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Review Article

Th17 Inducing Vaccine Against Tuberculosis May Cause Autoimmunity and Inflammation Mediated Adverse Effects

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Abstract

Tuberculosis (TB) is a big global health problem and an effective vaccine for control of this disease is urgently required. In the recent past, a concept has emerged wherein it has been shown that a $CD4^+$ Th1 cell stimulating anti TB vaccine can be more effective if it has $CD4^+$ Th17 cell stimulating property as well. With such an anti TB vaccine, the Th1 mediated immunity can further become stronger due to supportive effect of immune response induced by Th17 cell. Since Th1 and Th17 cells are pro inflammatory in nature, a TB vaccine capable of stimulating both of these cells may result in generation of a cumulative stronger pro inflammatory immune response. This raises an apprehension that such an increased immune response may cause adverse effects in the form of autoimmunity and inflammation in the vulnerable vaccinated subjects. Therefore, extensive studies to understand the spectrum and magnitude of occurrence of such diseases must be carried out with Th1 and Th17 inducing anti TB vaccine (s). This might help in understanding their risk/ benefit ratio while employing such Th1-Th17 inducing vaccines for clinical practice.

Keywords: Vaccine; Tuberculosis; Th17; Autoimmunity; Inflammation

Status of anti tuberculosis vaccine

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is a major global health problem as it is a leading cause of more than 1.5 million deaths and of occurrence of nearly 10 million new cases every year. With the existing facilities and currently available tools, billions of USD would be required every year to fight against TB [1] which would be a heavy burden on world economy. In such a scenario, an effective vaccine against TB can play a significant role in cost effective global control of TB. Currently, BCG is the only approved vaccine which is available for its use against TB which shows partially but significant protection against TB (particularly against disseminated and meningeal TB) in children. However, its efficacy against pulmonary TB in adults is widely (0 - 80%) variable, across geographically different populations in the world [2]. Therefore, a need for better TB vaccine is strongly felt. Over the years, efforts have been made for: (i) developing prime-boost strategies (wherein priming is done by BCG followed by boosting with some MTB antigen) to improve performance of BCG, (ii) designing improved formats of BCG and (iii) searching new superior alternate of BCG. Following these approaches, about a dozen of new candidate vaccines have been developed [3,4] which are at various stages of their evaluation.

Th17 may act as a supportive cell for Th1 inducing anti TB vaccine

After inhalation, in the form of aerosolized particles, MTB is engulfed, primarily, by macrophages and dendritic cells present in the lung alveoli. In 90-95% of healthy individuals MTB is killed and cleared by these phagocytic cells. Of the 5 - 10%, of the infected individuals, majority (90%) of the cases continue harboring MTB

in the dormant form without showing any clinical sign of TB. This type of infection is known as latent tuberculosis infection (LTBI). Further, those having LTBI have 5 - 10% risk for conversion to active TB during lifetime. On the other hand, MTB proliferate in infected phagocytes from 5 - 10% of the infected healthy subjects. In such an individual adaptive immune response comes into play where $CD4^+$T cells are stimulated by MTB which then tend to protect the host but fails to mount sufficient level of immunity to protect the host. Ultimately, such individuals develop active tuberculosis [5]. Therefore, pre exposure and post exposure anti TB vaccines to prevent development of active TB (directly after MTB infection and from activation of LTBI, respectively) are being searched for global control and elimination of TB.

On encountering with MTB, $CD4^+$ T cells differentiate into various subtypes known as Th1, Th2, Th17 and T regulatory cells (Tregs). Conventionally, $CD4^+$ helper type 1 (Th1) cell mediated immunity is considered to be protective against MTB infection (active TB and LTBI) [6]. Therefore, most of the strategies for searching vaccine(s) against TB have been focused on induction of immunity at the level of $CD4^+$ Th1 cell. In the recent past, the role of IL-17 producing $CD4^+$ Th17 cells towards protection against MTB infection (active TB and LTBI) has also been documented [7,8] wherein Th17 inducing MTB antigens could enhance the $CD4^+$ Th1 mediated protection as has been found with some promising candidate vaccines [9-13]. Thus, Th17 inducing antigens in anti TB vaccine could be supportive in tuning up $CD4^+$ Th1 mediated protective immunity against MTB.

Involvement of Th17 cell towards autoimmunity and inflammatory diseases

Autoimmunity is a phenomenon where immune system reacts against body's self components. The diseases caused by such an abnormal behaviour of the immune response are called autoimmune diseases. On the other hand, inflammation is an immunological reaction which takes place in the body tissues due to stimuli generated by invasion of tissue by the pathogen or by persistence of irritant in the tissue or by components produced during tissue injury. Inflammation complements autoimmunity leading to autoimmune diseases. Normally, immune system maintains a balance between various immune components in the host just to avoid immune-toxicity. Occurrence of autoimmunity and inflammation in healthy subjects are prevented by immune tolerance generated by Tregs. In this context, Tregs have a role in immune tolerance through suppressing $CD4^+$T helper cells (Th1 and Th17 cells) and thereby in protecting the host against occurrence of autoimmune and inflammation mediated diseases [14]. Contrary to this, Th1 and Th17 cells provoke inflammatory response. Primarily, Th1 cells produce IFN-γ and Th17 cells produce IL-17A, IL-17F and IL-22 [15]. Among the cytokines produced by Th17 cells, IL-17A is the most widely studied and distinctive cytokine. This cytokine is known to be implicated, as an important component, in protective immune response against microbes on the one hand and to mediate immune-pathogenesis for tissue damage through inflammation on the other hand. Biologically, Th17 and Tregs act oppositely and are, thus, inversely correlated with each other i.e. down-regulation at the level of Tregs may up-regulate the Th17 mediated pro-inflammatory response and vice-versa [16]. Any alteration in Treg/Th17 balance may disturb the immune homeostasis and a balance favoring Th17 cell can promote induction of autoimmune cells. The autoimmune cells, thus produced, interact with the corresponding antigens in tissues and proliferate further to give rise to more cells of their progeny. After encountering of the autoimmune cells with the respective antigens in the tissues, occurrence of inflammation is initiated by release of histamine, bradykinin and prostaglandins etc. by tissue insult. During inflammation immune cells like; T and B cells, neutrophils followed by macrophages and mast cells migrate to tissues where they produce cytokines (IFN-γ, IL-17A, IL-6, TNF-α, IL-1β, IL-8 etc.), autoantibodies, complement components (C3a and C5a), leukotrienes and proteolytic enzymes. All these components lead to infiltration of the involved tissue followed by its damage. If this process remains uncontrolled then tissue damage may progress further towards chronic inflammation which may stay for several months. Ultimately, tissues become fibrotic and thereby non functional due to replacement by fibrous connective tissues during repair and remodelling of damaged tissues.

Th17 inducing anti TB vaccine may cause induction of autoimmunity followed by progression to autoimmune and inflammatory diseases

The purpose of a vaccine is to produce protective immunity (after vaccination) against a targeted disease before or after its occurrence. It is well established that vaccination is a highly cost effective measure to eradicate and control communicable diseases. Thus far, vaccines have contributed significantly for effective control of several infectious diseases and thereby towards increasing the life expectancy. However, safety of vaccinated subjects is

extremely important as vaccines are administered, generally, to healthy subjects. A desirable vaccine is the one which has best efficacy with no or minimum side effects. Regarding Th17 inducing TB vaccine, presence of Th17 inducing or Tregs suppressing [5] antigens in TB vaccine might skew balance towards Th1 and Th17 mediated immune response which further might be intensified on encountering with the MTB derived antigens and/or with some other cross-reactive antigens prevailing in other microbes and/or in host tissues. Since both, Th1 and Th17 cells, are pro-inflammatory (though Th17 cell is considered to be more potent), a cumulative stronger pro inflammatory effect could be generated which may favor generation of autoimmune and inflammatory responses (following the phenomena described in the foregoing part of the article). This gives rise to an apprehension that, in addition to protection, vaccination with Th17 inducing vaccine may (i) trigger inflammatory response (as Th17 response is generated earlier than that by $CD4^+$ Th1 cells) in those subjects who are prone to such a pathophysiological phenomenon (ii) provoke the existing subclinical inflammatory disease to become overt (iii) exacerbate the existing inflammation mediated disease (iv) may promote relapse of any subsided or cured inflammatory disease and (v) may induce autoimmunity and thereby autoimmune disease. Thus, it appears that protective efficacy of Th17 inducing vaccine could be compromised by induction, progression and perpetuation of autoimmune and inflammation mediated adverse effects [17] in some vaccinated vulnerable subjects.

Conclusion

Considering all the facts together, it is worth suggesting that a Th1 as well as Th17 inducing vaccine against TB must be investigated extensively to understand whether such a vaccine could give rise to autoimmune and other inflammatory diseases. If yes, then what could be the spectrum and magnitude of such adverse events. Further, it would be important to understand whether such a Th1 as well Th17 inducing vaccine could be acceptable, in terms of risk/ benefit ratio. Even if the frequency is low, the adverse reactions should not be ignored and once observed they must be managed clinically, depending upon their seriousness. This, ultimately, can help in preventing the damage and impairment of the functions of involved tissues by Th1-Th17 inducing anti TB vaccine. Regarding management of Th17 induced autoimmune cum inflammatory diseases, anti IL-17 therapies appear to be promising [18]. Further, it is worth mentioning that search of non pathogenic or less pathogenic Th17 cell [8,19] inducing MTB antigens having ability to generate protective immunity against TB could be appreciable. The antigens thus selected may help in reducing the chances for generation of Th17 mediated autoimmunity and inflammatory diseases on their use as protective anti TB vaccines.

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Conflict of Interests

There is no conflict of interest to declare.

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