

# Immunological Mechanisms by Which Concomitant Helminth Infections Predispose to the Development of Human Tuberculosis

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**Abstract:** Helminthic infections afflict over 1.5 billion people worldwide, while *Mycobacterium tuberculosis* infects one third of the world's population, resulting in 2 million deaths per year. Although tuberculosis and helminthic infections coexist in many parts of the world, and it has been demonstrated that the T-helper 2 and T-regulatory cell responses elicited by helminths can affect the ability of the host to control mycobacterial infection, it is still unclear whether helminth infections in fact affect tuberculosis disease. In this review article, current progress in the knowledge about the immunomodulation induced by helminths to diminish the protective immune responses to bacille Calmette-Guerin vaccination is reviewed, and the knowledge about the types of immune responses modulated by helminths and the consequences for tuberculosis are summarized. In addition, recent data supporting the significant reduction of both *M. tuberculosis* antigen-specific Toll-like receptor (TLR) 2 and TLR9 expression, and pro-inflammatory cytokine responses to TLR2 and TLR9 ligands in individuals with *M. tuberculosis* and helminth co-infection were discussed. This examination will allow to improve understanding of the immune responses to mycobacterial infection and also be of great relevance in combating human tuberculosis.

**Key words:** helminth, immune response, mycobacterial infection, tuberculosis

## INTRODUCTION

According to the World Health Organization, *Mycobacterium tuberculosis* is a growing international health concern, since it is the leading cause of human deaths due to an infectious agent [1]. This problem is further complicated by the association of tuberculosis with human immunodeficiency virus/acquired immune deficiency syndrome, and by the emergence of multi-drug resistant strains of *M. tuberculosis* [2]. The current vaccine in use against tuberculosis is *Mycobacterium bovis* bacille Calmette-Guerin (BCG) [3,4]. However, its efficacy of protection against pulmonary tuberculosis is variable. One possible explanation could be immune alteration by the prevalence of chronic infections. Helminth infections are chronic in nature and can lead to considerable morbidity. Chronic helminth infection induces a wide range of immunomodulation mainly

characterized by dominant T-helper (Th) 2 type immune responses, characterized by Th2 related cytokines, such as interleukin (IL)-4, IL-5, and IL-13 that induce B cells to switch to IgE antibody production. In addition, helminths can modulate the host's adaptive immune responses by induction of T-regulatory (Treg) cells or secretion of the anti-inflammatory cytokines, IL-10 and transforming growth factor (TGF)- $\beta$  [5]. Such effects could induce a significant inhibitory effect on protective mycobacteria-induced immune responses and/or to control mycobacterial infection. Because immune responses are an important feature of helminthic and tuberculosis infections, this study provides a review of the mechanistic basis by which concomitant helminth infections have an impact on the host control of *M. tuberculosis* infection.

## IMMUNITY AGAINST TUBERCULOSIS

Protective immunity against mycobacteria is associated with antigen presentation by the antigen-presenting cells (APCs) to T cells [6]. Alveolar macrophages and lung epithelial cells are the first cells that encounter *M. tuberculosis* during primary infection. After infection with *M. tuberculosis*, via inhalation of

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droplets containing viable mycobacteria, APC acquire the ability to stimulate type 1 CD4<sup>+</sup> Th1 cells, as well as secretion of pro-inflammatory cytokines. The induction of these inflammatory responses initiates the development of a granulomatous lesion [7], where different T cell populations participate in protective immune responses [8]. Importantly, the effector function of CD4<sup>+</sup> Th1 cells is mainly mediated by the production of cytokines, such as IL-12 and IFN- $\gamma$  [9,10]. IFN- $\gamma$  secreted by activated T cells is an important mediator of the immune response to *M. tuberculosis*, because it up-regulates antimycobacterial processes and antigen presentation by macrophages. The cytokine IFN- $\gamma$  and natural killer (NK) cells act as the principal cellular activating factors in the control of mycobacterial infection. In fact, IFN- $\gamma$  and tumor necrosis factor (TNF)- $\alpha$  are critical for protection against tuberculosis and play a central role in granuloma formation. Activated T cells stimulate antimycobacterial machinery in macrophages, which includes reactive oxygen intermediates and reactive nitrogen intermediates. Additionally, nitric oxide is an effective host defense mechanism against mycobacteria and plays an essential role in killing *M. tuberculosis* by phagocytes. Moreover, CD8<sup>+</sup> T cells participate in the immune responses against tuberculosis via cytotoxic activity, IFN- $\gamma$  production, and memory immune responses to *M. tuberculosis* [11,12].  $\gamma\delta$  T-cells were shown to be involved in *M. tuberculosis*-induced immune responses by cytokine production in early phases of infection [13] and in cytotoxic functions [14,15]. The control of tuberculosis disease requires significant Th1 responses (IL-12, IFN- $\gamma$ , and TNF- $\alpha$ ), and Th17 responses (IL-17 and IL-23) [16,17]. Furthermore, *M. tuberculosis* contains well-characterized Toll-like receptor (TLR) ligands that are potent in vitro stimuli of a number of proinflammatory cytokines [18]. A role for TLR signaling in host resistance to *M. tuberculosis* is further supported by the observation that TLR2 and TLR9 are essential in mediating optimal resistance to *M. tuberculosis* [19]. New insights into these immunological pathways could be useful to control human tuberculosis.

### IMMUNOLOGY OF HELMINTH AND *M. TUBERCULOSIS* CO-INFECTION

Helminths and *M. tuberculosis* use several mechanisms to deviate immune responses and these mechanisms may interact with important consequences for the immunology of each infection. Studies examining association between helminth in-

fection indicators and tuberculosis disease demonstrated that worms may impair immunity against mycobacterial infections. In this context, Stewart et al. [20] have found that peripheral T-cells obtained from individuals with onchocerciasis respond poorly to *M. tuberculosis* antigens. This observation was in agreement with a previous report which demonstrated that infection with *Mycobacterium leprae* was twice as high in areas where onchocerciasis was hyperendemic [21]. Moreover, the current literature indicates that helminth-infected volunteers show significantly low Th1 type responses and IFN- $\gamma$  production to *M. tuberculosis* antigens compared to dewormed controls [22].

Studies have dissected the immune mechanisms triggered by each pathogen in isolation and investigated their interaction. In this regard, it has been demonstrated that immune-mediated protection against *M. tuberculosis* is characterized by strong *Mycobacterium*-specific Th1 responses and that coincident infections with helminths could modulate these immune responses by driving Th2 and/or Treg cells [23]. In addition, Oldenhove et al. [24] have found that enhanced Treg function associated with helminth infections may suppress Th1 responses directed against unrelated antigens. This finding was supported by a publication which demonstrated that intestinal helminth co-infection is associated with reduced Th1 responses in active tuberculosis [25]. In this regard, it has been demonstrated that in a murine model, a reduced Th1 response to *Mycobacterium avium* was established by a subsequent co-infection with *Schistosoma mansoni*, affecting Th1-cytokine production [26]. More recently, data from Babu et al. [27] indicated that helminth infection coincident with *M. tuberculosis* significantly diminishes *M. tuberculosis*-specific Th1 (IL-12/IFN- $\gamma$ ) and Th17 (IL-23/IL-17) responses in latent tuberculosis. In addition, it has also been shown that the poor immunogenicity of BCG vaccination in helminth-infected populations is associated with elevated TGF- $\beta$  production [28].

### IMMUNITY FOR HELMINTH INFECTIONS

Helminth infections are potent inducers of Th2 type responses and reduced Th1 type cytokines [29]. In contrast, a protective role for the Th1 response generated by IL-12/IL-23 has been suggested based on Mendelian susceptibility to mycobacterial and other infectious diseases in children with genetic defects of the IL-12/23-IFN- $\gamma$  circuit [30]. In addition, Metzger et al. [31] showed that IL-12 induces a switch in immunoglobulin isotypes by acting on B cells both directly and indirectly via T-

cell-derived IFN- $\gamma$ , resulting in enhanced production of IgG2a antibodies and inhibition of IgE and IgG1 synthesis. Importantly, it has been demonstrated that immunization by worm antigens amplifies Th2 responses in the mouse model [32,33], and in humans [34,35]. Furthermore, it has been reported that helminth infections induce suppressive T cells which produce inhibitory cytokines, such as IL-10 that suppress inflammatory responses [36].

### IMMUNOLOGY OF HELMINTH AND OTHER MYCOBACTERIUM CO-INFECTIONS

Helminth infection indicators are also associated with reduced efficacy of BCG vaccination. In this regard, it has been reported that BCG vaccination improved cellular PPD-specific immune responses in dewormed young adults, but not in placebo-treated subjects infected with intestinal helminths, demonstrating poor immunogenicity of BCG vaccination in worm-infected individuals compared to controls [22]. In contrast, data from Erb et al. [37] showed that infection with *Nippostrongylus brasiliensis* did not necessarily interfere with the efficient elimination of *M. bovis* BCG from the lungs of mice, and that *M. bovis* BCG infection after the helminth infection did not inhibit the generation of a helminth-induced Th2 response. It is possible that the Th1 response that was initiated after the development of the helminth-induced Th2 response shut down the Th2 response, so no effects on mycobacteria clearance could be observed in the helminth-infected mice. In this regard, data from Frantz et al. [38] indicated that *Toxocara canis* infection did not necessarily lead to increased susceptibility to pulmonary tuberculosis. A possible explanation for these divergent findings may lie in the fact that the impact of helminthiasis on the host response to *M. bovis* BCG is dependent on the type of helminth, and/or the intensity of infection. A previous study has indicated that schistosomal infection reduced the effect of BCG vaccination due to the potency of Th2 polarization induced by helminth infection that increases susceptibility to *M. bovis* BCG infection [39]. These data were supported by publications which demonstrated that the immunogenicity of BCG vaccination in children born to mothers with schistosomal infection during pregnancy is poor compared to children born to mothers without schistosomiasis, indicating that exposure to worm antigens while in the uterus could significantly impair responses to BCG-specific Th1 type responses [40,41]. This is important since the current BCG vaccination is mostly ad-

ministered directly after birth. The fact that BCG vaccination confers the least protection in developing tropical countries with high prevalence of helminthic infections indicates that an effective BCG vaccine for those people living in helminth-endemic parts of the world may need a modified adjuvant compared to a vaccine for use in areas where there is a low endemic prevalence of helminths. The influence of helminth infections on BCG vaccination efficacy should be taken in consideration when designing a new vaccine against tuberculosis. It is important to consider that it remains to be elucidated why some helminths modify the immunological responses to BCG while others do not.

On the other hand, in a case-control study it has been demonstrated that indeed there is a strong association between *Ascaris lumbricoides* infection and active pulmonary tuberculosis, indicating that immunological mechanisms induced by intestinal helminths affecting mycobacterial immunity could have clinical relevance [42]. In this regard, Tristao-Sa et al. [43] found high intestinal nematode infection rates in patients suffering from pulmonary tuberculosis, indicating that helminth-induced immunomodulation may affect the ability of the host to cope with *M. tuberculosis* infection. In addition, Bentwich et al. [44] found that such helminth-associated hyporesponsiveness is a result of chronic immune activation. Moreover, the findings of Diniz et al. [45] indicated a strong association between intestinal nematode infection and increased risk for multibacillary leprosy [45].

Studies on molecular immunological pathways that induce both Th2 and/or Treg responses indicate that the interactions of helminths with APCs are at least in part through TLRs [46]. In addition, TLRs form a key component of host immune responses against tuberculosis since the absence of TLR2 signaling affect mostly the long-term control of chronic *M. tuberculosis* infection. Furthermore, recent evidence indicates that optimal IL-12, IL-23, and IL-27 production by cells is through TLRs [47]. In this regard, it has been demonstrated that mice lacking the major adaptor protein MyD88 (myeloid differentiation factor 88), required for TLR signaling, are highly susceptible to *M. tuberculosis* infection [48]. At present, it has been reported that a different mechanism by which concomitant helminth infection predisposes to the development of latent tuberculosis is through a profound inhibitory effect on protective mycobacteria-specific TLR-mediated immune responses in latent tuberculosis [49]. In addition, these authors demonstrated that Toll-ligand-induced pro-inflammatory cytokine pro-

duction (IL-12, IFN- $\gamma$ , and TNF- $\alpha$ ) is diminished in the presence of helminth co-infection. Moreover, the definitive treatment of parasites significantly restores the pro-inflammatory cytokine secretion in patients with tuberculosis. Importantly, it has been demonstrated that the activation of TLRs by helminth derived molecules leads to different downstream activation of proteins, such as MAP kinases. In this context, it has been demonstrated that activation of APCs via TLRs can lead to activation of ERK [50].

Another important molecular mechanism of helminth-specific Th2 response is through maturation of dendritic cells [51]. In fact, immunological studies on the effects of helminth infections on tuberculosis indicated that macrophages and dendritic cells exposed to live microfilariae *in vitro* demonstrated reduced maturation after infection with *M. tuberculosis*. Moreover, dendritic cell-specific ICAM-3 grabbing non-integrin lectin receptor, used by *M. tuberculosis* to enter dendritic cells, was demonstrated to be reduced on the surface of dendritic cells preexposed to *B. malayi* microfilariae [52]. This finding was supported by a publication which demonstrated that regulation of some markers associated with dendritic cell maturation (MHC class II, CD40, and CD86) have been seen with proteins released by schistosome larvae, an helminth associated with a Th2 immune response [53]. Taken together, these findings indicate that helminths may impair immunity against mycobacterial infections by different molecular mechanisms of immunomodulation, affecting the ability of the host to respond to *M. tuberculosis*. Therefore, mass deworming of infected individuals could contribute toward control of human tuberculosis.

### CONCLUDING REMARKS

*M. tuberculosis* and helminth infections coincide geographically, and tend to induce opposing immune responses. The widespread existence of helminth infection in areas of high tuberculosis incidence may affect the ability of the host to respond to mycobacterial antigens. Antigens from helminths and mycobacteria have immunomodulatory activities that can affect immune responses in specific directions. Helminth infections have a significant influence on the immune system and there are immunological evidences demonstrating that helminths very clearly alter the magnitude of the mycobacteria-specific cytokine responses, altering the control of the mycobacteria growth. At present, animal models of tuberculosis and helminth co-infection showed that mycobacteria-induced

immune responses are suppressed by helminth infections. However, whether this interplay affects disease outcome in human tuberculosis remains an open question. Therefore, the *in vivo* relevance of these observations has to be more intensively examined by immunological studies. The responses to BCG vaccine are also not entirely conclusive and it might be important to address the question whether regular mass deworming could be of relevance in control of human tuberculosis. In addition, although there are studies showing an association between helminths and reduced Th1 immunity against *M. tuberculosis* infection, maternal anthelmintic therapy had no effects on child's immune responses to BCG vaccination. Finally, recent data on helminths/mycobacteria co-infection have focused on immunomodulation of mycobacteria-specific responses by chronic helminth infections. Thus, understanding the molecular mechanisms that mediate the effects that helminths have on the immune responses to mycobacterial antigens will provide us with information that can be exploited to control human tuberculosis. In addition, dissecting the signaling pathways that are triggered by helminth-derived molecules may help target pathways that would significantly reduce adverse effects by helminths.

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