Cellular Immunology and Serum Biology

OMMEGA Publishers
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Short Communication Open Access

Hurdles towards Developing Vaccine against Tuberculosis and Views for Possible Solutions

Om Parkash*

Scientist- F (Immunology), National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Tajganj, Agra, India

***Corresponding author:** Om Parkash, Scientist- F (Immunology), National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Tajganj, Agra-282004, INDIA; E-mail: om1234@gmail.com; op_v3@yahoo.com

Abstract

Effective anti TB vaccine is still an urgent requirement for global control of tuberculosis. Thus far, the efforts have been made, mostly, targeting $CD4^+$ IFN-γ^+ Th1 cells to generate immunity for anti TB vaccine. However, efforts on this line have not remained very encouraging. In the present communication, various views have been discussed together in a concise manner pointing out that down modulation at the levels of T regulatory cells (Tregs), intermittent generation of autophagy in antigen presenting cells (APCs) in the vaccinees and involving other immune cells for generation of immunity are worthwhile exploring to improve performance of existing vaccine BCG and/or develop other better anti TB vaccine(s). It would be interesting to understand the performance of anti TB vaccine considering these approaches in combination.

Received Date: October 10, 2016
Accepted Date: October 24, 2016
Published Date: November 1, 2016

Citation: Om Parkash. Hurdles towards developing vaccine against tuberculosis and views for possible solutions. (2016) Cell Immunol Serum Biol 2(2): 62- 63.

DOI: 10.15436/2471-5891.16.1162

Keywords: Tuberculosis; Vaccine; Immunity; Tregs; Autophagy; Multiplex

Introduction

According to the latest report of World Health Organisation (WHO), around 9.6 new cases of tuberculosis (TB) were detected and about 1.5 million died of TB during the year 2014[1]. The major factor that would further worsen the global TB situation is the emergence of drug resistant including multi drug resistant (MDR) and extensively drug resistant (XDR) and total drug resistant (TDR) strains of *Mycobacterium tuberculosis* (MTB). Moreover, prevalence of human immunodeficiency virus (HIV) infection in the general population also has added to the TB problem as HIV infected individuals are more prone to develop TB. In addition to human sufferings, TB causes a great economic loss (billions of US dollars) as well which could partially be due to expenses needed towards treatment of TB patients and their care. Mortality and morbidity caused by TB also lead to economic loss due to reduced work productivity as patients are unable to work efficiently or not work at all due to physical weakness. Consequently, patients have low or no earnings to support livelihood for themselves and their families. Thus, TB is considered to be severe global health problem and needs its urgent control. Currently, chemotherapy is the only strategy for cure of TB and thereby global TB control. However, TB treatment requires multiple drugs for long duration which involves cost and which could cause serious side effects in patients[2]. Also, MTB bacilli are vulnerable to develop drug resistance. Hence, chemotherapy may not be sufficient for global control of TB. Chemotherapy of TB involves about 8 - 10 billion US dollars per year which is far costlier than developing a preventive anti TB vaccine which is estimated to involve about less than one billion US dollars[3,4]. Keeping all the foregoing facts in view, developing an effective preventive vaccine has been given priority in the field of TB research.

Hurdles and Worthwhile Solutions towards Developing anti TB Vaccine

Over the years extensive efforts have been made for developing an effective anti TB vaccine. Most of the efforts have been targeted on inducing the $CD4^+$ IFN-γ^+ Th1 cells[5,6].Though large majority of such vaccines have proved to be promising at the experimental levels but failed in human trials. As yet, no promising vaccine is available for its application and global efforts in search of a successful anti TB vaccine are still continuing. Viewing published literature dealing with: generation of T regulatory cells (Tregs) by mycobacteria[7,8,9] and interaction between MTB and APCs i.e. macrophage and dendritic cells[10,11] it appears that hurdles towards better efficacy of anti TB vaccine

occurring at these levels need urgent attention. Here, an attempt has been made to point out, briefly, the dampening effect (at the levels of Tregs and APCs) on efficacy of anti TB vaccine. Further, apprehensions at the level of multiplex approach for vaccine development have also been discussed. Finally, worthwhile views to overcome such problems have been put forth to stimulate further research for improving performance of existing vaccine like BCG or developing other better anti TB vaccine(s).

(i) T regulatory cells and anti TB vaccine

Both, BCG and MTB are known to induce generation of Treg cells which in turn are considered to be suppressive for $CD4^+IFN\text{-}\gamma^+$ Th1 cell mediated immune response. Pre exposure of the host to environmental mycobacteria may lead to enhanced generation of Treg cells on subsequent entry of Mycobacterial antigens in the form of anti TB vaccine and MTB infection in the host[7,8,9]. Probably, countering of the down modulating effect of Tregs may be carried out, minimising deleterious effects, through blocking the suppressive effect at Treg levels or through diverting out the accumulation of Tregs from the vaccination site. On the other hand, eliminating Treg inducing antigens from the Mycobacterial candidate vaccines may also enhance the performance of the vaccines. All these approaches may be useful for enhancing the performance of BCG, a poorly effective well studied anti TB vaccine.

(ii) Failure to re-stimulate $CD4^+IFN\text{-}\gamma^+$ Th1 memory cells for persistence of vaccine generated immunity

Antigen presenting cells are considered to be incapable of killing engulfed MTB bacilli in susceptible host. Consequently, after MTB infection in the vaccinated individuals the MTB derived antigen presentation may not occur to re-stimulate the vaccine generated $CD4^+IFN\text{-}\gamma^+$ Th1 memory cells for further production of effector T cells to be involved in vaccine efficacy[10]. To overcome this hurdle, intermittent delivery of safe autophagy inducing agent may help in maintaining/sustaining the efficacy of TB vaccine in previously vaccinated individuals[11] through improving MTB killing capacity of APCs and thereby MTB derived antigen presentation. This approach may be useful in case of BCG and other $CD4^+IFN\text{-}\gamma^+$ Th1 inducing vaccines.

(iii) Multiplexing approach for anti TB vaccine and possible apprehensions

It is well known that apart from $CD4^+IFN\text{-}\gamma^+$ Th1, other immune cells like: Th17, CD8, natural killer (NK) cells, NKT cells, γδT cells and B cells also contribute towards protection against MTB infection[12,13]. Hence, it is tempting to speculate that, probably, multiplexed formulation of anti TB vaccines involving more than one relevant MTB antigens to stimulate $CD4^+IFN\text{-}\gamma^+$ Th1cells along with one or more of the aforementioned other immune cells may improve the protective efficacy of vaccine against TB[10-14]. However, multiplexing is not trivial rather it gives rise to several apprehensions, regarding their immunological behaviour, while developing multiplexed formulation of vaccine. Hence, each individual component for formulation needs to be analysed, beforehand, in terms of (i) optimal functional concentration at the antigen and cellular levels (ii) synergistic or additive effect in various combinations of immunogens and immune cells to obtain safe and improved performance of vaccine. Though it could be a challenging task to develop multiplexed vaccine considering diversity at antigen as well as immune response levels, such an approach may enable in designing a more potential anti TB vaccine. Nonetheless, efforts on these lines are called for.

Conclusions

The foregoing approaches may help either in enhancing the immunogenicity of anti TB vaccine or in sustaining the vaccine generated immunity or in broadening the vaccine generated immunity. While developing better anti TB vaccine it would be interesting to unravel the performance of these approaches in combination as well. Nonetheless, developing anti TB vaccine is still a challenge and the same may be met by evolving effective but safe strategy(ies).

Acknowledgements

Thanks to Infolep, Amsterdam, The Netherlands, for helping in providing the scientific literature. Thanks to Indian Council of Medical Research and to NJIL and OMD, Agra for their due supports.

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