Mycobacterial Diseases

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Revisiting Immunotherapy in Tuberculosis

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Abstract

The World Health Organization (WHO) estimates that one third of the global population is infected with Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), which is responsible for millions of death each year. Current therapy of TB consists of multiple expensive antibiotics and lengthy treatment, up to six months for drug-sensitive TB strains, and nine months to one year for drug-resistant TB strains. Therefore an alternative approach is urgently needed to fight this deadly disease. We propose immunotherapy which will enable to reduce length of treatment, toxic side effects, emergence of drug resistant variants, and prevent reactivation of the disease.

Keywords: *Mycobacterium tuberculosis*; Immunotherapy; Immunomodulators; Anti-tuberculosis therapy

Introduction

Tuberculosis has been known to human civilization from ancient times. Earlier this disease has been known as numerous names including consumption, phthisis pulmonary and the white plague. The organism causing modern tuberculosis is *Mycobacterium tuberculosis* evolved last 15,000 to 20,000 years ago in east Africa. It has been found in remnants from ancient Egypt, India, and China. Archaeologists detected spinal tuberculosis, known as Pott's disease in Egyptian mummies of 5000 years ago [1]. Even today after the progress of advanced method of screening, diagnostic and treatment for the disease, one third of the world's population has been exposed and is infected with that bacterium. The numbers are more than 90% in the developing world. However, only less than 10% of infected individuals exhibit tuberculosis disease, still it remains the most leading cause for the mortality from a single infectious disease throughout the world [2]. It is well established that immune response confines tuberculosis, but unable to clear from the body in most individuals. In opportunities, especially when immune system is perturbed, such as in HIV infections, there is a dramatic resurgence of tuberculosis with more than 8 million new cases worldwide each year and more than 2 million persons dying from it. The vast reservoir of tuberculosis may convert latent form to an active disease outbreak, unless a preventive measure is taken.

Robert Kotch in 1882 first demonstrated about this bacillus by stained with Zeihl Neelson and for this he awarded the Noble prize in 1905. And according to his name bacteria was named Kotch's bacteria. After the concept of Louis Pasteur's vaccine development two French scientists Albert Calmette and Camille Guerin grew the Kotch's bacillus in several media to increase the immunogenicity and decrease the virulence which led the vaccine named after those two scientists BCG (Bacillus Calmette Guerin), which was introduced in 1921 and after that till now it is the only vaccine and an estimated three billion people have received it [3]. In spite of its exiguous efficacy, BCG is widely used because no other better vaccine is available. Therefore, a better vaccine is needed for the prevention of epidemic of tuberculosis. Antibiotic therapy is available, but the course of treatment is lengthy and not cost effective. Therefore, rate of withdrawal from treatment is very high, especially in socio-economically less fortunate neighborhoods. Therefore, an alternative approach for the treatment of tuberculosis is essential.

Upon phagocytosis of *Mycobacterium tuberculosis*, macrophages secrete many antimicrobial effector molecules like ROI, RNI and various cytokines to ensure the killing of the harbored organisms. Phagocytosed microorganisms are subjected to degradation by acidic compartment of lysosome upon phago-lysosome fusion [4]. Bacteria tend to escape from the intracellular compartment of the phagocytic body and when it evantuates they lead to the disruption of the membrane of the phagocytic cells and multiply. Thereafter, blood monocytes and other inflammatory cells are attracted to the site of infection. Later these monocytes differentiate into macrophages which again readily ingest but do not destroy the mycobacteria. In this symbiotic stage, mycobacteria continue to grow. After two to three weeks antigen specific T cells comes to the action then activate macrophages to kill the intracellular mycobacteria [5].

BCG induces robust T helper (Th) 1 immune response, but this is not sufficient for host resistance against *Mycobacterium tuberculosis* (*Mtb*) infection. Previously it has been demonstrated that ESAT-6 promotes protective T Helper (Th) 17 Cell responses in a Toll-Like Receptor (TLR)-2-dependent manner [3]. Furthermore, ESAT-6-TLR-2 interactions promote the efficacy of TB vaccines by promoting Th17 cell differentiation. Therefore, ESAT-6 can contribute to vaccine preparations by promoting Th17 cell responses [3]. Although the role of Th17 in primary immunity against TB is unclear, several studies have provided evidence for a protective role of Th17 cells in secondary immune responses against Mtb [6]. For example, BCG infection induces strong IL-17-dependent memory responses in IFN-γ- deficient mice, which provides protection against disease upon subsequent challenge with Mtb [7].

Latent-TB, a condition in which bacilli survive within a human host for years without causing the disease, it is essential to understand how the bacilli provoke this latent metabolic condition and how is it able to hide from the immune response [8]. Recently it has been demonstrated that Mesenchymal stem cells (MSCs) are recruited to the TB granuloma which makes a niche for maintaining granuloma like structure. MSCs

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establish a dynamic balance between *Mtb* antigen specific T cells and the harboring bacteria by JANUS like positioning themselves in between T cells and harboring bugs. The astute mechanism of checking replication of bugs and the inactivation of T cells is achieved by the limited productions of nitric oxide (NO) by MSCs. Therefore MSCs play a key role in establishing latent TB [9]. This finding was further advanced by Das et al., indicating that viable non-replicated *Mtb.* bacteria is persisted within MSCs in bone marrow not only that after antimicrobial therapy they found viable within BM-MSCs [10]. From these studies it is clear that MSCs provide the niche where *Mtb* hides from aggressive host response and keep it in latent phase, which is still non treatable. Therefore, targeting MSCs could be an option for the treatment of latent TB.

Although currently used anti-TB drugs (ATT: Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) are considered as the drug of choice as these can cross blood brain barrier but there are several problems associated with it viz. hepatotoxicity, duration and complexity of treatment and the latter causes non-adherence to treatment. There is increasing incidence of MDR and XDR due to withdrawal from therapy [11]. Furthermore, there is a chance of TB reactivation and reinfection, suggesting that these antibiotics cause impairment in immune responses. Therefore, an approach to TB treatment that reduces immune impairment, length of treatment and toxicity is highly desired.

The continuous emergence of MDR bacteria drastically reduces the efficacy of ATT and in turn causes therapy to be failed. Drug resistance is the main challenge that now world is facing. There are many natural compounds that have been successfully tested for the therapy for MDR-TB. Natural products are crucial sources of new antimicrobials and immunomodulator because of their amazing chemical diversity and their validation through centuries of evolution [12-14]. Our ongoing research activities are mainly highlighted on using various immunomodulators and antimicrobial compounds from natural herb that may increase the efficacy of traditional antibiotics against tuberculosis.

We hypothesize that a combine therapy of ATT along with an immunomodulator that will successfully fulfill these criteria. In our effort in search of antibacterial drugs from natural source, we targeted several natural compounds, isolated from medicinal plant as well as Indian spices. The scope of this study is to use an immunomodulator compound with tuberculosis standard drugs to reduce many side effects and hepatotoxicity.

Immunomodulation is now emerging as alternative promising therapeutic candidate. This approach is based on the belief that a particular microbe causes disease in an organism due to the host's susceptibility [15] rather than due to the characteristics of the microbe alone. Bolstering the weakened immune system of the host may thus restore the equilibrium broken by the infection. The combination of an immunopotentiating agent to augment the efficacy of ATT has been considered previously [16,17] the efficacy of intradermal BCG and of oral levamisole in the induction of a mycobacteria specific immune response has been reported [18,19].

Conclusion

Current therapy of tuberculosis consists of use of specific antibiotics for a long period, which increases the possibility for the generation of antibiotic resistant strains. In fact, all the countries throughout the globe, irrespective of socio-economic status, are facing serious threat of multiple and severe multiple drug resistant (MDR and XDR) forms of tuberculosis. Therefore, there is an emerging need for an alternate method of tuberculosis treatment. Any therapy where therapeutic agent physically interacts with harboring bugs will generate drug resistance. Therefore, we propose immune therapy, where host is capable of eradicating harbored organisms. For this, we would explore natural resource, a vast untapped resource. However, an immunomodulator may not be sufficient for curing an established disease. Therefore, a combination of antibiotics and immunomodulator could be the key of therapy, to reduce the possibility of generation of drug resistant bacteria, reduce the treatment length, and reducing the possibility of reinfection and reactivation.

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