Patent Filarial Infection Modulates Malaria-Specific Type 1 Cytokine Responses in an IL-10-Dependent Manner in a Filaria/Malaria-Coinfected Population


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Patent Filarial Infection Modulates Malaria-Specific Type 1 Cytokine Responses in an IL-10-Dependent Manner in a Filaria/Malaria-Coinfected Population

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The effect of filarial infections on malaria-specific immune responses was investigated in Malian villages coendemic for filariasis (Fil) and malaria. Cytokines were measured from Ag-stimulated whole blood from individuals with Wuchereria bancrofti and/or Mansonella perstans infections (Fil*; n = 19) and those without evidence of filarial infection (Fil−; n = 19). Plasma levels of IL-10 (geometric mean [GM], 22.8 vs 10.4) were higher in Fil* compared with Fil−, whereas levels of IFN-inducible protein (IP)-10 were lower in Fil* (GM, 66.3 vs 110.0). Fil* had higher levels of spontaneously secreted IL-10 (GM, 59.3 vs 6.8 pg/ml) and lower levels of IL-2 (1.0 vs 1.2 pg/ml) than did Fil−. Although there were no differences in levels of Staphylococcus aureus enterotoxin B-induced cytokines between the two groups, Fil* mounted lower IL-12p70 (GM, 1.11 vs 3.83 pg/ml; p = 0.007), IFN-γ (GM, 5.44 vs 23.41 pg/ml; p = 0.009), and IP-10 (GM, 29.43 vs 281.7 pg/ml; p = 0.007) responses following malaria Ag (MalAg) stimulation compared with Fil−. In contrast, Fil− individuals had a higher MalAg-specific IL-10 response (GM, 7318 pg/ml vs 3029 pg/ml; p = 0.006) compared with those without filarial infection. Neutralizing Ab to IL-10 (but not to TGFβ) reversed the down-regulated MalAg-specific IFN-γ and IP-10 (p < 0.001) responses in Fil−. Together, these data demonstrate that filarial infections modulate the Plasmodium falciparum-specific IL-12p70/IFN-γ secretion pathways known to play a key role in resistance to malaria and that they do so in an IL-10-dependent manner. The Journal of Immunology, 2009, 183: 916–924.

N otwithstanding the marked reduction in reported cases of Plasmodium falciparum (Pf), malaria remains endemic in 109 countries worldwide. An estimated 189–327 million cases of malaria occur annually, with 86% occurring in sub-Saharan Africa. In 2006 alone, malaria claimed ~1.1 million lives in Africa, 85% occurring in children below the age of 5 years (1). Among the ~129 million people worldwide infected by one of the three causative agents of lymphatic filariasis (Wuchereria bancrofti (Wb), Brugia malayi, and Brugia timori), 33% live in parts of Africa (2) where malaria is highly endemic. Coinfection with malarial and filarial parasites is common (3–6), with documented prevalences of concomitant malaria and Wb ranging from 0.3 to 0.4% in India (3, 4) to 3.5% in parts of South America (5) and 4.3% in Kenya (6). More recently, Mansonella perstans (Mp) malaria coinfections were reported in 18% of pregnant women in a filarial-endemic region of Uganda (7).

Because malaria and filarial infections each induce discrete parasite-specific immune responses, it is likely that the immune responses directed at one parasite could (through bystander effects) alter the immune response to the other. More importantly, however, in those areas with intense Pf and Wb transmission such as Mali or parts of Papua New Guinea, malaria/filaria coinfection occurs at an early age (8), and modulation of the responses to malaria infection by concomitant filarial infection could, theoretically at least, dramatically alter clinical outcome and/or severity of malaria in nonimmune children.

Human studies have generated conflicting results on the effect of helminth infections on the acquisition and severity of malaria, in that helminth/malaria coinfection has been shown to both exacerbate (9–12) and (in other studies) modify the severity of the disease in human malaria (13–16). Animal models of malaria/filaria coinfection have also led to conflicting results. Using the filarial parasite Litomosoides sigmodontis and the rodent malaria Plasmodium chabaudi chabaudi AS, mice with both infections were shown to have more severe anemia and loss of body mass than did mice infected with the malaria parasite alone (17). In a different murine model, pretreatment of mice with irradiated Brugia pahangi larvae prevented cerebral malaria (in a Plasmodium
bergehi model) but induced more severe anemia that led to death (18). In a study of experimental coinfections in nonhuman pri-
mates, monkeys with circulating microfilariae developed less se-
vere malarial disease when challenged with *Plasmodium falciparum* parasites (19) than did monkeys without microfilariae.

That the cytokine milieu associated with filarial infections should have a modulating effect on responses to coinfecting patho-
gens has been inferred primarily by the bystander effects induced by filarial infections on responses to vaccine administration (20, 21). These data notwithstanding, a few studies have examined the bystander effects induced by filarial infections on responses to vaccine administration (20, 21). These data notwithstanding, a few studies have examined the bystander effects induced by filarial infections on responses to vaccine administration (20, 21). These data notwithstanding, a few studies have examined the bystander effects induced by filarial infections on responses to vaccine administration (20, 21). These data notwithstanding, a few studies have examined the bystander effects induced by filarial infections on responses to vaccine administration (20, 21).

**Malaria and filarial Ab**

Filarial Ab levels were determined using a *B. malayi* adult worm extract (BmA)-specific IgG and IgG4 ELISA as described previously (34). Malaria-specific IgG and IgG subclass Ab levels were determined using the recombinant Ag merozoite surface Ag (MS) e antigen of the 3D7 strain expressed in *Escherichia coli* and the apical membrane Ag (AMA)-1 of the 3D7 strain expressed in *Pichia pastoris* (provided by Dr. C. Long, Labora-

atory of Malaria and Vector Research (LMVR), NIAID, NIH) using a multiplex assay with suspension array technology (Luminex). The suspen-

sion array technology assay protocol used was modified from the technique utilized by Fouad and coworkers (27). Each FilAg-specific, down-regulated immune response mediated largely by IL-10 and IFN-γ secretion pathways known to play a key role in resistance to malarial par-

asites and do so in an IL-10-dependent manner.

**Materials and Methods**

**Study population**

The study was conducted in Tiénguébougou and Bougoudiana, two vil-

lages situated ~105 km northeast of Bamako, Mali, in a malaria-endemic area with seasonal transmission. Before the start of the study, screening of adults in the villages showed the prevalence of circulating filarial antigens (*TropBio*) (33) to be 53% in Tiénguébougou and 36% in Bougoudi-

ana, respectively. The prevalence of *M. perstans* microfilareemia by calibrated thick smear examination was 62% in Tiénguébougou and 63% in Bougoudiana.

The study was approved by the National Institute of Allergy and Infec-

tious Diseases (NIAID) Institutional Review Board and the Ethical Com-

mittee of the University of Mali (National Institutes of Health (NIH) Clin-

calTrials.gov identifier NCT00471666). Informed consent was obtained from all participants.

Thirty-eight volunteers (19 filaria uninfected (Fil−) and 19 filaria in-

fected (Fil+)) between 11 and 20 years of age were enrolled before the start of the malaria transmission season. Fil− had a negative test for circulating filarial Ag (FilAg) (ELISA; *TropBio*) and/or detectable micro-

filariae (Wb or Mp) in peripheral blood samples drawn between 10 p.m. and 2 a.m. Microfilaremia was assessed by calibrated thick smear (total blood volume, 60 μl). Fil+ had a negative test for circulating FilAg, and no microfilariae were seen on thick smear. Each Fil+ individual was matched by age with a Fil− individual.

**Cytokine analysis**

Cytokine analysis in supernatants and plasma was performed by suspen-

sion array technology in multiplex as described in (38). The assay was done using Milliplex kits for human IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IFN-γ, TNF-α, and IFN-inducible protein (IP)-10 (Millipore) according to the manufac-

turer’s protocol.

**Flow cytometry**

Cryopreserved fixed cells were thawed, washed twice with PBS and 1% BSA, and washed twice more in permeabilization buffer (eBioscience). The
cells were then stained with mouse anti-human CD3-allophycocyanin-Cy5.5, mouse anti-human CD4-PE-Cy5, rat anti-human IL-10-allophycocyanin-Cy7 (BD Pharmingen) and mouse anti-human CD25-allophycocyanin-Cy7. Cells were then stained with mouse anti-human CD3-allophycocyanin-Cy5.5, mouse anti-human CD4-PE-Cy5, rat anti-human IL-10-allophycocyanin-Cy7 (BD Pharmingen) and mouse anti-human CD25-allophycocyanin-Cy7. The study subjects were matched for age and sex, the Wilcoxon signed rank test was used for group comparisons, and the p values were corrected for multiple comparisons using the Holm correction method. All analyses were performed using Prism version 5.0 (GraphPad Software).

### Results

#### Characteristics of the study population and serologic responses

The study was conducted in two adjacent Malian villages endemic for malaria with a seasonal pattern of transmission before the malaria season. Thirty-eight age-matched subjects (19 Fil + and 19 Fil −), a subset of patients participating in a larger longitudinal study of clinical malaria, were enrolled. The demographics and parasitologic status of the subjects are shown in Table I. There were no significant differences in total leukocyte count or hemoglobin concentration between the two groups (Table I).

Although MSP1_{42}-specific and AMA-1-specific IgG levels were also comparable between Fil + and Fil − subjects (Table I), analysis of the antimalarial IgG subclass responses revealed that geometric mean (GM) AMA-1-specific IgG4 levels were significantly higher in Fil + compared with Fil − individuals (6.6 vs 1.3; p = 0.02). No other differences in malaria-specific IgG isotype levels were identified between the two groups.

FilAg (BmA)-specific IgG levels were comparable between Fil + and Fil −, suggesting that exposure to filarial parasitic was equivalent between the two groups; however, the GM levels of filaria-specific IgG4, known to be increased in active filarial infection (33), were, as expected, significantly higher in Fil + individuals (105.9, as compared with 43.73 in Fil −; p = 0.04) (Table I).

#### Cytokine levels in plasma and spontaneous cytokine secretion in whole blood cultures

Plasma levels of IFN-γ and IL-10 were determined in all subjects (Fig. 1A). The plasma levels of IL-10 (GM, 22.8 vs 10.4; p < 0.004) were significantly higher in Fil + compared with Fil −, as was the ratio of IL-10 to IFN-γ (GM, 13.4 vs 5.2; p = 0.01). In contrast, plasma levels of IP-10 were significantly higher in the Fil − compared with the Fil + group (GM, 110.0 vs 66.3; p < 0.02; data not shown). There were no significant differences between the two groups in any of the other cytokines measured in the plasma. Spontaneous production of IFN-γ, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IP-10, and TNF-α was assessed in whole blood cultures. As shown in Fig. 1B, the levels of spontaneously secreted IL-10 were significantly higher in Fil + compared with Fil − (GM, 59.3 vs 6.8; p = 0.01). There were no differences in the levels of other spontaneously produced cytokines between the two groups. The ratio of spontaneous IL-10: IFN-γ appeared to be higher in the Fil + group but did not reach statistical significance.

#### MalAg-driven cytokines

Malaria-specific induction of IL-12p70 (GM, 1.1 vs 3.8; p = 0.005), IP-10 (29.4 vs 281.7; p = 0.007), and IFN-γ (5.4 vs 23.4; p = 0.009) was significantly lower in Fil + compared with Fil − (Fig. 2). In contrast, Fil + produced significantly more IL-10 in response to MalAg than did Fil − (GM, 7318 vs 3029; p = 0.006). The ratio of IL-10 to IFN-γ was also significantly higher in Fil + (GM, 1186 vs 123.5; p = 0.0004). There were no differences in the levels of MalAg-induced IL-6, IL-17A, and

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**Table I. Study population**

<table>
<thead>
<tr>
<th>Filarial Status</th>
<th>Negative (n = 19)</th>
<th>Positive (n = 19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>15/4</td>
<td>14/5</td>
<td>NS</td>
</tr>
<tr>
<td>Wb circulating Ag + (n)</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>GM (U/ml) [95% CI]</td>
<td>0</td>
<td>320.4 [56.7–1810.0]</td>
<td></td>
</tr>
<tr>
<td>Mp/microfilariaemia (n)</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>GM (mg/ml) [95% CI]</td>
<td>0</td>
<td>33 [18.0–60.0]</td>
<td></td>
</tr>
<tr>
<td>AMA-1 Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM MFI [95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG1</td>
<td>4,593 [2,587–8,156]</td>
<td>6,298 [4,032–9,840]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG3</td>
<td>13.7 [2.5–75.2]</td>
<td>26.3 [4.3–159.8]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG4</td>
<td>6.6 [1.9–23.4]</td>
<td>1.3 [0.7–2.3]</td>
<td>0.020</td>
</tr>
<tr>
<td>IgE</td>
<td>20.92 [4.2–104.3]</td>
<td>35.55 [7.8–162.6]</td>
<td>NS</td>
</tr>
<tr>
<td>MSP1-specific Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM MFI [95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG1</td>
<td>1,977 [1,073–3,644]</td>
<td>1,326 [488.9–3,597.0]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG2</td>
<td>24.27 [4.5–131.1]</td>
<td>10.9 [3.1–38.3]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG3</td>
<td>4,270 [1,156–15,773]</td>
<td>4,270 [1,156–15,773]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG4</td>
<td>6.5 [1.9–25.7]</td>
<td>5.5 [1.3–22.8]</td>
<td>NS</td>
</tr>
<tr>
<td>IgE</td>
<td>18.3 [3.9–85.6]</td>
<td>14.1 [3.3–60.3]</td>
<td>NS</td>
</tr>
<tr>
<td>BmA-specific Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM MFI [95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (μg/ml)</td>
<td>64.37 [40.4–102.6]</td>
<td>105.6 [66.5–167.7]</td>
<td>NS</td>
</tr>
<tr>
<td>IgG4 (ng/ml)</td>
<td>43.73 [3.5–348.7]</td>
<td>605.9 [110.8–3,313]</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*CI, confidence interval; mfi/ml, microfilariae per milliliter; WBC, white blood count; MFI, mean fluorescence intensity.
TNF-α between the two groups. IL-2 and IL-4 were not detectable in response to MalAg (Fig. 2) in whole blood cultures from any of the subjects.

Cytokine responses to SEB, PPD, and FilAg stimulation

There were no differences between the groups in the levels of any of the cytokines produced in response to SEB stimulation, suggesting that there was no intrinsic difference in the capacity of the cells from either group to respond to a global stimulus (Fig. 3). In response to PPD (used here as a control Ag) stimulation, cytokine levels were similar between the two groups except for those of IL-2 (which was significantly lower in Fil− compared with Fil+; \( p = 0.02 \)) and IL-10 (with Fil− demonstrating higher production; \( p = 0.01 \)). In fact, filarial infection has been shown to be associated with down-regulation of IL-2 production and T cell proliferation, and the down-regulation was IL-10 mediated (39, 40).

Because patent filarial infection has been associated with parasite Ag-specific, down-regulated cytokine responses, filaria (BmA)-specific induction of IFN-γ, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IP-10, and TNF-α was assessed in both groups of subjects (Fig. 3). As expected, Fil+ had diminished production of IL-2 (\( p = 0.01 \)) and IP-10 (\( p = 0.04 \)) compared with Fil−. Surprisingly, there was also diminished production of IL-4 in BmA-stimulated whole blood cultures in Fil−, perhaps reflecting the contribution of cells other than T cells in the production of these cytokines (37) or down-regulation by the filarial parasites themselves (41). There were no differences in the levels of IL-6, IL-17A, and TNF-α between the two groups. Although more individuals in the Fil− group produced detectable levels of IFN-γ than those in the Fil+ group, the two groups did not differ in their IFN-γ response to BmA. BmA did not induce detectable levels of IL-12p70 in any of the cultures under the conditions tested.
Effect of anti-IL-10, anti-TGFβ, and both together on MalAg-induced IFN-γ, IL-12p70, and IP-10

To determine whether the decreased IL-12 and IP-10 response to MalAg in Fil− was due to the observed increase in IL-10, whole blood samples from Fil− were cultured in the presence of neutralizing anti-IL-10 Ab as well as in the presence of a neutralizing Ab to TGFβ (another known regulatory molecule) (Fig. 4A) and to a combination of anti-IL-10 and anti-TGFβ neutralizing Ab (Fig. 4B). The addition of neutralizing anti-IL-10 Ab induced a significant increase in the production of malaria-specific IFN-γ (49.6% increase; p = 0.02) and IP-10 (221.4% increase; p = 0.0005), but not IL-12p70, when compared with production in cultures with an isotype control Ab (Fig. 4A). Neutralizing anti-TGFβ had a small but significant effect on the production of malaria-specific IP-10 but not on the other cytokines measured. Production of IL-12p70, IP-10, and IFN-γ in the presence of the combination of anti-IL-10 and anti-TGFβ neutralizing Ab was comparable to that in the presence of anti-IL-10 alone (Fig. 4B).

CD4+CD25+ T cells are the major source of T cell-derived IL-10

To determine the source of IL-10, intracellular cytokine staining coupled with cell surface staining was performed in cells cultured with and without MalAg for 24 h in a small set of cultures. As can
be seen in Fig. 5 (and in additional data not shown), the frequency of CD4\(^+\)/H11001 CD25\(^+\)/H11002 IL-10\(^+\)/H11001 cells was 3- to 6-fold higher than the frequency of CD4\(^+\)/H11001 CD25\(^+\)/H11001 IL-10\(^+\)/H11001 cells.

**Discussion**

The regulatory networks induced during chronic helminth infection (particularly schistosome and filarial infections) have been implicated in both the modulation of parasite-specific immune responses and responses to nonparasite Ag, the latter through bystander effects (so-called “spillover suppression”) (42). Not only does the helminth-induced attenuation of the immune response extend to nonparasite soluble Ag but also to responses to orally and parenterally administered vaccines (20, 43, 44), other infectious diseases (e.g., *Helicobacter pylori*, *Mycobacterium tuberculosis*, *P. falciparum*, and HIV) (45–47), and aeroallergens (48). The mechanisms underlying this modulation of host responses to bystander Ag remain unknown, although IL-10 has been the cytokine most often implicated (39, 40, 49) in mediating these spillover effects.

Among the many infections purportedly influenced by concomitant helminth infection, *P. falciparum* holds primacy in that it is responsible for an estimated 286 million clinical cases and 1.2 million deaths yearly, with 91% of the cases and deaths occurring in Africa (1). The components of the immune response implicated as being the most effective in preventing malaria infection per se are proinflammatory mediators (IFN-\(\gamma\) and TNF-\(\alpha\)), and their efficacy appears to require induction early in infection (50); however, serious pathology associated with malaria infection has also been associated with the production of many of these same cytokines (IFN-\(\gamma\), TNF-\(\alpha\), IP-10, and IL-12) (51). Current understanding of the pathogenesis of acute malaria suggests that a failure to coordinate the up-regulation of anti-inflammatory responses (such as IL-10 and TGF\(\beta\)) following the increase in inflammatory mediators leads to exuberant overproduction of these proinflammatory cytokines and significant pathology (51, 52), including cerebral malaria (53), severe malarial anemia (54), and renal failure (55).

Studies in humans and in animal models have failed to provide an unequivocal conclusion about the role played by helminth infection on either susceptibility to malaria infection or the modulation of pathology in malaria-associated disease. In some animal models, helminth/malaria-coinfected animals have been protected against severe malaria (18), whereas other studies report an increased susceptibility to severe disease (17) or no effect on severe disease whatsoever (56). More recently, *Heligmosomoides polygyrus*-infected mice immunized with blood-stage parasites of *P. chabaudi chabaudi* AS produced lower levels of malaria-specific Ab and malaria-specific IFN-\(\gamma\) but higher levels of IL-4, IL-13, IL-10, and TGF\(\beta\) (57), whereas others, using a similar model, showed that concurrent *H. polygyrus* had no effect on the development of cerebral malaria (56).

Helminth/malaria coinfection studies in humans have also produced quite disparate results, with some studies showing more severe malaria in the presence of helminth coinfections (9–12) and others showing helminth-induced protection against malaria-associated disease (13–16). Despite the differences in conclusions of each of these studies, all appear to be constant in their suggestion...
that the immune response to MalAg was influenced by the concomitant helminth infection.

There have been relatively few studies in humans examining the immune responses to MalAg in the context of a coinfected helminth parasite. A recent study in Ghana where Pf malaria, intestinal helminths, and Schistosoma hematobium are coendemic found that children from a rural area with S. hematobium and hookworm infection produced higher levels of IL-10 in response to malaria-infected erythrocytes compared with helminth-free children from an urban setting (23). In the current study, we found that patent filarial infection was associated with significantly higher IL-10 production in response to MalAg stimulation as well as significantly lower levels of IL-12p70 and IFN-γ, and IP-10. IL-12p70, IFN-γ, and IP-10 have each been shown to play critical roles in mediating the outcome in malaria infection (26, 27, 58, 59). That the IL-12/IFN-γ axis is important in protection against malaria disease in human populations has been lent additional credence by two studies in which the early induction of IFN-γ was associated with the prevention of clinical malaria (60, 61), as well as by studies of mice and nonhuman primates (62, 63). Thus, the diminution of malaria-specific induction of IL-12/IFN-γ by concomitant filarial infection may have important implications for ongoing studies evaluating the clinical outcome of malaria.

An unexpected finding of the present study is that the production of IP-10, a molecule implicated in mediating disease in malaria, was also down-regulated in cells from patients with filarial infection (see Fig. 3). Cerebral malaria has been shown in some experimental models to be mediated by IP-10 and other end products of IFN-γ-mediated signaling (64–66). In a mouse model of cerebral malaria, IP-10 and other CXC chemokines such as CXCL9 were capable of mediating the recruitment of pathology-inducing T cells into the brain (65, 66). A study in India (67) reported that plasma levels of IP-10 were higher in patients with cerebral malaria compared with those with mild malaria, with the highest levels of IP-10 being in those with fatal cerebral malaria.

Thus, the lower levels of IL-12p70, IFN-γ, and IP-10 produced by Fil+ individuals in response to MalAg stimulation may affect susceptibility to severe malaria. In fact, the severity of the malaria has not been associated solely with levels of inflammatory cytokines but rather with the ratio of these mediators to IL-10 (31, 32). The role of IL-10 in malaria pathogenesis is controversial. Some studies reported that low levels of IL-10 were associated with anemia (68); however, several studies have shown that high plasma levels of IL-10 during malaria appear to protect patients against cerebral malaria but are associated with anemia, high parasite density, and other markers of severe disease (31, 69, 70). Interestingly, in the present study the ratios of IL-10 to IFN-γ in plasma as well as the ratio of in vitro malaria-induced IL-10 to IFN-γ was significantly higher in the Fil+ group compared with the Fil− group.

IL-10 appears to be pivotal in the modulation of type I responses to MalAg (and presumably to malaria infection). Whether the increased production of IL-10 is merely a reflection of a greater number of regulatory T cells (as suggested by Rubtsov et al.) (71), direct inhibition of Th1 cells, or modulation of APC function (72) remains to be determined. What is clear, however, is that IL-10 down-regulates proinflammatory cytokines (73) and indirectly suppresses the production of IFN-γ by directly modulating the production of IL-12p70 (74, 75).

In the current study, we found that IL-10 was produced primarily by CD3+CD4+CD25+ cells (see Fig. 5). These data corroborate data seen in studies of filaria-infected expatriates (76); we did not, however, examine IL-10 production in monocytes, previously shown to be an IL-10 source in filaria-infected individuals from India (39).

Our data clearly demonstrate the modulating effects of chronic filarial infection on the Th1/proinflammatory responses to MalAg in a filarial/Pf coendemic region of West Africa. Specifically, the presence of concomitant filarial infection modulates the Pf-specific production of IL-12p70, IFN-γ, and IP-10 in a manner dependent on IL-10. Although the clinical impact of these immunologic changes remains to be determined, these data suggest that coinfections should be taken into consideration when designing vaccine strategies or other intervention trials in areas where helminth infections coexist with other nonhelminth infectious diseases.

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Disclosures

The authors have no financial conflict of interest.

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