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MODULATION OF TUBERCULOSIS-RELATED IMMUNE RESPONSES BYHELMINTHS

By

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Abstract

Tuberculosis (TB) continues to be a major worldwide health problem, with 9.4 million newly emerging active tuberculosis cases and causes nearly 2 million deaths annually. Currently, experimental evidence for an strong association between helminths and diminished T helper (Th)1 immunity against *Mycobacterium tuberculosis* infection is based on studies which show that helminth-induced Th2, T regulatory (Treg) responses and alternatively activated macrophages contribute to enhanced susceptibility to TB. In this context, it has been shown that Th1 response is reduced in helminth coinfected TB patients. This article discusses what is presently known about the types of immune responses modulated by helminths to diminish the protective immune response to TB.

Key words: Helminths, immune responses, tuberculosis.

Introduction

In many regions of the world, a high prevalence of helminth infections and *Mycobacterium tuberculosis* infections can be found (Hotez *et al,* 2011; WHO 2012). Coinfection with different helminths could be an important event with the possibility to increase *M. tuberculosis* infection in endemic areas. To date, there are more than 20 helminth species infecting humans (Bethony *et al,* 2006; Hotez *et al,* 2011). Despite the recent advancements in research, helminth infections affect 1.5 billion people worldwide. Given the overlapping geographic distribution of *M. tuberculosis* and helminths infections, there is a pressing need to investigate whether tropical helminthic infections might enhance TB progression to disease.

Tropical helminthic infections induce a wide range of immunomodulation mainly characterized by increased production of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 that induce B cells to switch to IgE secretion (Reina *et al,* 2011) while blocking Th1 cytokines such as IL-12 & interferon (IFN)-γ (Méndez-Samperio, 2012). Helminth infection has also been associated with regulatory B cells that can induce the secretion of IL-10 (Hussaarts *et al,* 2011), and affect the expansion of immune responses with the ability to skew development of macrophages from classically activated macrophages to alternatively activated macrophages which can be induced by IL-4, and IL-10 (Mosser and Edwards, 2008). In coinfected individuals, helminth induced strong anti-inflammatory response might be an important mechanism to prevent the development of a Th1 response which is critical for host resistance against TB (Flynn *et al,* 2011). Importantly, helminths target both, Th1 response and macrophage anti-*M. tuberculosis* effector immune responses.

This study reviews evidence weight supporting an association between helminths and diminished protective immune response to TB.

Evidence for an association between tropical helminthic and tuberculosis disease is based on studies which show that worms may impair immunity against mycobacterial infections. In this context, it has been demonstrated that infection with *M. leprae* was twice as high in areas where onchocerciasis was hyperendemic (Prost *et al,* 1979). Stewart *et al.* (1999) showed that peripheral T-cells obtained from individuals with on-

chocerciasis respond poorly to *M. tuberculosis* antigens. Elias *et al*. (2001) found that helminth-infected volunteers with significantly low Th1 type responses and IFN-γ production to *M. tuberculosis* antigens compared to dewormed controls. They showed that chronic worm infection of mice reduces immunogenicity (Elias *et al,* 2008). Moreover, the current literature indicates that intestinal helminth co-infection has a negative impact on anti-mycobacterial immune response (Resende *et al*, 2007). Diniz *et al*. (2010) reported that intestinal helminths may decreases Th 1 type responses in tuberculoid leprosy patients.

Studies have dissected the immunological mechanisms by which concomitant helminthic infections modulate protective response to TB and showed that chronic helminth infection reduces the immune response to mycobacteria infection by driving Th2 and/ or Treg cells (Salgame, 2005). Also, data from Babu *et al.* (2009a) indicated that helminth infection coincident with *M. tuberculosis* significantly diminishes *M. tuberculosis*-specific Th1 (IL-12/IFN-γ) and Th17 (IL-23/IL-17) responses in latent tuberculosis, indicating the important inhibitory effects of TH2 cytokines on TH1 response. More evidence to support helminth-induced immunomodulatory effect on *M. tuberculosis* infection came from Babu *et al.* (2009b) who found that patients coinfected with *Filaria* and *M. tuberculosis* exhibited a significant reduction of both Toll-like receptor (TLR)-2 and TLR-9 expression and in proinflammatory cytokine production. Interestingly, immunological studies on the effects of helminth infections on TB demonstrated that dendritic cells exposed to live microfilariae *in vitro* induced reduced maturation after infection with *M. tuberculosis* (Talaat *et al,* 2006). Taken together, these reports indicate that helminths may impair immunity against TB by different molecular mechanisms of immunomodulation. Thus, mass deworming of infected individuals might be useful to control human TB.

To date, the current vaccine in use against tuberculosis is *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG). However, its efficacy of protection against pulmonary tuberculosis is variable (0-80%) (Crampin *et al,* 2009). A possible explanation of such variation might be the presence of chronic helminth infection. Elias *et al.* (2005) reported that the poor immunogenicity of BCG vaccination in helminth-infected populations is associated with elevated TGF-β production. In contrast, Webb *et al.* (2011) found that a single-dose of anti-helmintic treatment during pregnancy had the ability to mount a Th1 immune response to BCG vaccination on an infant's immune response. Nevertheless, it is important to conduct studies in humans to determine whether helminth infection later in life will impact on the immune protective efficacy of BCG.

More evidence of helminth-induced immunoregulation during mycobacterial infection has identified helminth-induced alternatively activated macrophages as the immunological basis for enhanced susceptibility of coinfected hosts to TB (Potian *et al,* 2011). Furthermore, the same group showed that modulation of pulmonary TB-immune responses by helminths is due in part by engaging the IL-4 receptor pathway.

In addition to murine models, mathematical or computer-based in-silico models have been development to understand how systemic immunomodulation by helminths could affect immunity on TB. Marino *et al.* (2011) used a hybrid multicompartment model of granuloma formation in tuberculosis. Interestingly, the use of a mathematical model approach to study complex immunity of coinfected hosts suggest that the effective helminth reduction in coinfected animals is due at least in part to bacteria-induced neutrophil response (Thakar *et al,* 2012).

Conclusion

The effect of helminths on modulating immune responses to TB is varied. However, the experimental evidence indicated here-

in provides a strong plausibility that mycobacteria-induced immune responses are suppressed by helminth infections. It is important to note the urgent need to conduct studies in humans to determine whether helminth infections increase TB incidence and affect the protective immune response to BCG. Besides, it might be important to address the question whether regular mass deworming could be of relevance in control of human TB. Finally, dissecting the molecular mechanisms that mediate the effects that helminths have on the immune responses to mycobacteria will provide us with information that would significantly reduce the negative influence of helminths on the induction of protective immunity against TB.

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