Atopic Phenotype Is an Important Determinant of Immunoglobulin E–Mediated Inflammation and Expression of T Helper Cell Type 2 Cytokines to Ascaris Antigens in Children Exposed to Ascariasis

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Studies have shown a strong inverse relationship between atopy and geohelminth infection, indicating that atopy may protect against geohelminth infection. Resistance to ascariasis in atopic individuals may occur through greater immunoglobulin E–mediated responses and expression of T helper cell type 2 (Th2) cytokines to parasite antigens. To investigate the effect that atopy has on the immune response to Ascaris antigens, school-age children were recruited from rural schools in Ecuador. Immunologic variables were compared between children stratified by atopic and/or A. lumbricoides–infection status; the variables included cytokine expression by peripheral-blood mononuclear cells (PBMCs) and histamine release in response to Ascaris antigens. Atopic children had both greater frequencies of PBMCs expressing interleukin (IL)–4 and IL-5 and enhanced histamine release, compared with those in nonatopic children. Stratification by atopic and A. lumbricoides–infection status revealed the greatest histamine and Th2 cytokine responses in the stratum of atopic, noninfected children. Multivariate regression analyses showed significant effects for atopic status but not for infection status on Th2 cytokine expression and histamine release.

Ascaris lumbricoides is the most prevalent of intestinal helminth or geohelminth parasites and is estimated to infect one-quarter of the world’s population [1]. In areas where the parasite is endemic, first exposures to infection with A. lumbricoides occur in early childhood and may persist into adulthood through repeated re-infections. Chronic, high-intensity infections with A. lumbricoides are associated with significant childhood morbidity [1, 2].

The immune response to geohelminth parasites has close parallels with that associated with allergic sensitization and allergic disease. Both allergy and helminth infections are associated with tissue mastocytosis, elevated numbers of peripheral-blood eosinophils, high levels of polyclonal and specific IgE, and CD4+ T cells that preferentially secrete the Th2 cytokines interleukin (IL)–4, IL-5, and IL-13 [3, 4]. The high expression of Th2 cytokines that is typical of both human geohelminth infection [5] and experimental infections in animal models [6, 7] may mediate protective immunity against these parasites [7].

Several epidemiological studies have reported an inverse relationship between atopy and infection with geohelminth parasites, including ascariasis [8–10], and have shown reduced parasite burdens for hookworm [11] in atopic humans, compared with those in nonatopic humans. Such data could be interpreted to suggest that the atopic phenotype provides protection against geohelminth infection and could have afforded an evolutionary advantage to our ancestors, who may have been exposed to high levels of geohelminth infection [12].

Mast cell activation by specific IgE plays a central role in the initiation of allergic disease [3] and may
also play a role in the initiation of inflammatory reactions that kill or expel helminth parasites [5, 6, 13]. Atopic individuals have a propensity to produce higher levels of specific IgE to environmental aeroallergens [14] and to A. lumbricoides [12] and appear to be more sensitive to allergen-induced activation of mast cells and basophils [15, 16].

Because the induction of protective immune responses to ascariasis may require the activation of mast cells by parasite-specific IgE, causing either inflammatory killing reactions directed against migratory larvae or the expulsion of juvenile and adult worms from the intestinal lumen, we hypothesized that, in response to parasite antigens, atopic children living in an area where ascariasis is endemic would show evidence of enhanced basophil histamine release and would express Th2 cytokines with greater frequencies than would nonatopic children.

**POPULATION, MATERIALS, AND METHODS**

**Study population.** The present study was conducted in a tropical/subtropical region of the districts of Pedro Vicente Maldonado and Puerto Quito, Pichincha Province, Ecuador, at altitudes between 200 m and 600 m. Study subjects were school-age children attending schools visited as part of a cross-sectional study of geohelminth infection and atopy [10]. Informed consent was obtained from parents or guardians, and the human-experimentation guidelines of the Department of Health and Human Services and St. George’s Hospital Medical School were followed. The protocol was approved by the institutional review board of the National Institute of Allergy and Infectious Diseases and the ethics committee of the health foundation SALUDESA.

**Allergen skin testing.** Skin-prick testing was performed with the following allergens and controls: glycerol/saline control (Greer Laboratories), Dermatophagoides pteronyssinus (ALK-Abello), D. farinae (ALK-Abello), grass mix (Greer Laboratories), tree mix (Greer Laboratories), American cockroach (Greer Laboratories), Alternaria tenuis (Greer Laboratories), cat (Greer Laboratories), and histamine control (10 g/L; ALK-Abello). Allergens were scratched onto the volar side of the forearm by use of ALK-Abello plastic bifurcated lancets, and reaction sizes were recorded after 15 min by measurement of the wheel sizes. Reactions were considered to be positive if the wheel diameter was at least 3 mm greater than that produced by the saline control.

**Sampling of subjects.** Blood samples (10 mL) were collected into Vacutainer tubes (Becton Dickinson) containing sodium heparin. A single stool sample was collected from each subject and was examined for the presence of geohelminth eggs by use of the modified Kato-Katz technique [17]. Kato-Katz slides were examined within 90 min of preparation. All subjects were offered treatment with 400 mg of albendazole.

**Antigens.** Antigens used included purified protein derivative (PPD; Statens Serum Institute) and the following Ascaris antigens: a PBS-soluble extract of adult A. lumbricoides worms (ASC) and excretory/secretory antigens from A. suum larvae developing from L2 to L3 (L2/L3) and from L3 to L4 (L3/L4). The preparation of the Ascaris antigens has been described elsewhere [18]. All Ascaris antigen preparations were analyzed for the presence of endotoxin by use of the limulus lysate assay (BioWhittaker); endotoxin levels were below the limits of detection in all samples.

**Measurement of antibodies.** Levels of A. lumbricoides-specific IgG1 and IgG4 were measured as markers of exposure to geohelminth infection (including ascariasis [18]) and infection chronicity [10], respectively, and were determined in plasma samples, as described elsewhere [18], with ASC as the coating antigen. Levels of IgE specific to D. pteronyssinus, cat, Ascaris, and American cockroach allergens were determined by use of the CAP system (Pharmacia Diagnostics). The assay used for detection of total IgE has been described elsewhere [10].

**Histamine-release assays.** Histamine release by heparinized whole blood in response to parasite antigens, at a concentration of 0.03 μg/mL, was performed by use of commercial assays (Histamine Enzyme Immunoassay Kit; Immunotech), according to the manufacturer’s instructions.

**Cytokine enzyme-linked immunospot (ELISPOT) assays.** Peripheral-blood mononuclear cells (PBMCs) were isolated from whole blood by centrifugation on lymphocyte separation medium (Organon Teknika). After washing, the cells were plated at a concentration of 2.5 × 10⁴ cells/mL (200 μL/well) in tissue culture medium (RPMI 1640; BioWhittaker) supplemented with 10% fetal calf serum (Atlanta Biologicals), 0.08 mg/mL gentamicin (Life Technologies, Gibco BRL), and 2 mmol/L L-glutamine (Biofluids). Antigen was added to the cell suspension at the following concentrations: PPD, 10 μg/mL; ASC, 10 μg/mL; L2/L3, 5 μg/mL; and L3/L4, 5 μg/mL. ELISPOT assays were performed for interferon (IFN)–γ, IL-4, and IL-5, as described elsewhere [18]. ELISPOT plates were read blind to A. lumbricoides infection and allergen skin-test status.

**Statistical analysis.** Because of a shortage of blood, not all assays were performed on all individuals. For the purposes of analysis, the study population was stratified according to the presence or absence of A. lumbricoides infection (Ascaris” or Ascaris”, as determined by stool examination) or allergen skin-test reactivity (SPT+ and SPT_) and into 4 groups on the basis of A. lumbricoides infection and the presence or absence of allergen skin-test reactivity: Ascaris”/SPT-, Ascaris”/SPT+, Ascaris”/ SPT+, and Ascaris”/SPT-. Differences between immunologic variables stratified according to binary variables (SPT+ vs. SPT− and Ascaris” vs. Ascaris”) were assessed by use of the Mann-Whitney U test. Differences between immunologic variables for the 4 groups were assessed either by use of the Kruskal-Wallis test (for comparisons among the 4 groups) or the Mann-Whitney U test (for comparisons between 2 of the groups); 2 groups were compared only when there was evidence of significant intergroup
heterogeneity among the 4 groups. Comparison of proportions was performed by use of the χ² test. The effects that A. lumbricoides–infection and/or SPT status had on loge-transformed immunologic variables were evaluated by use of univariate and multivariate linear regression analyses. The effects that interactions between A. lumbricoides–infection and SPT status had on the magnitude of immunologic variables were assessed by use of likelihood ratio tests. Statistical analyses were performed by use of Intercooled Stata 7 software (Stata Corporation). Statistical significance was inferred by P < .05.

**RESULTS**

**Characteristics of subjects.** Ninety-nine (75.0%) of the 132 subjects had positive stool examinations for A. lumbricoides infection; 25 (18.9%) had evidence of skin-test reactivity to at least 1 of the 7 allergens tested. Positive reactions to individual allergens were as follows: D. pteronyssinus, 9.1%; D. farinae, 5.3%; grass mix, 3.0%; tree mix, 5.3%; American cockroach, 11.4%; A. tenuis, 0.8%; and cat, 1.5%. All of the subjects had positive skin-test reactions to the positive histamine control. Age, sex, and parasitologic characteristics of the study population stratified into the 4 groups according to A. lumbricoides–infection and SPT status are shown in table 1. No other geohelminth species was detected in stool samples. Almost all of the subjects had detectable levels of A. lumbricoides–specific IgG1 (only 2 of the children did not), indicating universal exposure to geo-helminths in the study population. Because of potential antigenic cross-reactivity between A. lumbricoides and Trichuris trichiura, both of which are highly endemic in the study area, specific antibodies may reflect exposure to or infection with either parasite. SPT status was not associated with differences in levels of allergen-specific IgE (American cockroach, D. pteronyssinus, and cat; data not shown), and no significant differences in levels of allergen-specific IgE among the 4 groups stratified by A. lumbricoides–infection and SPT status were found (table 1)—median levels were negligible in all 4 groups.

**Table 1. Age, sex, parasitologic characteristics, and antibody levels, in children stratified into 4 groups according to A. lumbricoides–infection status (Asc/M or Ascaris †) and allergen skin-test status (SPT ‡ or SPT †).**

<table>
<thead>
<tr>
<th>Category, parameter</th>
<th>SPT+/Asc/M (n = 23)</th>
<th>SPT+/Ascaris † (n = 84)</th>
<th>SPT+/Asc/M (n = 10)</th>
<th>SPT+/Asc/M (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>10 (5–17)</td>
<td>11 (5–19)</td>
<td>10 (6–14)</td>
<td>11 (7–15)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>6:17</td>
<td>49:35</td>
<td>5:5</td>
<td>7:8</td>
</tr>
<tr>
<td>Geohelminths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. lumbricoides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Intensity, GM (range), epg</td>
<td>0</td>
<td>13,161 (71–211,083)</td>
<td>0</td>
<td>10,729 (213–112,748)</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>39.1</td>
<td>79.2</td>
<td>50.0</td>
<td>73.3</td>
</tr>
<tr>
<td>Intensity, GM (range), epg</td>
<td>6.8 (0–355)</td>
<td>143.5 (0–390,500)</td>
<td>10.4 (0–1948)</td>
<td>103.7 (0–4757)</td>
</tr>
<tr>
<td>A. duodenale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>13.1</td>
<td>0</td>
<td>20.0</td>
</tr>
<tr>
<td>Intensity, GM (range), epg</td>
<td>0</td>
<td>0.8 (0–497)</td>
<td>0</td>
<td>1.1 (0–639)</td>
</tr>
<tr>
<td>Any geohelminth, prevalence</td>
<td>39.1</td>
<td>100</td>
<td>50.0</td>
<td>100</td>
</tr>
<tr>
<td>Antibodies, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgE, IU/mL</td>
<td>863 (60–18,603)</td>
<td>4940 (53–31,250)</td>
<td>475 (290–14,469)</td>
<td>1890 (51–30,050)</td>
</tr>
<tr>
<td>Anti-Ascaris IgG1</td>
<td>46 (0–257)</td>
<td>91 (1–434)</td>
<td>76 (0–172)</td>
<td>95 (5–668)</td>
</tr>
<tr>
<td>Anti-Ascaris IgG4</td>
<td>9 (0–72)</td>
<td>17 (0–1000)</td>
<td>0 (0–88)</td>
<td>6 (0–936)</td>
</tr>
<tr>
<td>Anti-Ascaris IgG2</td>
<td>4.2 (0–33.4)</td>
<td>15.6 (0–100)</td>
<td>2.4 (0–94.1)</td>
<td>12.6 (0–8.6)</td>
</tr>
<tr>
<td>Anti-Ascaris IgG2</td>
<td>0 (0–3.6)</td>
<td>0 (0–8.4)</td>
<td>0.2 (0–1.3)</td>
<td>0 (0–5.9)</td>
</tr>
<tr>
<td>Anti-Ascaris IgG2</td>
<td>0 (0–8.4)</td>
<td>0 (0–4.7)</td>
<td>0 (0–9.3)</td>
<td>0 (0–3.7)</td>
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<tr>
<td>Anti-cat IgE, kU/L</td>
<td>0 (0–13.8)</td>
<td>0.8 (0–25.1)</td>
<td>0 (0–9.6)</td>
<td>0 (0–7.9)</td>
</tr>
</tbody>
</table>

**NOTE.** epg, No. of eggs per gram of stool; GM, geometric mean.

* Units are arbitrary.
certain cytokine responses, to Ascaris antigens (figure 2) in a population with universal exposure to geohelminth parasites (table 1).

**Association between SPT status and the Ascaris-specific immune response.** Evidence was found for enhanced histamine release induced by larval-stage antigens (P = .006, for L2/L3) in the SPT+ subjects, but evidence was not found for such induction by adult antigens. Frequencies of Th2 cytokine-expressing PBMCs stimulated with parasite and nonparasite antigen were significantly elevated in the SPT+ subjects, compared with those in the SPT- subjects (IL-4: P = .003, for PPD; IL-5: P = .01, for PPD; P = .009, for ASC; P = .003, for L2/L3; P = .01, for L3/L4). No significant differences in the expression of IFN-γ were observed between the SPT+ and SPT- subjects.

**Relationship between A. lumbricoides-infection and SPT status in the determination of the Ascaris-specific immune response.** Our data show that both A. lumbricoides-infection and SPT status may influence the magnitude of anti-Ascaris immune responses. To examine the relative effects that A. lumbricoides-infection and SPT status have on Ascaris-specific immunity, the subjects were stratified into 4 groups according to A. lumbricoides-infection and SPT status, as described above. The 4-group stratification showed negligible intergroup differences in levels of polyclonal IgE and A. lumbricoides-specific IgG1 and IgE (table 1); however, there were significant intergroup differences in levels of A. lumbricoides-specific IgG4 (P = .003) that seemed to be largely accounted for by negligible antibody levels in the Ascaris+/SPT+ group (P = .007, for Ascaris+/SPT- vs. Ascaris+/SPT+).

Significant intergroup differences were observed for histamine release by whole blood stimulated with larval antigens (P = .001, for L2/L3; P = .05, for L3/L4), with the greatest histamine release being observed in the Ascaris+/SPT+ group (Ascaris+/SPT- vs. Ascaris+/SPT+: P = .001, for L2/L3; P = .04, L3/L4) (figure 1B). Histamine release appeared to be similar in the Ascaris+ subjects, irrespective of SPT status (figure 1B). The 4-group stratification of the data for Th2 cytokine expression (figures 3A and 3B) showed significant intergroup differences for PBMCs stimulated with ASC (P = .002, for IL-5) and L2/L3 antigens (P = .002, for IL-4). Again, many of the intergroup differences appeared to be associated with enhanced Th2 cytokine secretion by the Ascaris+/SPT+ subjects (Ascaris+/SPT- vs. Ascaris+/SPT+: P = .03, for IL-4 to L2/L3; P = .05, for IL-5 to ASC), and the same trend was observed for the other Ascaris antigens. Increased Th2 cytokine secretion was observed in the Ascaris+/SPT+ subjects, compared with that in the Ascaris+/SPT- subjects, in response to the nonparasite antigen, PPD (P = .003, for IL-4; P = .02, for IL-5). No differences among the 4 groups in the expression of IFN-γ to parasite antigens were found (figure 3C).

Because the relationship between A. lumbricoides-infection and SPT status as determinants of the magnitude of histamine release and Th2 cytokine expression appears to be complex and may be confounded by other factors (e.g., age, sex, and infections with other geohelminth parasites), the relationship between these factors as determinants of these immunologic variables was examined by use of univariate and multivariate linear regression analyses (table 2). Univariate analyses showed that A. lumbricoides-infection status had significant effects on the frequencies of IL-4- and IL-5-expressing PBMCs stimulated with adult or larval antigens, but none of these remained significant.
Figure 2. Frequencies of parasite antigen–stimulated peripheral-blood mononuclear cells (PBMCs) expressing interleukin (IL)–4, IL-5, and interferon (IFN)–γ, in children stratified according to Ascaris lumbricoides–infection status (Ascaris+ or Ascaris−). Box plots represent median values (central lines), interquartile ranges (top and bottom box margins), 95% confidence intervals (bars), and outlying values (circles). Antigens are purified protein derivative (PPD), adult Ascaris antigen (ASC), and larval-stage Ascaris antigens (L2/L3 and L3/L4).

DISCUSSION

We have investigated the relationship between measures of the anti-Ascaris immune response and allergen skin-test reactivity in children living in an area of Ecuador where geohelminth infection is endemic and where we have previously demonstrated a strong inverse relationship between allergen skin-test reactivity and A. lumbricoides infection [10]. As determined by measurement of A. lumbricoides–specific antibodies, almost all of the children in the present study had evidence of exposure to geohelminth parasites irrespective of allergen skin-test reactivity, and a high proportion of the children were infected at the time of sampling. Our data have shown that children with evidence of skin-test reactivity to aeroallergens have enhanced allergic responses to Ascaris antigens, as measured by basophil histamine release induced by parasite antigens and elevated frequencies of PBMCs expressing the Th2 cytokines IL-4 and IL-5.

The human immune system is likely to have evolved in the context of heavy helminth infestation and intense exposure to helminth antigens; allergic inflammation may, therefore, have developed as an important protective host mechanism for preventing the establishment of helminth infection and controlling parasite numbers [19]. Different components of the allergic Th2 response (e.g., IgE, eosinophils, and mast cells), either singly or in combination, appear to mediate protective immunity against different helminth infections in experimental animal models [7]. Although we were not able to demonstrate statistically significant differences in the prevalence of intensity of infection with A. lumbricoides or other geohelminth parasites between atopic and nonatopic individuals in the present small study, there were trends toward reduced prevalence and intensity of ascariasis and trichuriasis in the nonatopic subjects; moreover, a larger study of 2865 schoolchildren, of which our study population was a subset, showed strong inverse correlations between the prevalence of infection with A. lumbricoides, T. trichiura, and A. duodenale and allergen skin-test reactivity [10]. Furthermore, the data from the larger study showed that risk for atopy became lower as infection intensity increased, indicating that chil-
dren with evidence of allergen skin-test reactivity had reduced infection intensities of *A. lumbricoides* and *T. trichiura*. Together, these data suggest that children with evidence of allergen skin-test reactivity are less likely to be infected with *A. lumbricoides* and other geohelminth parasites and that this resistance to parasite infection is associated with enhanced Th2 cytokine and IgE-mediated inflammatory responses to parasite antigens.

Previous studies have provided evidence for resistance to reinfection with *A. lumbricoides* following anthelmintic treatment in a subgroup of individuals living in communities in which infection is endemic [20]. Resistance to reinfection with *A. lumbricoides* has been associated with high levels of anti-parasite IgE [21], IgE to the principal *Ascaris* allergen, ABA-1 [20], and elevated levels of eosinophilic cationic protein and other acute inflammatory markers [20]. Elevated levels of anti-parasite IgE and circulating eosinophilic degranulation products are markers of a polarized Th2 cytokine response, and, although we did not specifically examine resistance to infection in the present study, our findings for the atopic subjects (who appeared to be relatively resistant to infection with *A. lumbricoides*, compared with the nonatopic subjects) support a potential role for Th2 cytokine responses in mediating protective immunity against ascariasis and other geohelminth infections in humans. A recent study that examined Th2 cytokine production by *Ascaris* antigen–stimulated whole blood in children living in a community in which endemicity is high provided evidence for an inverse relationship between Th2 cytokine production and infection intensity in older children [22]. The strongest evidence for a protective role played by Th2 cytokine responses against helminths in humans derives from studies of reinfection with schistosomes after chemotherapy. These studies have demonstrated associations between individual components of the Th2 cytokine response (e.g., peripheral eosinophilia [23], levels of anti-parasite IgE [24, 25], and production of IL-5 in lymphocyte cultures stimulated with parasite antigen [26]) and resistance to reinfection. Genetic studies have suggested that resistance to infection with schistosomes is linked to a region on chromosome 5q31-q33 that contains several Th2-response genes [27].

We have shown previously that anti-parasite cytokine responses in young adults infected with *A. lumbricoides* and living in communities in which endemicity is high are strongly Th2-polarized, compared with those in uninfected control subjects from a nearby town where exposure to infection was likely to be limited [18]. In this study, we compared infected and uninfected children residing in the same communities (in which helminth infection was endemic) and showed that Th2 (IL-4 and IL-5) and perhaps Th1 (IFN-γ) cytokine responses appeared to be modulated in infected children. Similar findings have been reported from a region of Brazil where helminth infection is endemic [28]. The explanation for this may be

**Figure 3.** Frequencies of parasite antigen–stimulated peripheral-blood mononuclear cells (PBMCs) expressing interleukin (IL)–4, IL-5, and interferon (IFN)–γ, in children stratified into 4 groups according to *Ascaris lumbricoides*–infection status (*Ascaris* or *Ascaris*) and allergen skin-test status (SPT+ or SPT−). Box plots represent median values (central lines), interquartile ranges (top and bottom box margins), 95% confidence intervals (bars), and outlying values (circles). Antigens are purified protein derivative (PPD), adult *Ascaris* antigen (ASC), and larval-stage *Ascaris* antigens (L2/L3 and L3/L4).
antigen was dependent on IL-5 expression by PBMCs stimulated with adult-derived basophil histamine release induced by larval antigens and parasite antigens and (2) the effect of allergen skin-test reactivity of the magnitude of Th2 cytokine expression induced by parasite antigens was observed in children who were free of infection and had positive allergen skin tests. Multivariate analyses indicated that (1) allergen skin-test reactivity and not A. lumbricoides–infection status was the primary determinant of the magnitude of Th2 cytokine expression induced by parasite antigens and (2) the effect of allergen skin-test reactivity on basophil histamine release induced by larval antigens and on IL-5 expression by PBMCs stimulated with adult-derived antigen was dependent on A. lumbricoides–infection status (i.e., was greatest in the Ascaris+ subjects).

Infected individuals living in areas where the parasite is endemic are likely to harbor chronic infections and may develop down-regulatory mechanisms that limit allergic inflammatory responses to ascarisi. Down-regulatory mechanisms that may be important in limiting both Th1 and Th2 inflammatory responses to helminth parasites include the production of cytokines such as IL-10 [29–32]. Our observations of reduced Th1 and Th2 cytokine responses to parasite antigens in infected individuals is consistent with a modified Th2 response [33], an immune phenotype that was first described for individuals with little or no allergic responsiveness to cat allergen despite high levels of exposure [34] and that has been extended to explain nonresponsiveness in helminth-infected populations [33]. The down-regulatory mechanisms that modulate allergic responses to parasite antigens during chronic helminth infection may also modulate immune responses to aeroallergens [35].

Several epidemiological studies have shown strong inverse associations between allergen skin-test reactivity and geohelminth infection [8–10]. Because most studies have been cross-sectional, the direction of this causal relationship is not clear—geohelminth infection may protect against allergen skin-test reactivity or allergen skin-test reactivity may protect against geohelminth infection. An intervention study provided evidence that anthelmintic treatment of geohelminth-infected children resulted in an increase in the prevalence of atopy, indicating that geohelminths are the antecedent exposure [12]. Our data have provided evidence that children who are atopic (or allergen skin-test reactive) have stronger allergic responses to parasite antigens than do nonatopic children. It is possible that the expression of atopy may vary over time in a single individual and may depend on the balance of environmental exposures (protective vs. risk exposures). Individuals with strong genetic traits associated with atopy may be more likely to have positive allergen skin tests to environmental allergens and may be more resistant to geohelminth infection but, given adequate exposure to geohelminths, may develop chronic infections that, in turn, may cause a down-regulation of allergic inflammation and result in negative allergen skin tests. Here, this tendency was observed as reduced Th1 and Th2 cytokine expression in the Ascaris+/SPT+ subjects, compared with that in the Ascaris-/SPT+ subjects.

In the present study, we used allergen skin-test reactivity as a marker for the presence of atopy. Atopy is an immune phenomenon that can be defined as the presence of either a positive skin test to extracts of inhalant allergens or the presence of allergen-specific IgE in serum. In studies conducted in induc-
trialized countries, positive allergen skin tests and the presence of allergen-specific IgE are strongly associated [36, 37], but, in rural regions of Africa, this relationship appears to be weak or nonexistent [38, 39]. In the present study, the presence of allergen skin-test reactivity and allergen-specific IgE in serum did not appear to be associated (table 1). Possible explanations for the disassociation between the 2 markers of atopy are potential of preexisting IgE responses to inhalant allergens by geohelminth infection [13] and false-positive serologic reactions caused by cross-reactivity between geohelminth antigens and inhalant allergens [40].

In conclusion, our findings have indicated that there are important differences in the immune responses to Ascaris antigens among children exposed to ascariasis according to the presence or absence of skin-test reactivity to common environmental allergens. Our data have shown that (1) children with positive allergen skin tests have greater frequencies of PBMCs that express Th2 cytokines (IL-4 and IL-5) on stimulation with Ascaris antigens and release more histamine from peripheral-blood basophils in response to larval-stage antigens than do children with negative allergen skin tests and (2) responses are greatest in children not infected with A. lumbricoides. Because atopic individuals may be more resistant to geohelminth infection and, when infected, harbor smaller parasite burdens than do nonatopic individuals, high Th2 cytokine expression and enhanced IgE-mediated inflammation (allergen-induced release of histamine by basophils) may be correlates of protective immunity against ascariasis. The data suggest that allergen skin-test reactivity or the atopic phenotype, not infection status, is the primary determinant of the allergic inflammatory response to ascariasis. Moreover, our data demonstrate that a modified antigen-specific T helper response occurs during patent intestinal human helminth infection (figure 2), a modification that may reflect ongoing regulatory networks of antigen-specific and antigen-nonspecific T cells [33].

Acknowledgments

We thank the children, parents, and teachers in the study communities, for their cooperation, and Brenda Rae Marshall, for editorial assistance.

References


