

## Tuberculosis the Ancient Disease Needs Intervention of Modern Tools

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*'If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more.'* - Robert Koch, 24 March 1882

Despite the best attempts made by modern science over the past years, tuberculosis remains a persisting problem killing more than 2 million people every year [1]. Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* [2]. In fact, the recent upswing in the cases of TB has been related to the low economic conditions of the third world countries, HIV and multi drug resistance exhibited by *Mycobacterium tuberculosis*. There are a number of unanswered questions such as why is the immune system unable to control the infection? How does *Mycobacterium tuberculosis* cause lung tissue damage? And why is it that most of the infected people never fall sick?

Théophile Laennec began understanding the pathogenesis of tuberculosis at the beginning of the 19<sup>th</sup> century. This work was further advanced by Jean-Antoine Villemin in 1865 who demonstrated the transmissibility of *Mycobacterium tuberculosis* infection and by Robert Koch who identified the tubercle bacilli as the etiologic agent [3]. Immunization using the Bacillus Calmette Guerin (BCG) vaccine was first carried out in 1921 in Paris and is the only available prevention for TB till date [4]. The works of Selman Waksman yielded the antibiotic – Streptomycin, which was the first antibiotic to be used against tubercle bacillus [5].

Though BCG is the most commonly used vaccine against TB, it only provides a transient immune response to *Mycobacterium tuberculosis*, not a complete protection against the disease [6]. Another drawback of the BCG vaccine is that its efficacy varies from 0 to 80% with consistently low efficacies in tropical regions such as Africa and India. Factors such as inappropriate treatment, storage of vaccine and inadequate strains of BCG have been attributed to the failure of the vaccine [7]. Another hypothesis suggests the loss of a number of genes over a period of time as the reason for impotence of the vaccine [8]. The inability to stimulate the correct blend of T cells required for a protective immunity and the lack of appropriate antigens is yet another reason for the failure of BCG [9]. These factors have led to further research into development of a better vaccine against tuberculosis especially in the third world countries where BCG has yielded poor results in the past few decades.

Advances in vaccinology including strategies for intracellular antigen presentation in conjunction with newer tools such as systems biology can help understand the mechanisms of the tubercle bacilli better. The latest research brings forth the significance of gene-gene interactions in regulation of resistance to the disease in humans [10]. Additionally, it has also been suggested to apply host genetics to vaccinology to design interventions that would help human immune system in combating mycobacteria. DNA vaccine technology, subunit vaccine consisting of one or more defined products in adjuvant

formulations and viral delivery systems as effective antigen delivery systems have also been suggested as potential vaccine candidates [11,12].

As one-third of the world's population has latent-TB, a condition in which mycobacteria can survive within a human host for years without causing the disease, it is imperative to understand how the bacilli induce this latent metabolic state and how is it able to hide from the immune response [13]. It is also important to focus studies on the factors leading to reactivation of the bacilli in some individuals. One of the hypothesis suggests that the bacilli are disseminated to several different locations within the human host to maintain latency in addition to being harboured in a granulomatous lesion in lungs [14]. The granuloma acts as a protective microenvironment for the bacilli to resist the host immune response and is composed of macrophages, dendritic cells and neutrophils. Another hypothesis suggests that the latent bacilli enter a state in which they are no longer acid-fast (a condition required for microscopic detection) or are present in such low numbers that they are not detected microscopically and hence persist for long periods of time [15]. It is important to address a few questions to successfully eradicate the problem of TB: a) What causes the infective bacilli to become latent or vice-versa? b) Are these latent bacilli able to resist the antimicrobial action of drugs by disseminating throughout the body or stay within the pulmonary scar tissue? c) What is the genetic basis of this latency in tuberculosis?

Ongoing research projects worldwide are now focusing on understanding the host immune response to *Mycobacterium tuberculosis* with emphasis on the role of macrophages, Th1 and Th2 response, cytokine/chemokine network and the effector functions of CD4+ and CD8+ T cells [16]. The protective effect of interferon gamma producing CD4+ T cells has been established without doubt in combating the infection. It is also re-asserted by the increased incidence of tuberculosis in AIDS patients having a low CD4 T cell count [17]. In

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addition, CD8 T cells are now known to play a significant role in latent TB infection by directly lysing the bacilli containing macrophages [18]. Research studies are trying to unfold the role of the unconventional T cells such as CD-1 restricted  $\alpha\beta$  T cells in protective immunity to TB [19]. A greater understanding of the disease is being afforded by studies in transgenic animal models. Studies are also investigating the molecular basis of susceptibility and resistance in murine model of tuberculosis [20]. It is well known that helper T (Th) cell subsets play a central role in the outcome of TB pathogenesis. While Th1 and Th17 cells confer resistance, Th2 and T regulatory cells enhance disease progression. However, the precise activity of these subsets of Th cells during the progression of infection has not been well studied. Investigations are going on to study the activity of different Th subsets in reporter knock-in and knock-out animals and their co-relation with disease progression [21].

Besides being a potent risk factor for TB, HIV presents a huge challenge to TB control. It enhances the chances of reactivation of latent TB as well as increase the rate of disease progression once reactivated. In fact, TB is the most common cause of death in HIV positive patients [22]. Additionally, the risk of transmission to HIV negative or healthy individuals also increases. Most of the outbreaks of TB associated with HIV pandemic usually occur with multi-drug resistant strains of *Mycobacterium tuberculosis* [23]. In addition to lowering the CD4 T cell count, HIV also affects macrophages and cytokine production making it difficult for the host control an initial TB infection. Co-infection with HIV leads to a disruption of the immune response within the granuloma causing an uninhibited bacterial growth and dissemination within the host [17]. MDR (multi-drug resistant) tuberculosis and emerging resistance to drugs such as rifampicin and isoniazid is becoming prevalent with increasing frequency. It is established that spontaneous chromosomal mutations are responsible for genetic resistance to drugs in mycobacteria. Also, clinically drug resistant TB develops as a result of poor patient adherence to treatment regimen. The subsequent transmission of such drug resistant strains to healthy individual accentuates the problem of the disease dissemination [24].

Geographical overlap, HIV pandemic and emerging multi-drug resistant strains of *Mycobacterium tuberculosis* pose a major challenge both scientifically and logistically to the development of a vaccine for TB. There is still little or no knowledge of the immunological biomarkers of protection. A perfect pre-clinical animal model is yet to be developed. Lack of availability of field sites for phase IIb/III is one of the major road-blocks to the development of a vaccine for TB. On a larger scale, the problem also lies in estimating the correct incidence of TB in third world countries with loop holes in different methods of measurement of incidence such as existing surveillance system and vital registration system. It is impossible to eradicate TB without an effective vaccine which can help control the transmission of drug-resistant variants of the bacilli. Some of the loop holes in development of a vaccine include: a) what genes are expressed by the bacilli during the latency period? b) What are the specific immunological or environmental factors that lead to reactivation? c) Why is it that the bacilli prefer to be recognized by the human immune system rather than mutating?

There is an aim to eradicate tuberculosis as a public health problem by 2050 by the world health organisation. However, the need of the hour is for the scientific achievements to be accompanied by political back up so that sufficient resources are available for vaccine

development. There is a need to improve TB data collection at all the point-of-care units and health facilities. There is also a requirement to develop specific and more sensitive diagnostic tests to identify the drug-resistant TB. Scientists across the globe need to optimally utilise the advances made in genomics, proteomics and systems biology to identify the suitable biomarkers of the disease. Newer research need to focus on oral vaccine and/or aerosolised vaccines that will be easier to administer and inexpensive. TB is often described as a disease older than history, it is time for researchers, scientists and policy makers to work hand in hand to eradicate this ancient pandemic.

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