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The impact of mucosal infections on acquisition and progression of tuberculosis

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More than one-third of the world's population, or over 2 billion people, are infected with *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis in humans. Why only 10% of those infected develop active disease while the remainder harbor latent infection remains one of the greatest scientific and public health mysteries. Bacterial persistence is characterized by a dynamic state of immunological tolerance between pathogen and host. The critical role of CD4$^+$ T cells in defense against intracellular pathogens became evident during epidemiological studies of HIV-1 infection, which showed a clear inverse relationship between CD4$^+$ T-cell count in peripheral blood and increased risk of infection with *M. tuberculosis*, pneumocystis and *Toxoplasma gondii*. There is also growing evidence of a common mucosal immune system, whereby immune cells activated at one mucosal site may disseminate to remote effector sites. In this commentary, we review emerging evidence from human studies that the outcome of *M. tuberculosis* infection is influenced by concurrent mucosal infections, using *Helicobacter pylori* and geohelminths as examples. Understanding how the complexity of microbial exposures influences host immunity may have important implications for vaccine development and therapeutic interventions.

INTRODUCTION

The mucosa of the gastrointestinal and respiratory tracts comprise the largest surfaces in contact with the external milieu. This system is designed to provide a physico-chemical barrier against dissemination of pathogenic mircroorganisms while sampling a vast array of foreign antigens, presenting them to the immune system, and adapting them to the presence of foreign microbial communities.[1] In addition to pattern recognition and secretory antibody defenses, mucosal-associated lymphoid tissue (MALT)—populated by distinct dendritic, T, B, and accessory cell populations—acts as an inductive tissue for priming of antigen-presenting cells at remote effector sites via the "common mucosal immune system".[2,3] Gut-associated lymyphoid tissue—the subset of MALT that exists in the gastrointestinal tract—is a major site for induction of T regulatory cells necessary for microbial tolerance.[4] With recognition of the common mucosal immune system and its unique properties, the development of mucosal vaccines and therapies has become an area of intense research interest.[2,5,6]

In this commentary, we briefly review epidemiological evidence that the clinical outcome of the respiratory infection caused by *Mycobacterium tuberculosis* may be modulated by mucosal infections that are endemic in the same populations. As examples, we focus on *Helicobacter pylori* and gastro-intestinal helminthiasis, two major gut-associated "pathobiontic" infections that frequently co-exist in TB-infected hosts (**Figure 1**). We propose that colonization with these pathogens exerts competitive effects on regulation of the immune response to *M. tuberculosis*: *H. pylori* promoting a Th1-type response consistent with control of TB, and helminthiasis promoting a Th2-type response that may disregulate responses to tuberculosis (TB). In each case, the newly recognized Th17 lineage[7–10] may also have a role. These lines of investigation are just beginning, and further mechanistic as well as immuno-epidemiological research is needed. Understanding how common, naturally occurring mucosal infections influence immunity to TB may lead to further insights into the therapeutic properties of the common mucosal immune system.

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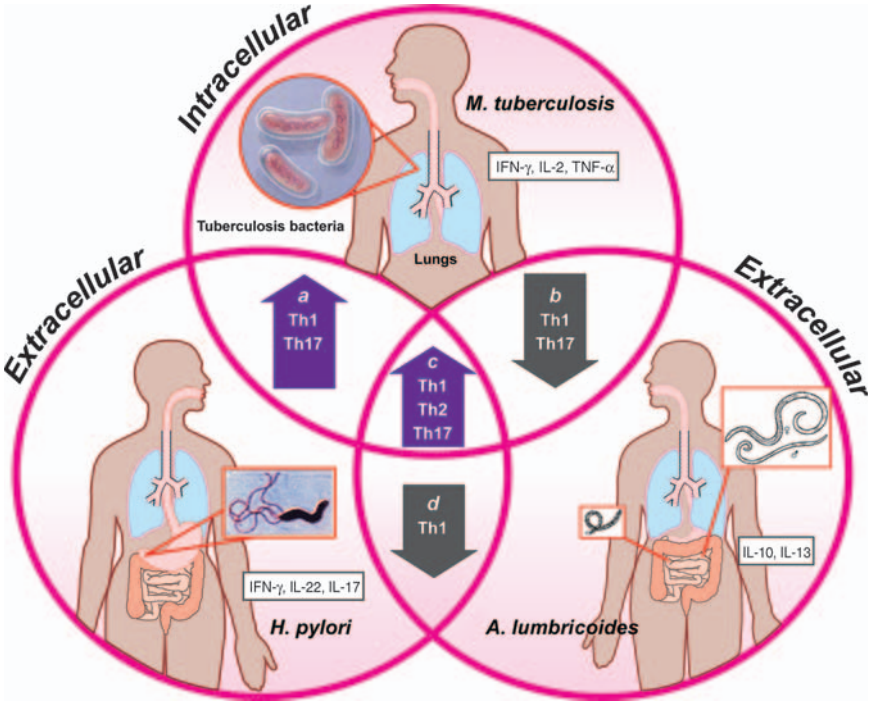

Figure 1 Hypothetical framework for interaction of protective immune responses to *Mycobacterium tuberculosis* (*Mtb*) infection in the setting of (**a**) *H. pylori*, (**b**) intestinal helminth, and (**c**) triple infection: (**a**) *Mtb/H. pylori* coinfection may enhance pro-inflammatory signals (e.g., interferon (IFN)-γ) involved in control of TB infection,[68,85] while (**b**) *Mtb*/helminth co-infection may suppress pro-inflammatory responses to *Mtb* infection via the Th2 pathway.[53,54] The presence of all three infections (**c**) would be expected to heighten pro-inflammatory and anti-inflammatory signals. Also, as shown in (**d**), *H. pylori* and helminth co-infection may suppress proinflammatory responses to *H. pylori* infection.[81,82] IL, interleukin; TNF, tumor necrosis factor.

IMMUNO-EPIDEMIOLOGY OF TB

The intracellular pathogen *M. tuberculosis* has co-existed in human populations for at least 50,000 years.[11] Spread from person to person via aerosol droplets, *M. tuberculosis* infects one-third of the world's population, or over 2 billion people. Despite dramatic declines in incidence and prevalence of TB infection in industrialized countries, there are over 8 million new cases of *M. tuberculosis*, 1.5 million deaths, and 40 million new infections each year.[12] Although TB typically occurs in poor socio-economic conditions, even under these circumstances, a competent human immune system is equipped to control the infection. Of those exposed to TB, only 30%[13,14] are thought to develop the state of latent infection, during which the host remains clinically well, but bacilli survive within T-cell activated granulomas in a dormant or slowly replicating state.[15] Of those harboring a latent infection, on average, only 5–10% will progress to active clinical disease, the majority within 2–3 years of exposure. Approximately 50% of those with active disease will survive without treatment, although each could infect an additional 10–20 contacts during the period of active disease.[12,16]

Protective immunity to TB is predominately cell-mediated and incompletely understood. Although the precise mechanisms are controversial, TLR-mediated innate immunity and microbicides present in the airways, and are likely to play a role in resistance during the initial phases of acute infection.[17] The only vaccine currently in use, the live attenuated *M. bovis*-derived Bacille–Calmette–Guerin (BCG) vaccine, stimulates a wide spectrum of cellular immune responses, but has highly variable efficacy, and does not protect against adult pulmonary disease.[18,19] Based on animal models of BCG vaccination, T-cell recall responses are delayed approximately 2 weeks post-challenge, representing a significant delay in T-cell priming.[20] For this reason, mucosal Th17 vaccines based on early recruitment of neutrophils with production of interleukin (IL)-17 and mediators such as IL-23 in the alveolar passages are a promising area of investigation.[9] Mucosally administered TB vaccines may offer properties superior to the intramuscular route.[21]

With the establishment of latent *M. tuberculosis* infection, a network of pro-inflammatory and regulatory circuits is invoked to sequester bacilli-infected macrophages within granulomae. Both tumor necrosis factor-α and interferon (IFN)-γ derived from activated T cells appear to be essential for maintaining the integrity of granulomae and preventing reactivation.[22] Central memory T-cells expressing IL-2 also appear to be important for clearance of infection and resolution of fibrosis.[23–25] To circumvent these defenses, *M. tuberculosis* inhibits phagolysomic fusion and acidification within macrophages.[15,26] In household-contact biomarker studies, early progression has been associated with alterations in the production of regulatory Th-2 cytokines, such as IL-4 and IL-10.[27,28] Thus, the balance of effector and suppressive immune responses appears to be important in the host's prolonged management of TB infection.[29] In longitudinal studies, many acquired immuno-suppressive conditions are known to disrupt this balance

and increase the risk of active disease, including HIV infection,[30,31] malnutrition,[32] Vitamin D deficiency,[33] diabetes,[34] and anti-tumor necrosis factor-α therapy.[35] With insights from systems biology models, a dynamic spectrum of TB infection, continuously mediated by micro-environmental factors, has been postulated.[17,36] Understanding the role of concurrent mucosal infections like *H. pylori* and gastro-intestinal helminthiasis may lead to better delineation of this spectrum.

INTESTINAL HELMINTHS AND *M. TUBERCULOSIS*

Over a quarter of the world's population is infected with the soil-transmitted intestinal helminths, including the roundworm *Ascaris lumbricoides*, the hookworms *Necatoramericanus* and *Ancylostomaduodenale*, the whipworm *Trichuristrichiura*, and *Enterobiusvermicularis*, and *Strongyloides* spp.[37,38] Despite their species diversity, gastrointestinal helminths (and also many non-mucosalworms) elicit a stereotypic human immune response. Classically, this is characterized by secretion of IgE and IgG4 isotype with concurrent eosinophilia,[39] and polarization of CD4+ T cells towards a Th2 phenotype,[40–42] on which expulsion depends.[43] This "modified" Th2 phenotype is associated with production of the cytokines IL-4, IL-9, IL-10, IL-13,[44] as well as induction of Foxp3+ Treg cells and regulatory cytokines TGF-β and IL-10.[45] In endemic regions, worm burdens tend to peak by adolescence, suggesting the development of partial resistance with age.[40] Conversely, the virtual disappearance of helminths from the human microbiome of high-income countries has been linked with the rise in atopic and auto-immune conditions,[46] possibly due to effects on Treg induction. Based on these findings, helminth-based therapies for conditions such as multiple sclerosis and inflammatory bowel disease are an active area of investigation.[47,48]

Although there are few studies, epidemiological evidence suggests that helminth infections may diminish immune responses to TB antigens. In humans, chronic intestinal helminathiasis is associated with immune hypo-responsiveness,[49,50] including a "bystander effect", to oral cholera[51,52] and BCG vaccines.[53] In a randomized control trial, Elias *et al.*[54] reported that albendazole deworming was associated with significant improvements in purified protein derivative-induced IFN-γ production following BCG vaccination of Ethiopian adults. In a second trial, this team also reported that co-infected adults not receiving anti-helminthic treatment had increased production of PPD-induced TGF-β 3 months following BCG vaccination.[53] In a Brazilian cohort, TB patients with intestinal parasites had lower IFN-γ and higher IL-10 levels compared with TB patients without intestinal parasites.[55] In *in vitro* T-cell functional studies in blood from Indonesian school children, researchers found that geohelminth-associated regulatory T-cell responses suppressed IFN-γ responses to BCG and *Plasmodium falciparum*, an effect that was reversed with removal of CD4+CD25^{hi} T cells.[56] These studies offer evidence that both inflammatory and regulatory signals involved in control of TB infection can be modified by concurrent intestinal helminth infection. Some filarial worms and tissue-invasive cestodes, beyond the scope of this commentary, are also thought to affect responsiveness to mycobacterial antigens, although the mechanisms may differ.[49] Although environmental mycobacteria are widely considered to block immune responses to TB antigens,[57] their distribution does not account for the wide variability in responses to BCG. The role of concurrent helminth infections needs to be more systematically explored in the context of TB vaccine and immunogenicity trials.

H. PYLORI AND *M. TUBERCULOSIS*

H.pylori, a bacterium that colonizes the gastric mucosa and epithelial lining of the human stomach, remains one of the most common chronic mucosal infections in the world,[58] infecting approximately 80% of those in TB-endemic regions. Typically acquired in early life via oral–oral or fecal–oral pathways,[59] chronic infection is now known to be the preeminent cause of gastric cancer and peptic ulcer disease.[60–62] All infected hosts develop a superficial gastritis that typically persists asymptomatically for many decades. In addition to specific IgA, IgM, and IgG responses, this gastritis is associated with induction of IL-8 by epithelial cells,[63] as well as a locally vigorous, cell-mediated immune response, characterized by increased mucosal concentrations of the inflammatory cytokines IFN-γ, tumor necrosis factor-α, IL-1β, and IL-6.[64] The cytokine IL-12 is present in large numbers of mononuclear cells and appears to be involved in differentiating naive T-cells into a Th1 phenotype.[65] Although the predominate profile during infection is inflammatory, the IL4 antagonist, IL-4δ2, T-regulatory-activated IL-10, as well as B-cell responses, may be permissive for chronic *H. pylori* colonization via counter-regulatory mechanisms.[66] The role of IL-17 in inflammation and recruitment of neutrophils at the site of infection is an area of intense investigation.[67,68]

As helminth infections vary with respect to their immunological effects, so too, *H. pylori* strains elicit different immune responses.[69] Of particular note, some *H. pylori* strains contain a pathogenicity island,[70] a 30-gene cassette encoding a Type IV secretion system that translocates virulence factors to the host cytosol.[71] This pathogenicity island induces increased inflammation with higher risk of ulcer disease[72] and gastric cancers.[73,74] Host polymorphisms are also thought to exacerbate this interaction.[75] Other differences in *H. pylori* strain, such as expression of the active form of the immunogenic vacuolating antigen[76] or preservation of the outer membrane protein BabA (which mediates adhesion to human Le^b blood group antigens), may also influence immunological reactions by affecting attachment and neutrophil recruitment.[64]

Dramatic declines in the incidence of *H. pylori* infection occurring in industrialized regions during the twentieth century have corresponded with increases in the prevalence of allergy-like symptoms[77] as well as upper gastrointestinal diseases.[78] These trends have prompted some investigators to speculate that in regions of high infant mortality, immune-regulated *H. pylori* infection confers survival advantages against deadlier infections of early childhood.[79] For example, in Northern

Californian Hispanic households, *H. pylori* infection was associated with protection from household gastroenteritis.[80] That concurrent helminth infection has been observed to alter the inflammatory response to *H. pylori* in rodent[81] and human[82] studies could support the notion that the two infections exert competitive regulatory effects on cell-mediated immunity when present in the same host.

Because social conditions contributing to the prevalence of *M. tuberculosis* and *H. pylori* are similar, cross-sectional studies of disease association tend to yield conflicting results.[83,84] Few studies have correlated immune responses to *H. pylori* and TB infection in co-infected hosts. In a preliminary finding, we have reported that Northern Californians seropositive for *H. pylori* and testing positive for latent TB have enhanced IFN-γ production and a dominant Th1-type cytokine profile in response to specific TB antigens.[85] We also reported that, compared with latently infected household contacts who did not progress to active TB disease during 2 years of follow-up, Gambian TB patients were one-third as likely to be *H. pylori* seropositive. However, in Gambian and Pakistani household contacts exposed to an infectious case of TB, baseline *H. pylori* infection was not associated with secondary case activation after 2 years. In cynomolgus macaques, those with natural *H. pylori* infection were one-third as likely to progress to TB 6–8 months after *M. tuberculosis* challenge.[85] Although these lines of investigation provide preliminary evidence of enhanced immunity to TB with *H. pylori* infection, challenges in study design remain to be overcome. These include the relatively poor predictive value of immunodiagnostics in the setting of primary progressive TB,[86] the need to identify more prevalent intermediate markers of progression, and the suboptimal performance of *H. pylori* serology in the developing world.[85]

If *H. pylori* influences the immune response to TB infection, there are several possible mechanisms. For example, *H. pylori* could promote a "Th2–Th1 switch" in early life, such that Th1-type responses to an unrelated MALT infection are permanently heightened. Such a "hygiene hypothesis" has been proposed for hepatitus A virus.[87] Studies comparing BCG immunogenicity in infants and adolescents from developing and industrialized countries also support this type of phenomenon.[88] In a second model, active, asymptomatic, *H. pylori* gastritis would provide a continuous source of inflammatory stimulation. Such a "bystander" model was recently described for mice infected with mucosal herpes viridae and protected from subsequent challenge by *Y. pestis* and *L. monocytogenes*. This model may apply uniquely to chronic mucosal infections.[89] Though more speculative, *H. pylori*-induced IL-17 might have a role in early T-cell recruitment to the lung compartment, thereby enhancing initial resistance to latent TB infection. Another possibility is that dysregulation of the *H. pylori*-associated gastric T-regulatory system compromises systemic Th1 responses involved in control of a TB infection. In separate laboratory studies, the IL-4 inhibitor, IL4δ2 splice variant, has been implicated both in upregulation of the Th1 dominant *H. pylori* Cag A response[90] and downregulation of the Th2-mediated response associated with progression of latent TB infection.[91]

TOWARD A MICROBIOMIC PERSPECTIVE

The human immune system has evolved in the face of a panoply of commensal and mutual infections.[92] Classic mucosal defenses, including organogenesis of lymphoid follicles, induction of secretory IgA, and recruitment of the cell-mediated armentarium appear to be seeded and orchestrated by the establishment of microbrial communities in early life.[93,94] Growing evidence implicates the human microbiome as a major regulator of immunopathologies associated with diverse conditions such as inflammatory bowel disease,[95] obesity,[96] allergies,[97] and even psychopathology.[98] Understanding the interactions of naturally occurring mucosal infections such as *H. pylori*, intestinal helminths, and *M. tuberculosis*—three distinct parasitic infections present in the same ecosystem for millennia, exerting contrasting immunoregulatory effects, to which the normal human immune is substantially adapted—offers a potentially informative "microbiomic" perspective for vaccine and immunodiagnostic research. The evidence presented here remains preliminary and belies the need for more original work. The research infrastructure now assembled for TB vaccine trials provides a well-organized platform to roll out interdisciplinary prospective studies of major public health importance.

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DISCLOSURE

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