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REVIEW

Antibodies and tuberculosis

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SUMMARY

Tuberculosis (TB) remains a major public health problem internationally, causing 9.6 million new cases and 1.5 million deaths worldwide in 2014. The Bacillus Calmette-Guérin vaccine is the only licensed vaccine against TB, but its protective effect does not extend to controlling the development of infectious pulmonary disease in adults. The development of a more effective vaccine against TB is therefore a pressing need for global health. Although it is established that cell-mediated immunity is necessary for the control of latent infection, the presupposition that such immunity is sufficient for vaccine-induced protection has recently been challenged. A greater understanding of protective immunity against TB is required to guide future vaccine strategies against TB.

In contrast to cell-mediated immunity, the human antibody response against *M.tb* is conventionally thought to exert little immune control over the course of infection. Humoral responses are prominent during active TB disease, and have even been postulated to contribute to immunopathology. However, there is evidence to suggest that specific antibodies may limit the dissemination of *M.tb*, and potentially also play a role in prevention of infection via mucosal immunity. Further, antibodies are now understood to confer protection against a range of intracellular pathogens by modulating immunity via Fc-receptor mediated phagocytosis. In this review, we will explore the evidence that antibody-mediated immunity could be reconsidered in the search for new vaccine strategies against TB.

Contents

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1. Introduction

Tuberculosis (TB) is the leading cause of death from bacterial infection worldwide, with 9.6 million cases and 1.5 million deaths in 2014 [1]. The Bacillus Calmette–Guérin (BCG) vaccine was introduced to prevent disease during the mid-20th century but, despite widespread coverage, has failed to control the spread of TB in high burden areas [1]. The continuing rise of infections in such areas despite vaccination is in part due to the BCG vaccine's variable efficacy in preventing the development of adult pulmonary TB [2,3]. Expectoration of *Mycobacterium tuberculosis* (*M.tb*), the causative agent of TB, by adults with active pulmonary disease drives the ongoing transmission of the disease. There is an urgent need for a more effective vaccine against TB, as the *WHO Stop TB* collaboration's goal of eliminating TB as a threat to global health cannot be reached even with optimal implementation of current interventions [4].

The existence of natural immunity against TB is supported by the observation that nine out of ten individuals appear able to control infection with *M.tb* in a state of clinical latency [5]. However, the precise immune requirements needed for this immunity are incompletely defined, and hence the immune response to target by vaccination remains elusive [6]. The contribution of cell-mediated immunity (CMI) here has been firmly established in past decades, and it is thus reasonable that a vaccine against TB should induce a $CD4^+$ T-cell response against immunodominant T-cell antigens [6]. The MVA85A is one such vaccine and was recently tested in two landmark efficacy trials [7,8]. Despite demonstrating protection in some animal models, and inducing antigen specific CD4+ T-cells, MVA85A was unable to add to the protection assumed to be provided by BCG [7,8]. Many candidate vaccines against TB target a similarly narrow immune repertoire, and thus the disappointing outcome of the MVA85A trials has provided impetus to explore a wider range of immune responses in protection against TB [9,10].

Antibody-mediated immunity (AMI) is one such approach. As *M.tb* is a facultative intracellular pathogen, it has been postulated that antibodies either have no protective benefit or may even contribute to immunopathology in active disease [11]. Surmounting this presumed lack of functional antibodies in TB presents a substantial challenge for the next generation of vaccines against TB, as antibody titre and specificity remains the predominant correlate of vaccine-induced immunity for many other diseases [12]. Even in diseases where antibodies produced during infection fail to confer protection, vaccines have been designed to induce antibodies capable of protecting from disease. Such 'synthetic' or non-natural immunity utilizing antibodies may present a novel testable vaccine hypothesis against TB. Here we will explore the recent expansion of evidence that a role for antibodies in immunity is worthy of consideration in designing future vaccine strategies against TB.

1.1. Humoral immunity during natural infection with TB

1.1.1. Variation in human antibody responses against M.tb

It has long been known that natural infection induces the formation of antibodies against *M.tb*. In the late 19th century it was thought that antibodies formed in inoculated animals would be able to treat infection in patients as this approach was successful in pneumococcal disease [13]. The inconsistent trial results that followed were an early clue to the complexity of the antibody response against *M.tb* [13].

Studies following on from these original trials demonstrated that 90% of TB patients have raised titres of serum immunoglobulin against mycobacterial antigens at the time of clinical presentation [14]. However, the antigens targeted by individual patients vary widely, as one study showed that out of a panel of ten culture filtrate proteins secreted by *M.tb*, no single antigen was universally recognized by serum from patients with active TB [14]. The correlation between antibody responses and active TB disease led to investigation of antibodies as diagnostic markers rather than a therapeutic strategy, but these efforts were discouraged by the WHO in 2012, due to suboptimal sensitivity and specificity in studies [15]. It should be noted however that this recommendation was only directed towards the diagnostic use of current commercially available tests and not towards investigation into the function of antibodies in immunity against TB as a whole. Many factors influence the development of antibodies during the course of infection including latency, stage of infection, HIV and host genotype as summarized in Table 1.

1.1.2. Markers of humoral immunity in recent studies

A consistent finding in whole blood transcription studies in active TB, spanning geographical locations and in HIV-1 co-infection, is the up-regulation of the high-affinity antibody receptor FCγR1A [16–18]. Fcγr1A binds antibody principally of the IgG1 and IgG3 subtype and is expressed mainly in macrophages and dendritic cells [19]. The expression of complement C1q, which forms immune complexes with immunoglobulin, is also elevated during active TB and is associated with increased disease severity [17,20].

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