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Review

The role of B cells and humoral immunity in *Mycobacterium tuberculosis* infection

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ABSTRACT

Mycobacterium tuberculosis remains a major public health burden. It is generally thought that while B cell- and antibody-mediated immunity plays an important role in host defense against extracellular pathogens, the primary control of intracellular microbes derives from cellular immune mechanisms. Studies on the immune regulatory mechanisms during infection with *M. tuberculosis*, a facultative intracellular organism, has established the importance of cell-mediated immunity in host defense during tuberculous infection. Emerging evidence suggest a role for B cell and humoral immunity in the control of intracellular pathogens, including obligatory species, through interactions with the cell-mediated immune compartment. Recent studies have shown that B cells and antibodies can significantly impact on the development of immune responses to the tubercle bacillus. In this review, we present experimental evidence supporting the notion that the importance of humoral and cellular immunity in host defense may not be entirely determined by the niche of the pathogen. A comprehensive approach that examines both humoral and cellular immunity could lead to better understanding of the immune response to *M. tuberculosis*.

1. Introduction

Mycobacterium tuberculosis remains a significant public health burden worldwide. The World Health Organization reported that in 2012, there were 8.6 million incident cases of tuberculosis [1]. That same year, the disease killed 1.3 million people, 170,000 of whom died from multidrug-resistant infection [1] Co-evolution of the tubercle bacillus with the human host for centuries [2–4] has bestowed upon this pathogen a remarkable adaptability and tenacity for survival in an infected host, facilitated by a wide array of sophisticated mechanisms to modulate and to evade the host immune response [5,6]. A naïve host develops primary tuberculosis upon the first encounter with *M. tuberculosis* [7]. Most of the infection is restricted and well contained at the primary site of bacterium-host interaction and the local draining lymph nodes, which together, are called the Ghon complex [7]. It is generally accepted despite being well controlled, the bacilli are not eradicated due to the unique ability of *M. tuberculosis* to enter a dormant state to establish a clinically silent latent infection that can subsequently reactivate to cause active diseases, sometimes decades later [8–10]. Post-primary tuberculosis, which occurs in a sensitized host, accounts for most of the cases that manifest active diseases, and is generally caused by exogenous reinfection or reactivation of latent bacilli [7]. The mechanisms underlying tuberculous reactivation remain to be clearly defined; but it is well established that a host with compromised immune function, such as individuals with HIV infection and those receiving tumor necrosis factor (TNF) blockade therapy, is at increased risks for developing disease recrudescence [11–13]. The latently infected constitute a reservoir of individuals that is critical for the perpetuation of the tubercle bacillus. These unique properties to persist in and transmit insidiously among the population render eradication of *M. tuberculosis* difficult [14]. In the post primary stage of infection, *M. tuberculosis* has the propensity to promote the development of caseating pneumonia in the sensitized host that can lead to tissue necrosis and eventual cavitation [7]. These immunopathological changes, whose underlying mechanisms have not been

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clearly characterized, enable effective bacterial transmission and therefore play an important role in the pathogenesis of the tubercle bacillus [7,15].

A most effective way to combat an infectious disease is through immunization with efficacious vaccines [16]. For example, the existing measles vaccine costs approximately $17/disability-adjusted life year, making it one of the most cost-effective health interventions in developing countries [17]. The development of a reliable and effective vaccine against *M. tuberculosis*, however, has not been straightforward [18–20]. This difficulty is, at least in part, due to the complex life cycle of *M. tuberculosis* in the host [6], which elicits a spectrum of immunological responses not yet completely characterized; and the lack of a well-defined molecular and biochemical signature of protection against infection [19,21]. The only anti-tuberculosis vaccine currently in use is bacillus Calmette–Guèrin (BCG) [22]. Although this vaccine effectively protects against severe childhood tuberculosis, its efficacy against adult pulmonary disease is inconsistent [23–26]. Concerted efforts of the tuberculosis community, however, together with advances in the fields of immunology and vaccinology [17,27,28], should hold promise for the rational design of effective vaccines against *M. tuberculosis* [18–20].

Characterization of the immune response to *M. tuberculosis* has largely focused on cell-mediated immunity [18–20]. This approach is not without reasons. For example, the inconsistent efficacy of passive serum therapy in treating tuberculosis in the late nineteenth century, which was likely due to the use of non-standardized protocols and reagent, had cast doubt on the significance of humoral immunity in the control of *M. tuberculosis* [29,30]. This doubt has been further bolstered by the generally accepted concept that while cell-mediated immunity plays a critical role in defense against intracellular pathogens, their extracellular counterparts are best controlled by B cell and humoral immune response [31–33]. Based on this latter concept, vaccine development against intracellular pathogens, including *M. tuberculosis*, has taken a mostly T cell-centric approach [34]. There exists, however, experimental evidence that humoral immunity can impact substantially on host defense against pathogens with a preferred intracellular niche (reviewed in [35,36]). Taking a more comprehensive approach, encompassing both cell-mediated and B cell and humoral immunity, to characterizing immune responses to *M. tuberculosis* will likely gain new insights that can help design anti-tuberculosis strategies, including immunotherapies and vaccines.

2. The role of B cells and humoral immunity in regulating the immune response against intracellular pathogens

Accumulating evidence suggest that the concept of division of immunological labor in host defense against intracellular and extracellular microbes, as discussed above, is not absolute. It is becoming clear that B cells and immunoglobulins contribute significantly to shaping the immune response to and/or engendering protection against pathogens such as *Chlamydia trachomatis*, *Coxiella burnetii; Salmonella* spp., *Leishmania* spp., *Francisella tularensis*, *Plasmodium* spp., *Cryptococcus neoformans*, *Trypanosoma cruzi*, and *Ehrlichia chaffeensis* [37–50], whose life cycle includes a significant intracellular sojourn of varying extent. In fact, a conjugate vaccine has been made that protects against the intracellular pathogen *S. typhimurium* by antibody-mediated immunity alone [51]. Of note, as obligatory an intracellular organism as *Ehrlichia* is [39] the life cycle of this bacterium has a transient extracellular phase that may lead to its susceptibility to the antimicrobial effects of antibodies that may be mediated through direct interaction between immunoglobulins and the target pathogen. This scenario is applicable to *M. tuberculosis* as emerging evidence support the notion that extracellular tubercle bacilli are likely not an uncommon entity in an infected host, particularly one (such as humans) in whom necrosis is part of the immunopathological process [52,53]. Direct contact with target pathogens is, however, not requisite to the execution of the antimicrobial effects of antibodies. For example, certain contact-independent mechanisms against viruses, the quintessential intracellular pathogens, protect by attenuating viral transcription and replication via the binding of antibodies to specific antigens of the virion present on the membrane of infected cells [54–56]. It also has been reported that immunoglobulins, such as certain anti-DNA antibodies [57] and virus-specific IgA [58,59], can gain entry into cells. Whether these latter mechanisms modulate the host response to intracellular bacteria remains to be determined. What is clear is that the multifaceted B cells, by virtue of their ability to present antigens, produced antibodies and cytokines, can exert significant effect on the T cell compartment that is deemed critical in defense against intracellular pathogens [60,61] (Fig. 1). Results from infectious diseases models involving a wide variety of organisms, including intracellular bacteria such as *Chlamydia* [62] and *Fransicella* [63], have provided ample evidence supporting a role for B cell and humoral immunity in regulating T cell memory [64–73] and recall immune response [60,61] – two immunological elements critical to vaccine efficacy [28,74]. Characterization of the mechanisms by which B cells and the humoral immune response interact with cellular immunity during infection in general, and those caused by intracellular pathogens in particular, should provide information that can be useful for the design of antimicrobial strategies including vaccine development.

3. B cells regulate T cell immunity through antigen presentation

It has been well recognized that upon exposure to pathogens, CD4+ T cells of the responding host play a critical role in shaping B cell responses, including expansion, somatic hypermutation, antibody affinity maturation and class switching, the development of memory B cells and plasma cells, and cytokine production [75–77]. The significance of this interaction between B cells and follicular helper CD4+ T cells (Tfh), which takes place primarily in the germinal center (GC), has been underscored recently in the context of the development of broadly neutralizing antibodies against HIV [78–80]. Quantitative and qualitative analyses of the GC reaction in HIV infection models have revealed that the capacity to generate effective broadly neutralizing antibodies correlates with the Tfh response [78–80]. The roles B cells in modulating the T cell compartment are, however, less well characterized; and when studied, the results could be inconsistent [60,81]. This inconsistency could be due to differences in the experimental systems employed for the studies as well as non-B cell immunological abnormality intrinsic in the commonly used B cell-deficient μMT mice [60,81,82]. The availability of Rituximab, a B cell-depleting monoclonal antibody that has seen increasing use in recent years to treat a wide variety of human diseases, has provided a venue for examining the role of B cells on T cells. indeed, studies using this system have provided evidence whose results support an important role for B cells could influence T cell functions in humans [60].

The importance of T cell help for antibody production by B cells was discovered over half a century ago [83,84]. MHCII-restricted presentation by B cells and T-cell antigen specificity were subsequently described as important features of this collaborative interaction [85,86]. These work set the stage for the characterization of GC in secondary lymphoid tissues, the anatomical locale in which CD4+ Tfh cells helps B cell activation, which culminates in the generation of memory B cells plasma cells [75–77] to establish