298	52 ± 54	< 0,05

The Ethical Committee of the Climério de Oliveira Hospital/Federal University of Bahia approved the present study, and an informed consent was obtained from all study participants or their legal guardians.

S. mansoni antigens - The antigens used in this study included three recombinant proteins, Sm22.6, Sm14, and P24, a fraction of *S. mansoni* soluble adult worm antigen (SWAP) obtained by anionic chromatography (FPLC), named PIII, besides SWAP and SEA (soluble egg antigen). The proteins were provided by the Institute of Biological Science, Departament of Biochemistry and Immunology, UFMG, Brazil. The recombinant proteins were cloned in *E. coli* and they were tested for lipopolysaccharide (LPS) contamination using a commercially available LAL Chromogenic Kit (CAMBREX). The levels of LPS were bellow 0.25 ng/ml (Sm22.6 = 0.132 ng/ml, Sm14 = 0.210 ng/ml and P24 = 0.135 ng/ml).

Cell culture and cytokine measurement - PBMC were obtained through the Ficoll-Hypaque gradient and adjusted to a concentration of 3 x 10^6 cells/ml in RPMI 1640 containing 10% of normal human serum (AB^+, heat-inativated), 100 U/ml penicillin, 100 mg/ml streptomycin, 2 mM L-glutamine, 30 mM HEPES (all from Life technologies GIBCO BRL, Gaithersburg, MD). Cells were cultured in vitro with antigens Sm22.6, Sm14, P24, PIII, SWAP, and SEA (10 µg/ml) in the presence or absence of Polymyxin B (10µg/ml) in order to neutralize the effect of LPS in induce cytokine production. Cultures stimulated with LPS (0.15 ng/ml) and with the mitogen phytohemaglutinin (PHA, at a final dilution of 1:100) were used as controls. Cultures stimulated with LPS were incubated at 37ºC, 5% CO_2 for 6, 12, 24, and 48 h, while cultures stimulated with *S. mansoni* antigens and PHA

were incubated for 48 h. After incubation, the supernatants were collected and maintained at 20ºC, for later measurement of IL-10. Levels of IL-10 were determined by an ELISA sandwich technique, using commercially available kits (R&D Systems), and the results were expressed in picograms per milliliter based on a standard curve.

Addition of polymyxin B to the cultures - Suspension of PBMC ($3x10^6$ cells/ml) were pre-incubated with Polymyxin B (Calbiochem, Germany) in the concentration of 10 and 20 µg/ml for 30 min at 37ºC, 5% CO_2. They were then incubated with the different recombinant antigens (10 µg/ml) or LPS (0.14 ng/ml) and the cultures were incubated for 6 to 48 h as described above. Polymyxin B (10 or 20 µg/ml) was also added to cultures every 12 h.

Statistical analysis - Wilcoxon matched pairs test were used to compare the levels of IL-10 in supernatants of PBMC cultures with or without Polymyxin B. Kruskal-Wallis test was used to compare the levels of Il-10 induced by the different antigens. Statistical significance was established at the 95% confidence interval.

RESULTS

Effect of PMB in block the effect of LPS in induce IL-10 production - The production of IL-10 in 6, 12, 24, and 48 h-cultures stimulated with LPS in the presence or absence of PMB is shown in Fig. 1. Compared to cultures without PMB, there was a significant reduction in the levels of IL-10 by addition of this antibiotic to the cultures in all time-points evaluated. The mean levels of IL-10 in cultures without PMB were 314 ± 341 pg/ml, 469 ± 364 pg/ml and 317 ± 378 pg/ml at 12, 24, and 48 h of cultures, and after the addition of PMB the levels decreased to 15.6 ± 9.5 pg/ml (p = 0.06), 38 ± 55 pg/ml (p = 0.03) and 15,6 ± 9.5 pg/ml (p = 0.03). The reductions in IL-10 production in cultures of 12, 24, and 48 h were 95.0, 91.2, and 95.1%, respectively.

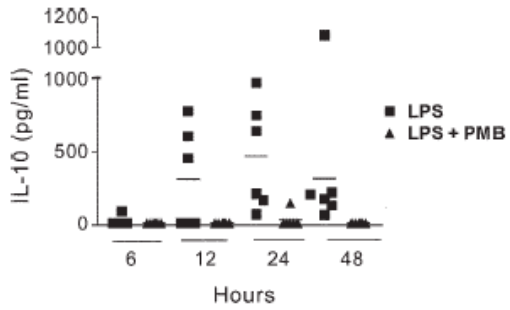

Fig. 1: effect of Polymyxin B on LPS-induced cytokine production in vitro. PBMCs of individuals chronically infected with *Schistosoma mansoni* (n = 6) were cultured with LPS (0.15 ng/ml) in the presence or absence of Polymyxin B (PMB, 10 µg/ml). IL-10 was measured using a sandwich ELISA technique. There was a significant reduction in the levels of IL-10 when PMB was added to the cultures ($p < 0.05$).

Polymyxin B was used in the concentration of 10 and 20 µg/ml of cultures and similar levels of reduction in cytokine production were observed (data not shown). Therefore, we decided to use the lower concentration of PMB (10 µg/ml of cultures) in cultures stimulated with *S. mansoni* recombinant antigens. We tested the viability of cells in cultures with Polymyxin B using trypan blue stain and observed that the viability was about 98%.

Production of IL-10 in cultures stimulated with S. mansoni antigens - The IL-10 production induced by *S. mansoni* antigens is shown in Fig. 2. We observed that all antigens evaluated in this study induced IL-10 production in infected individuals (Fig. 2A). The level of this cytokine were 408 ± 514 pg/ml to rSm22.6, 401 ± 383 pg/ml to rSm14, 484 ± 245 pg/ml to PIII and 579 ± 468 pg/ml to rP24 antigen. There was no significant difference in the levels of IL-10 induced by the different antigens (p > 0,05). In cultures stimulated with SWAP and SEA the levels of IL-10 were 140 ± 291 pg/ml and 46 ± 43 pg/ml, respectively).

Fig. 2B shows the levels of IL-10 production in asthmatic infected individuals. Similarly, all antigen induced IL-10 production. The levels of this cytokine in cultures stimulated with rSm22.6, rSm14, PIII, and rP24 were 156 ± 247 pg/ml, 292 ± 243 pg/ml, 184 ± 209 pg/ml, and 565 ± 377 pg/ml. The antigen rP24 induced higher levels of IL-10 compared to the other antigens ($p < 0.05$). All antigens induced higher levels of IL-10 in comparison with SWAP and SEA ($p < 0,001$).

Levels of IL-10 were below the detection limit in un-stimulated cultures, and these cytokines were detected in high levels (≥ 1500 pg/ml) in the supernatants of PBMC cultures stimulated with PHA (not shown).

DISCUSSION

S. mansoni infection seems to be protective against asthma (Medeiros et al. 2003, Araujo et al. 2004). Using

mice models of *S. mansoni* infection it has been demonstrated that this parasite also protects against the development of auto-immune disease such as diabetes, experimental auto-immune encephalopathy, and Crohn's disease (Cooke et al. 1999, Elliott et al. 2003, La Flamme et al. 2003, Sewell et al. 2003, Zaccone et al 2003). Some of these studies suggest that IL-10 is a key cytokine involved in the modulation of the inflammatory immune response observed in these diseases. IL-10 is produced by cells of individuals chronically infected with *S. mansoni* and there are some *S. mansoni* antigens able to induce IL-10 production in vitro. On the other hand, there is impaired production of IL-10 in asthmatic individuals, even when their cells are stimulated in vitro with dust mite antigens (Araujo et al. 2004) and LPS (Borish et al. 1996, Tomita et al. 2002). In this study we evaluated the ability of some schistosome vaccine candidate antigens, ie, Sm14, Sm 22.6, p24, and PIII in induce IL-10 production by cells from asthmatic infected individuals. Some of these antigens protect mice against liver fibrosis, the major pathology associated with schistosomiasis, and induce IL-10 production in individuals chronically infected with *S. mansoni* (Brito et al. 2000, Zouain et al. 2000, Pacifico et al. 2006). Contributing to the choice of these antigens is the fact that they are proteins from the tegument and do not cross react with egg antigens, that are known to be involved in the pathogenesis of schistosomiasis (Simpson et al. 1990).

All *S. mansoni* antigens used in this study induced high levels of IL-10 by cells of individuals chronically infectec with the parasite, p24 being the major inductor of this cytokine in asthmatic infected individuals.

Due the fact that the antigens Sm14, Sm22.6, and p24 used in this study were recombinantly cloned in *E. coli,* Polymyxin B was added to the cell cultures to block the effect of endotoxin to stimulate IL-10 production. Indeed, the use of Polymyxin B in control cultures stimulated with LPS completely abrogated IL-10 production. As the antigens used in this study have the ability to induce IL-10 and are possibly capable of modulating the inflammatory immune response, they may be produced in a non-bacterial vector for future use as vaccines or treatment to certain immunologic-based disorders.

It is known that during *S. mansoni* infection cells from the innate immune response, T cells and T regulatory cells are able to produce IL-10 (Hesse et al. 2004). There are some *S. mansoni* antigens described in the literature, such as LNFPIII (Okano et al. 2001, Thomas et al. 2003) and fosfatidilserine (PS) (van der Kleij et al 2004) that also induce IL-10 production by the cells from the innate immune system. We are currently evaluating if the *S. mansoni* antigens used in this study are able to induce IL-10 by cells from uninfected asthmatics. These studies may result in new strategies to prevent allergic diseases.

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