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A Perspective on the Success and Failure of BCG

Pawan Kumar*

Dr. BR Ambedkar Cancer Hospital, All India Institute of Medical Sciences, Ansari Nagar, Delhi, India

***Corresponding author:** Pawan Kumar, Dr. BR Ambedkar Cancer Hospital, All India Institute of Medical Sciences, Ansari Nagar, Delhi, India, Email: pkscmm@gmail.com

Opinion

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Abstract

TB continues to be one of the major public health threats. BCG is the only available vaccine against TB and confers significant protection against childhood disease. However, the protective efficacy of BCG against adult pulmonary TB, which represents the major burden of disease, is highly variable. Why BCG exhibits differential efficacy against childhood TB and the adult pulmonary disease remains an open question. Noticeably, TB is a heterogeneous disease occurring in different forms and having distinct mechanisms of pathogenesis. While the incompetence of their relatively immature immune system to contain the bacilli is responsible for TB pathogenesis in infants, an aggravated immune response to Mtb has been blamed for the development of adult pulmonary TB. Available data suggest that EMb plays a key role in heightening the immune response against Mtb. In this article, variable efficacy of BCG against adult pulmonary TB is explained by taking into account the heterogeneity of TB, mechanisms of TB pathogenesis, and the effect of EMb on anti-Mtb immunity. It is believed that refined understanding of the success and failure of BCG will help in the development of effective anti-TB vaccines.

Keywords: Tuberculosis; BCG; Vaccine; Heterogeneity; Immune Response; Environmental

Abbreviations: TB: Tuberculosis; MTB: Mycobacterium Tuberculosis; BCG: Bacillus Calmette-Guerin; EMB: Environmental Mycobacteria; LTB: Latent Tuberculosis

Introduction

Tuberculosis (TB) continues to be one of the major public health threats, accounting for approximately 1.5 million deaths per year globally. BCG (Bacillus Calmette-Guerin), which was developed nearly 100 years ago, is the only available vaccine against TB. Although BCG confers significant protection against childhood manifestations of TB, its protective efficacy against adult pulmonary TB is highly variable [1]. Why BCG is effective against childhood TB but exhibits variable efficacy against the adult pulmonary disease remains an open question. Mycobacterium tuberculosis (Mtb) is the causative agent of TB. It shares an intricate relationship with the host immune system and leads to different clinical outcomes. Owing to their incompetence to contain Mtb infection, TB occurs as primary disease commonly affecting extra-pulmonary sites in infants and young children. On the other hand, TB affects the lung tissues in most immunocompetent adults and its pathogenesis has been attributed the aggravated anti-Mtb immunity. Available data suggest that environmental mycobacteria (EMb) play a key role in aggravating the anti-Mtb immune responses. In the present manuscript, differential efficacy of BCG is explained by taking into account the heterogeneity of TB, mechanisms of TB pathogenesis, and the effect of EMb on anti-Mtb immunity. It is believed that a refined understanding of the success and failure of BCG will help in the development of effective TB vaccines.

BCG Vaccine

BCG was derived by French researchers Albert Calmette and Camille Guerin by in vitro passaging M. bovis for nearly 13 years. Clinical studies with BCG took place in France and Belgium in the 1920s and demonstrated its efficacy against childhood TB [2]. As the success of BCG against childhood TB was observed in these and other European countries, World Health Organization (WHO) recommended expansion of the BCG vaccination program to TB-endemic countries. Despite more than 3 billion people receiving BCG, TB continues to be a major public health threat. The most important drawback of BCG is its variable efficacy (ranging from nil to 80%) against adult TB. Palmer and colleagues were first to recognize that BCG is more effective against adult TB at higher latitudes 1. Various factors including strain variations and poor cold- chain maintenance were suggested to be responsible for the variable efficacy of BCG against adult disease. However, as the same BCG strains exhibited higher anti-TB efficacy in other countries, and were effective against leprosy in areas of their poor anti-TB efficacy, role of these factors in variable efficacy of BCG against adult TB was proved to be unfounded [3]. Palmer et al. explained the failure of BCG by taking into account the exposure to EMb. They suggested that EMb imparts some degree of protective immunity against Mtb and that BCG could improve on this naturally acquired protection only slightly [4]. An alternate view was presented by Anderson et al., who stated that pre-existing antimycobacterial immune response evoked by EMb blocks duplication of BCG, compromising its ability to induce protective immunity against Mtb [5]. As BCG is a live attenuated vaccine, its duplication in immunized people was considered as a precondition for induction of effective immunity against Mtb. In either case, augmenting antimycobacterial immune response with booster doses of BCG could have been a potent strategy to enhance the anti-TB efficacy of BCG. However, repeated BCG injection does not confer additional protection against adult TB, although the protection against leprosy is improved [6]. Also, it is unlikely for the infants to receive significant EMb Exposure for they are vaccinated soon after birth. Therefore, failure of BCG against adult pulmonary TB despite conferring significant protection against the childhood disease warrants a retrospection of our understanding of TB pathophysiology.

Heterogeneity of TB

TB is a heterogeneous disease occurring in different patterns and presentations [7]. Two distinct presentations of TB can be seen in infants and immunocompetent adults [8,9]. In infants, Mtb infection leads to a primary disease with a high mortality rate. This form of disease commonly affects extra-pulmonary sites and in severe cases, can occur in disseminated form (miliary TB) [9]. On the contrary, initial Mtb infection in immunocompetent adults is contained mostly as latent TB (LTB). This state of asymptomatic infection may persist in most but 5-10% of people, who would develop active disease during their lifetime [10]. Active TB in immunocompetent adults preferably affects lung tissue. The primary and extra-pulmonary nature of TB in children is suggestive of their incompetence to contain bacilli. In keeping with this, immunological milieu in young children is skewed towards the TH2 side with dampened TH1 type of immunity and inflammatory pathways [11] Moreover, CD4+ T cells in young children are recent thymic emigrants with defective functionality and differentiation bias towards TH2 effector cells [12]. That is why most children would respond poorly to mycobacterial antigens during tuberculin skin testing (TST) and interferon-γ release assay (IGRA) [9]. On the other hand, immune system is effective against
Mtb in most adults. These people mount a robust TH1 type of immune response to Mtb, resulting in sequestration of infected macrophages into lung granulomas and containment of infection as LTB [13]. Paradoxically, host immune system has also been implicated in the reactivation of latent infection into active TB in immunocompetent adults [14].

Protective Versus Pathological Immunity During Mtb Infection

Host response to Mtb begins with its recognition by resident lung macrophages which, along with dendritic cells, induce adaptive immune responses to bacilli. TH1-polarized CD4+ T cell are the key orchestrators of protective immunity against Mtb [13]. Antimycobacterial functionalities of CD4+ T cells are partly mediated by TNF-α and IFN-γ which induce bactericidal mechanisms in infected macrophages and facilitate their sequestration in granulomas [10]. Other cell types including CD8+ T cells, NK, and NKT cells have also been shown to contribute towards host resistance to Mtb 10. Latent TB (LTB), which follows initial Mtb infection in most adults, is considered a state of protection against the bacilli [15]. It is characterized by a moderate anti-Mtb immune response in comparison to active TB wherein aggravated antimycobacterial immunity is of common occurrence [14]. Heightened IFNγ+CD4+ T-cell response to mycobacterial antigens (as evidenced by tuberculin reaction, IGRA, and in vitro assays) is frequently observed in active TB patients [16,17] and is an important parameter distinguishing active TB from latent infection [18]. Indeed, increased IFN-γ levels in different tissues is one of the most common and consistent observations during active TB [10]. Interestingly, IFN-γ levels directly correlate with TB severity and subside with its successful treatment [10]. TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), which develops with the reactivation of asymptomatic Mtb infection in a subset of antiretroviral therapy (ART)- treated HIV-infected people, provides direct

evidence for the pathological role of aggravated immunity during Mtb infection. ART-mediated decline in viral load results in the over- expansion of Mtb-specific CD4+ T cells in the coinfected AIDS patients [19]. Lower baseline CD4+ T-cell count and rapid increase in these cells are the major risk factors associated with the development of TB-IRIS [20]. Consistently, ART-treated people who are destined to develop TB-IRIS exhibit a stronger TH1-type of CD4+ T-cell response to Mtb antigens [19]. Similar results have been obtained from animal studies, wherein the human condition was mimicked by adoptively transferring CD4+ T cells to M. avium-infected, TCRα−/− mice [21]. After receiving CD4+ T cells, these animals developed an aggravated immune response to the bacilli, exhibited wasting, lost weight, and eventually died of exacerbated immunity [21]. Importantly, development of immune reconstitution disease in these animals was mediated by hyperactive IFN-γ+ CD4+ T cells.

The course of Mtb infection in PD-1−/− mice also implicates aggravated CD4+ T-cell response in TB pathogenesis. PD-1 is a cell surface receptor involved in the negative regulation of T-cell responses [22] and its deficiency results in significantly increased susceptibility to mycobacterial diseases, compared with wild-type mice [23]. Mechanistic studies have shown that PD-1−/− mice mount hyperactive CD4+ T-cell response to mycobacteria, which drive Mycobacterial pathogenesis in these animals [24]. In agreement with animal studies, PD-1 blockade in cancer patients (a type of immunotherapy) has resulted in multiple cases of TB [25]. Noticeably, PD-1 blockade-mediated TB development is associated with increased frequency of Mtb-specific IFN-γ+ CD4+ T cells [25].

Significantly higher risk of TB in the immunocompetent adults cured of its previous episode also implicates aggravated CD4+ T-cell response in TB development [26]. Mtb-specific CD4+ T- cell responses are elevated during active TB, and a proportion of these cells can persist as memory cells after successful treatment [27,28]. It has been estimated that ~70% of people cured of pulmonary TB exhibit positive tuberculin reaction and IGRA up to 30 years after treatment [29]. With Mtb reinfection, these hosts are more likely to mount hyperactive CD4+ T-cell responses leading to active TB.

Dissection of Success and Failure of Bcg

Protective Efficacy of BCG Against Childhood TB

As discussed above immune system in children is poorly developed with dampened TH1 responses and inflammatory pathways [11]. Infant CD4+ T cells exhibit defective functionality and differentiation bias towards TH2 effector cells [12]. BCG vaccination alters the immune profile and promotes Mtb-specific TH1-polarized immune responses in these subjects [30]. Vekemans, et al. demonstrated that frequencies of IFN-γ-producing cells and the levels of IFN-γ produced in response to PPD in BCG-vaccinated infants are comparable with those in adults [31]. Strong lympho-proliferative response and TH1 cytokine secretion in BCG-vaccinated infants have been demonstrated by other researchers [32,33]. BCG has also been shown to induce mycobacterium-specific cytotoxic T lymphocyte responses in neonates [32,34]. Although CD4+ T cells are the mains source of TH1 cytokines in BCG-vaccinated infants, CD8+ T cells have also been shown to produce a significant amount of these cytokines [35]. Interestingly, BCG can also activate unconventional γδ T cells which play a bridging role between innate and adaptive immunity against Mtb [36,37]. Interestingly, in contrast to abundant TH1 cytokines, BCG-vaccinated newborns demonstrate relatively lower levels of IL-4 and IL-10 35. A few studies have also examined the status of immunological memory in BCG-vaccinated infants. It has been observed that newborn BCG vaccination leads to the development of a memory CD4+ T-cell population with phenotypic characteristics of central memory cells and functional attributes of effector memory cells [38]. In a follow-up study, levels of IFN-γ, IFN- γ+CD4+ T cells, and IFN-γ+ γδ T in <1-year-old BCG-vaccinated children were found to be comparable with those present at different time points till ≥5 years [39]. Interestingly, Kagina, et al. demonstrated a superior CD4+ T-cell memory response with BCG administered at 10 weeks [40]. Owing to TH1-polarized response and immunological memory, BCG-vaccinated infants are more likely to respond rapidly and robustly to Mtb infection, resulting in effective containment of the bacilli. Accordingly, BCG confers significant protection against childhood manifestations of TB.

Variable Efficacy Of BCG Against Adult Pulmonary TB

Host response to Mtb is more complex in adults. Although a few TB cases in them can be attributed to hereditary or acquired defects in immune system, a majority of adult pulmonary TB patients demonstrate an aggravated immune response to Mtb. It has been observed that the maximum burden of adult pulmonary TB lies in the tropics [41]. Notably, people living in the tropics also exhibit stronger tuberculin reactions and anti-Mtb immune responses. Higher prevalence of skin test reactivity to PPD-B (M. avium-intracellulare antigen) suggests the greater abundance of EMb in tropics compared with temperate zones. In the Chingleput trial area, for example, ~90% of 10 to 14-year-old participants exhibited strong reactivity to PPD-B [42]. For they carry multiple cross-reactive antigens, EMb can directly modulate the host response to Mtb. Accordingly, a more strong response to Mtb is observed in tropics and in

elder people, who are more likely to have received greater EMb exposure compared with younger ones. In the south India trial, 62.0%/48.4% tuberculin positivity (>12 mm with 3 IU of PPD-S) was observed in 15 to 24-year-old male/female participants, which reached 81.8%/64% in 25-34 years old male/female participants [43]. Similar results have been obtained in other trials including Karonga Prevention Study 6. On the other hand, no participants in the 5-14 years age group developed grade II or III Heaf reactions (with PPD-S) and only ~15% /~20% of 15-24 years old participants exhibited grade II/ grade III Heaf reactions respectively in a clinical study in the United Kingdom [44]. It can be inferred that owing to frequent EMb exposure, a large proportion of immunocompetent adults mount a heightened immune response to mycobacterial antigens in the tropics. As an aggravated antimycobacterial immune response leads to TB pathogenesis, many of these people are bound to reactivate LTB into the active disease. Supporting this, people with stronger tuberculin reactions have been found to carry a higher risk of active TB. Similarly, a higher risk of active TB has been observed in household contacts (of active TB patients), who develop stronger tuberculin reactions [14,18]. Interestingly, more intense tuberculin reactions are observed in males, which correlate with the higher prevalence of adult TB in them [6,42]. It is plausible that frequent EMb exposure and resulting augmentation of antimycobacterial immune responses increase the risk of active TB by mechanisms analogous to those in people cured of the previous episode of the disease. The host immunological differences also provide an explanation for the variable efficacy of BCG against pulmonary TB in tropics and temperate zones. As most immunocompetent adults would develop a heightened antimycobacterial immune response in the tropics, BCG, which acts by promoting TH1-type of anti-Mtb immunity, exhibits minimal efficacy against adult pulmonary TB in these regions. On the contrary, lesser abundant EMb has a limited effect on antimycobacterial immunity at higher latitudes. Therefore, BCG-mediated immune response persists without significant modulation and vaccinated people are protected against adult pulmonary TB in these areas. The effects of EMb on anti-Mtb immune response and the efficacy of BCG are depicted in Figure 1. However, it is worth mentioning that other factors such as malnourishment and air pollution can also modulate the host antimycobacterial immunity and the vaccine efficacy. Tuberculin reactions and TB incidence in rural versus urban populations firmly support the above explanation of the variable efficacy of BCG. It has been observed that within the same geographical region, rural population demonstrates a higher prevalence of non-specific tuberculin sensitivity [3]. In a trial in rural versus urban settings, BCG efficacy against pulmonary TB was found to be 18% in rural areas compared with 42% in urban ones [45]. In fact, lowest efficacy of BCG in tropics is observed in the studies carried out in rural areas [3]. Evidently, aggravated anti-Mtb immunity plays the roles in both higher susceptibility to pulmonary TB and the lower efficacy of BCG against it.

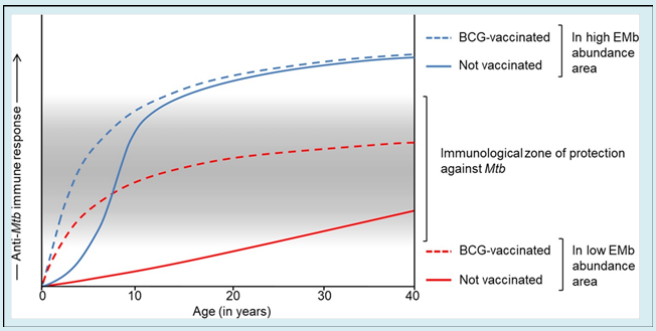

Figure 1: Effect of BCG on the host response to Mtb and its modulation by environmental mycobacteria (EMb). Host-pathogen interaction during Mtb infection plays a key role in defining the infection outcome and is substantially modulated by EMb. In young children, the immune system is poorly developed with dampened TH1 responses and inflammatory pathways. That is why young children are inefficient in containing Mtb infection and develop severe disease with high mortality rate. BCG vaccination promotes TH1 type of immune responses to Mtb in infants, resulting in the effective containment of the bacilli (dashed blue and red lines). Therefore, BCG exhibits significant protection against TB in infants and young children. Owing to the presence of cross-reactive antigens, EMb also activate a degree of immunity against Mtb and therefore, confers some degree of protection against childhood TB in unvaccinated children (blue line). In contrast to young children, an aggravated immune response to Mtb has been blamed for the reactivation of latent infection into active TB in immunocompetent adults. Available data suggest that frequent exposure to EMb plays a key role in heightening the anti-Mtb immunity. Therefore, aggravated immune response to Mtb and higher incidence of adult pulmonary TB are reported from EMb abundant areas (dashed blue line). Repeated EMb exposure also aggravates anti-Mtb immunity in BCG- vaccinated people, resulting in the higher incidence of pulmonary TB in these people and low efficacy of BCG in EMb abundant areas (normal blue line). On the other hand, BCG-mediated immunity against Mtb is not significantly modulated in areas of low EMb abundance (dashed red line). Therefore, vaccinated people exhibit a moderately intense anti-Mtb immune response which confers significant protection against adult pulmonary TB in these areas.

Concluding Remarks

TB is a heterogeneous disease with different mechanisms of pathogenesis. The incompetence of their poorly developed

immune system to contain Mtb is responsible for TB pathogenesis in infants. BCG promotes a TH1-type of anti-Mtb immunity in infants and therefore, confers significant protection against childhood TB. In immunocompetent adults, development of pulmonary TB has been attributed to aggravated anti-Mtb immunity. Since EMb play a key role in heightening antimycobacterial immunity, higher incidence of adult pulmonary TB is reported from EMb-abundant areas. Evidently, BCG would not be effective against pulmonary TB in these areas. On the contrary, EMb do not substantially modulate the BCG-mediated immunity, which remains moderately intense, in the areas of low EMb abundance. Therefore, BCG demonstrates significant protective efficacy against adult TB in these areas. In the light of the above, we propose that a different vaccination approach against adult TB is required in the tropics. Most likely, an effective vaccine against adult TB in these areas would focus on moderating Mtb-specific IFN-γ+CD4+ T-cell responses and balancing pro- and anti- inflammatory pathways. That's probably how we can prevent adult pulmonary TB and save millions of lives.

Conflict of Interest

There are no financial conflicts of interest to disclose.

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