Published in final edited form as:

Curr Opin HIV AIDS. 2012 May ; 7(3): 231–238. doi:10.1097/COH.0b013e3283522c3d.

Impact of filarial infections on coincident intracellular pathogens: *Mycobacterium tuberculosis* and *Plasmodium falciparum*

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Abstract

Purpose of review—To examine the consequences of the immune modulation seen in chronic filarial infection on responses to intracellular pathogens (and their antigens) that are often co-endemic with filarial infections, namely *Plasmodium* and *Mycobacterium tuberculosis*.

Recent findings—Much of the recent data on filaria/mycobacteria or filaria/*Plasmodium* co-infection has focused on the modulation of mycobacteria-specific or malaria-specific responses by chronic filarial infection. As such, filarial infections very clearly alter the magnitude and quality of the mycobacteria-specific or malaria-specific cytokine responses, responses that have been typically associated with control of these intracellular pathogens.

Summary—Although phylogenetically distinct, mycobacteria and *Plasmodium* spp. often share the same geographical niche with filarial infections. The complex interplay between filarial parasites that are associated with immunomodulation and those microbial pathogens that require a proinflammatory or unmodulated response for their control is easily demonstrable *ex vivo*, but whether this interplay affects disease outcome in tuberculosis or malaria remains an open question.

Keywords

filarial infections; immunomodulation; malaria; tuberculosis

INTRODUCTION

Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filaria species infect humans. Of these eight, four – *Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa* – are considered to be significantly pathogenic in humans. Filarial parasites, infecting an estimated 200 million persons worldwide, are

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Conflicts of interest: This work was supported by the Intramural Research Program of the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, and National Institutes of Health, USA.

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transmitted by specific species of mosquitoes or other arthropods and have a complex life-cycle including infective larval stages harbored by insects and adult worms that reside in either lymphatics or subcutaneous tissues of humans. The offspring of adults are microfilariae that either circulate in the blood or migrate through the skin and are the major antigenic reservoir in the host. The *Rickettsia*-like endosymbiont *Wolbachia* has been found intra-cellularly in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* and has been suggested to mediate some of the pathology associated with these infections.

The overlapping geographic distributions of filarial infections, malaria, and tuberculosis (particularly in Africa and on the Indian subcontinent) demonstrate very clearly that, on a population level, the potential for interaction among these pathogens can occur. Because each of these organisms has quite different anatomic predilections, the interplay among them is most likely indirect and related, in large part, to the differing immunological responses each pathogen induces as well as to the compartments (anatomic and cellular) each pathogen is associated with. Moreover, the temporal differences in the acquisition of the infections must also play a significant role. For example, in most co-endemic regions, acquisition of filarial infections precedes infection with *Mycobacterium tuberculosis* (Mtb), whereas malarial infection occurs early in life and likely precedes the acquisition of both filaria and *M. tuberculosis* infections.

The hallmark of the immune response in individuals with patent (or active) filaria infections of all species is a profound inability of CD4⁺ cells to proliferate or produce cytokines associated with a Type-1 (IL-2 and IFN- γ) and Type 2 (IL-5) response following parasite antigen stimulation *in vitro*. This parasite-specific anergy is mediated primarily by IL-10 and, to a lesser extent, by TGF- β . Although the immune downmodulation associated with filarial infections is parasite antigen-specific relatively early in infection, over time some bystander effects on nonparasitic antigen-specific responses, routine vaccinations, allergic processes, and autoimmune diseases have been noted (Fig. 1).

Despite the differences in basic biology, compartmental niches, genetic components, and host-cell reservoirs between *Plasmodium* species and Mtb, the approach taken in this review will examine the interface between the tissue invasive filariae and either tuberculosis or malaria. Because of the profound differences between *Plasmodium* species and Mtb, each will be considered separately in the context of co-infection.

FILARIA INFECTIONS AND MYCOBACTERIA INFECTIONS

In the nontuberculous *M. leprae* infection, the incidence of lepromatous leprosy was twice as high in areas where onchocerciasis was co-endemic than in those areas without onchocerciasis [1]. Onchocerciasis has also been shown to modulate delayed type hypersensitivity to tuberculin skin testing in adults in Mali [2] and in Chad [3] and to mycobacteria antigens (*in vitro*) in children [4]. In contrast, coincident lymphatic filarial infection had no significant influence on tuberculin skin test positivity in a population endemic for both *W. bancrofti* (Wb) and hookworm infections and tuberculosis in South India [5].

The question of whether bacillus Calmette-Guérin (BCG) vaccination at birth may bias the immune response toward a lasting Type-1 response and consequently decrease susceptibility to filaria infection is still unanswered, although a number of longitudinal cohort studies are hoping to address this specifically. The immunogenicity of BCG vaccination has been shown to be impaired in nonfilarial nematode-infected individuals and this is associated with enhanced TGF- β production but not enhanced Th2 responses [6,7]. On balance, in-vitro responses to nonparasitic antigens including the mycobacteria antigens [purified protein derivative (PPD), culture filtrate protein (CFP), and crude Mtb extract] appear to remain

largely intact (as measured by lymphocyte proliferation and/or IFN- γ production) in those with filarial infection (Table 1), and Type-1 responses to mycobacteria antigens are relatively normal [28], although several studies have documented a poor response to PPD *in vitro* in onchocerciasis [16,29].

FILARIAL MODULATION OF IMMUNE RESPONSES IN MYCOBACTERIAL INFECTIONS

The control of tuberculosis requires clearly delineated Th1 responses (IL-12, IFN- γ , and TNF- α) and, to a lesser extent, Th17 responses (IL-17A and IL-23), with both T-cell subsets playing important roles in the induction and maintenance of protective immune responses in mouse models of infection [30,31] or for control of infection (as seen in latent tuberculosis) [32,33]. Because immune-mediated protection against Mtb is characterized by strong *Mycobacterium*-specific Th1 responses, it has been postulated that coincident infections with filaria parasites could modulate these immune responses by driving Th2 and regulatory T cells (Tregs) that induce anti-inflammatory responses (Fig. 2). Indeed, while latent tuberculosis is characterized by the predominant secretion of the Th1-associated and pro-inflammatory cytokines – IL-1 β , IL-6, IL-8, IL-12, and IFN- γ , early filarial infection is characterized by a mixed (proinflammatory/Th1/Th2) response that transitions to a more downregulatory cytokine phenotype in chronic infection, dominated by IL-10. Multiple mechanisms could therefore potentially influence how filarial infections affect the immune responses to tuberculosis. Although the most direct approach to identifying the mechanisms underlying regulation by filaria parasites of infections with outcomes of and the immune response to tuberculosis would be in co-infected small animal models, there is a paucity of published studies using filaria/mycobacteria co-infected animals. Thus far, unpublished studies using mycobacteria infections of *Litomosoides sigmodontis*-infected mice or mice made microfilaremic with *B. malayi* have failed to demonstrate a significant impact of the filarial infection on mycobacterial colony counts, susceptibility to Mtb, or overall survival. However, mice infected with the intestinal helminth, *Nippostrongylus brasiliensis*, were shown to exhibit a transient impairment of resistance to primary infection and a severe impairment of resistance to secondary infection with Mtb. Moreover, IL-4R receptor-mediated alternative activation of macrophages was shown to be primarily responsible for this impaired resistance [34[■]].

The effect of preexposure to filaria parasites on the responses of antigen-presenting cells (APCs) to subsequent Mtb infection has been studied using dendritic cells and macrophages *in vitro*. It was shown that dendritic cells and macrophages are comparatively less mature in phenotype and secrete significantly fewer proinflammatory cytokines in response to Mtb infection in the context of coincident exposure to filaria parasites. In addition, the surface expression of one of the receptors used by Mtb to enter APCs, DC-SIGN (CD209), is also downregulated by preexposure to filaria parasites, suggesting that these cells are rendered less susceptible to Mtb infection. Finally, filarial infections have been shown to have a major immunological impact on the mycobacterial antigen-specific immune responses in latent tuberculosis [27[■]]. Thus, PPD-specific and CFP-specific Th1 and Th17 responses are significantly lower in latent TB-infected individuals with lymphatic filariasis compared with those without filarial infections. This downmodulation is not mediated through IL-10 or TGF- β but through the increased expression of the negative costimulatory molecules – CTLA-4 (cytotoxic T-lymphocyte antigen 4) and PD-1 (programmed death 1) [27[■]]. Filarial infections also have the additional effect of modulating the expression and function of Toll-like receptors (TLRs), specifically TLR2 and TLR9, and this attenuation can be corrected by antifilaria chemotherapy [35].

This situation suggests that filarial infections can modulate various levels of Mtb-specific responses though whether this mediates predisposition to the development of active tuberculosis awaits clarification. From a purely mechanistic point of view, filarial infections – because of their chronicity and the prototypical immune responses (e.g. Th2, IL-10, TGF- β , Tregs) they engender – clearly should modulate those responses (IL-12, IFN- γ , and IL-17) associated with susceptibility to active tuberculosis. Definitive proof, however, of this phenomenon is lacking not only in animal models of filaria/mycobacteria co-infections, but also in population-based human studies.

FILARIA AND *PLASMODIUM* CO-INFECTION

Human filaria and *Plasmodium* infections are the most prevalent vector-borne parasitic diseases worldwide and they thrive in the same geographical regions. Of the pathogens that can concomitantly occupy the same circulatory niche in the human host, malaria holds primacy as the disease-causing bloodstream infectious agent. In some areas of the world with anopheline transmission of lymphatic filariasis (e.g. West Africa, Papua New Guinea), the two infections are transmitted by the same mosquito vector [36–38].

The presence of the two parasites in the same host (co-infection) has been described in different parts of the world with varying prevalence. For example, the prevalence of people co-infected with malaria and Wb ranged from 0.3 to 0.4% in India [39,40], was 3.3% in parts of South America [38], 4.3% in Kenya [41], and 11.1% in Tanzania [42]. *Mansonella perstans* (Mp) and *Plasmodium* co-infections were reported in 18% of pregnant women in a filarial-endemic region of Uganda [43]. Filaria co-infections with *Plasmodium* have been studied in both animal models and humans [26,44–46, 47[■],48[■],49].

FILARIAL MODULATION OF IMMUNE RESPONSE IN MALARIA

Individually, filarial and malaria infections induce contrasting immune responses (Fig. 2) with human filarial infection being associated with expansion of Foxp3-expressing natural (nTreg) and IL-10-producing and TGF- β -producing adaptive (Tr1 and Th3, respectively) regulatory T cells [50–52,53[■],54] and *P. falciparum* infection being characterized by the production of proinflammatory cytokines including – among many others – IL-1, IL-6, IL-12, CXCL-9, CXCL-10, TNF- α , IFN- γ , and associated Th1 cytokines [55,56,57[■],58,59].

Protection against malaria is postulated to be mediated by both cell-mediated and humoral (cytophilic antibodies) immune responses [55]. Of all the studies of helminth and *Plasmodium* co-infections in animal models, only very few have used the animal models of filarial infection (Table 2) to study the modulation of malaria-specific immune responses. In these few, no unifying theme has emerged in that one study found that co-infection exacerbated malaria severity [45], whereas several others found that filarial infection protected mice against severe disease [44,46,48[■]]. This ambiguity might be partially attributable to differences in the species of malaria parasites or filarial organisms [60,61] and/or in differences in mouse strains used [62].

Using a co-infection model with *P. chabaudi chabaudi* AS and *L. sigmodontis* in BALB/c mice, co-infected mice had more severe disease compared with malaria only infected mice. Malaria was more severe in a microfilaremic mice compared with microfilaremic mice, and this situation was associated with increased IFN- γ production [45]. In this mouse model, however, *Plasmodium* infection is not lethal but induces proinflammatory cytokines that help control parasitemia [63] with the levels of proinflammatory cytokines being the determinant of successful control or exacerbation [64]. In a model using CBA/J mice, irradiated infective larva (L3) of *Brugia pahangi* and *P. berghei*-infected erythrocytes, co-infected mice induced high levels of Th2 cytokines and protected mice from cerebral

malaria [46]. This filaria-induced resistance to cerebral malaria was recently confirmed in a *P. berghei* and *L. sigmodontis* co-infection model in C57BL/6 mice that was IL-10 dependent and related to reduced T-cell infiltration of the brain [48[■]]. In a more permissive BALB/c mouse model, it was found that 30% of mice infected with *L. sigmodontis* failed to develop parasitemia after *P. berghei* sporozoite infection, with microfilaremic co-infected mice exhibiting greater resistance to malaria parasitemia than in a microfilaremic co-infected mice [44]. These mouse studies, in aggregate, suggest that modulation of malaria infection by filaria parasites depends on the patency of the filarial infection and the regulatory environment induced when infection reaches patency.

Although several studies have reported concomitant malaria and filarial infections in areas around the world, only a few studies have investigated the impact of filarial infection on the immune response to malaria (Table 3). In a human *L. loa* and *P. malariae* co-infection study, frequencies of Th2 cells were significantly higher in co-infected compared with those with *P. malariae* only infected patients [49].

More recently, a series of studies in Mali co-endemic for the filaria parasites Wb and Mp and *P. falciparum* has demonstrated that patent filarial infection was associated with lowered production of malaria-specific IL-12p70, CXCL-10, and IFN- γ that was IL-10-dependent [26]. Using multiparameter flow cytometry, filarial infection was shown to be associated with low frequencies of malaria-specific Th1, 'TNF- α ', and Th17 CD4⁺ T cells but higher frequencies of nTreg and aTreg/Tr1 and a complete absence of multifunctional Th1 cells [47[■]]. As Th1 differentiation is under the control of IL-12 production by APCs [66–68], the role of APCs in this Th1 downmodulation was investigated and it was found that filaria parasite-mediated suppression of the interferon regulatory factors (IRFs), particularly IRF-1 specifically in myeloid dendritic cells regulates IL-12 production and may underlie the Th1 downmodulation seen in *Plasmodium*/filaria co-infection [65].

CONCLUSION

Although phylogenetically distinct, mycobacteria and *Plasmodium* spp. often share the same geographical niche with filarial infections. As such, they cannot always be studied in isolation, but rather the important interactions among them must be considered. The complex interplay between filaria parasites that are associated with immunomodulation and those microbial pathogens that require a proinflammatory or unmodulated response for their control is easily demonstrable *ex vivo*, but whether this interplay affects disease outcome in either Mtb infection or malaria remains an open question.

REFERENCES AND RECOMMENDED READING

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- of special interest
- ■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 285).

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KEY POINTS

- Filarial infections profoundly modulate mycobacteria antigen-specific and malaria antigen-specific immune responses *in vitro* through filaria-induced IL-10 or TGF- β and through the increased expression of the negative costimulatory molecules – CTLA-4 and PD-1.
- The effect of filarial infections on the disease (tuberculosis and malaria) progression and/or outcome is still unknown.
- There is a lack of suitable animal models or large human studies of mycobacteria/filaria or malaria/ filaria co-infections to definitively ascertain the interplay between filaria and malaria or tuberculosis.

FIGURE 1.

Responses as a function of time in human filarial infections and following antifilaria chemotherapy. Top panel shows eosinophil levels and IgE and IgG4 antibody levels as a function of time following infection with the filaria parasites *Wuchereria bancrofti* and *Brugia malayi*. Bottom panel shows representations of CD4⁺ T-cell responses to parasite antigens and to bystander antigens. Dashed vertical line in each panel represents when intervention took place.

FIGURE 2.

Proposed impact of chronic filarial infections on immune responses to tuberculosis (both latent and active) and malaria. Malaria-infected red blood cells (IRBC) induce dendritic cells to produce proinflammatory cytokines that mediate the differentiation of T helper 1 (Th1) and 17 (Th17) cells. Th1 cells produce IL-2, IFN- γ , TNF- α , and LT- α that promote the phagocytosis of malaria parasites. *Mycobacterium tuberculosis* (Mtb) infects dendritic cells and macrophages; these infected cells produce proinflammatory cytokines that mediate the differentiation of Th1 and Th17 cells. Th1 cytokines produced induce the differentiation of classically activated macrophages (CAM) that promote the containment of Mtb-infected macrophages. The filaria induces basophils to produce IL-4 and mediates the differentiation of Th2 cells that produce additional IL-4. Filarial parasites also modulate dendritic cell function to induce the differentiation of natural (nTreg) and adaptive (aTregs including IL-10 producing type 1 regulatory T cells [Tr1] and TGF- β -producing Th3 cells) regulatory cells. These regulatory cells and cytokines suppress the function of Th1, Th17, and dendritic cells. The cytokines IL-10 and IL-4 inhibit the Mtb-infected CAM and promote the differentiation of Mtb-infected alternatively activated macrophages (AAM).

Table 1

Human studies on the effect of filarial infections on mycobacteria-specific responses

Filarial infection	Region	Proliferation/IFN-γ to PPD/BCG (in vitro)	Increased after anthelmintic therapy	Reference
<i>Wuchereria bancrofti</i>	Cook Islands	Intact	ND	[8]
<i>Brugia malayi</i>	Indonesia	Intact	ND	[9]
<i>B. malayi</i>	Indonesia	Intact	No	[10]
<i>W. bancrofti</i>	India	Diminished	ND	[11]
<i>W. bancrofti</i>	India	Intact	ND	[12]
<i>W. bancrofti</i>	Haiti	Intact	ND	[13]
<i>Onchocerca volvulus</i>	Sierra Leone	Diminished	No	[14]
<i>O. volvulus</i>	Sudan	Diminished	No	[15]
<i>O. volvulus</i>	Guatemala	Intact	No	[16]
<i>W. bancrofti</i>	India	Intact	ND	[17]
<i>W. bancrofti</i>	Haiti	Intact	Yes	[18]
<i>W. bancrofti</i>	India	Intact	ND	[19]
<i>W. bancrofti</i>	India	Intact	ND	[20]
<i>B. malayi</i>	Indonesia	Intact	ND	[21]
<i>W. bancrofti</i>	India	Intact	ND	[22]
<i>W. bancrofti</i>	India	Intact	ND	[23]
<i>O. volvulus</i>	Ecuador	Diminished	ND	[4]
<i>W. bancrofti</i>	Cook Islands	Intact	ND	[24]
<i>Loa loa</i>	Gabon	Diminished	ND	[25]
<i>W. bancrofti</i> / <i>Mansonella perstans</i>	Mali	Intact	No	[26]
<i>W. bancrofti</i>	India	Diminished	ND	[27 ^a]

ND, not determined

Table 2

Filaria and malaria, co-infection studies in animal models

Mouse strain	Malaria parasite	Filaria species	Disease outcome in co-infected mice	Reference
BALB/c	<i>Plasmodium chabaudi</i>	<i>Litomosoides sigmodontis</i> (no microfilaria)	Severe disease, higher IFN- γ responses	[45]
CBA/J	<i>Plasmodium berghei</i>	<i>Brugia pahangi</i> (irradiated larvae)	Decreased severity of cerebral malaria	[46]
BALB/c	<i>P. berghei</i> (ANKA)	<i>L. sigmodontis</i> (with microfilaria)	Resistance to sporozoite challenge	[44]
C57BL/6	<i>P. berghei</i> (ANKA)	<i>L. sigmodontis</i>	Decreased incidence of cerebral malaria	[48 ^a]

Table 3

Impact of filarial infection on malaria immune response in humans

Filarial infection	Region	Age of study group (size)	Impact of filarial infection on malaria-specific immune response	Reference
<i>Loa Loa</i>	Gabon	>20 (49)	High frequency of Th2 cytokine-producing CD4 ⁺ T cells	[49]
<i>Wuchereria bancrofti</i>	Mali	10–20 (38)	Impaired production of malaria-specific IFN- γ , CXCL-10 and IL-12p70 in an IL-10-dependent manner	[26]
<i>Mansonella perstans</i>				
<i>W. bancrofti</i>	Mali	10–20 (38)	Decreased frequency of malaria-specific Th1, Th17 and ‘TNF- α ’ decreased proportion of Th17 single, double and triple producers	[47 [■]]
<i>M. perstans</i>			Absence of Th1 multiple producers	
<i>W. bancrofti</i>	Mali	10–20 (38)	Impairment of interferon regulatory factors expression in mDCs	[65]
<i>M. perstans</i>			Reduced frequency of IL-12 p70-producing mDCs	

mDCs, myeloid dendritic cells.