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Mini Review

Down Modulation at the Levels of T Regulatory Cells (Tregs) May Enhance the Immunogenic Behaviour but not the Protective Efficacy of $CD4^+IFN\text{-}\Upsilon^+Th1$ Cell Inducing Vaccine(s) Against Tuberculosis

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Abstract

Developing anti Tuberculosis (TB) vaccine is a top priority for global control of TB. Since BCG (Bacille Calmette–Guérin) has limited protection against *Mycobacterium Tuberculosis* (MTB) infection, efforts are being made to further improve its protective efficacy. Priming with BCG followed by boosting with heterologous MTB antigen has been one of the strategies to enhance performance of BCG. An immuno-phenomena for such boosting involves up-regulation of BCG primed $CD4^+IFN\text{-}\Upsilon^+Th1$ cells by down modulating the immunosuppressive T regulatory cells (Tregs) with heterologous MTB antigens. However, with such an approach despite of enhancing the $CD4^+IFN\text{-}\Upsilon^+Th1$ cell mediated immunnity (CMI) the protective efficacy of vaccine remains poor as has been observed in case of a trial where priming of $CD4^+IFN\text{-}\Upsilon^+Th1$ with BCG was followed by boosting with Tregs down modulating but $CD4^+IFN\text{-}\Upsilon^+Th1$ cell stimulating recombinant MVA85A antigen (a MTB derived 85A antigen expressed in Vaccinia virus). The possible cause for failure of such a strategy for improving the protective efficacy of BCG could be the evasive behaviour of invading MTB towards killing by antigen presenting cells (APCs: there could macrophages and dendritic cells) in the infected host. As a result of which there occur no/insufficient presentation of MTB derived antigens to re-stimulate the vaccine generated memory $CD4^+IFN\text{-}\Upsilon^+Th1$ cells to provide protection. Hence, searching an efficient vaccine for TB is still a challenge and needs more novel investigations.

Keywords: Tuberculosis; $CD4^+IFN\text{-}\Upsilon^+Th1$; Immuno-regulation; Tregs; Vaccine

Introduction

Tuberculosis is still a major public health concern as every year nearly 1.5 million people die due to this disease [1]. After transmission of *Mycobacterium tuberculosis* (A etiological agent for TB) to the healthy subjects, tuberculosis is caused in about 5-10% of the MTB infected hosts which in turn may be due to lack of sufficient immunity against MTB in such individuals. Prevention of occurrence of TB disease in the infected hosts can be carried out through induction of immunity, in advance, against MTB by vaccinating the healthy subjects with vaccine against TB. Such a preventive approach through immuno prophylaxis could be highly cost-effective for global control of TB. However, despite of several intense efforts towards searching anti TB vaccine at various global laboratories, no sufficiently better vaccine against TB has replaced BCG, as yet. Nevertheless, some searched candidate vaccines appear to be promising which are in the pipe line for their evaluations [2-4].

After infection with MTB, 90-95% of the healthy human beings do not develop TB disease by protection either through innate or adaptive immunity or both. Following evasion of the innate immunity by MTB, adaptive immunity is generated to defend the hosts [5-7]. Keeping this in view, efforts for developing anti TB vaccines are being made, mostly, to induce cell mediated immunity at the level of $CD4^+IFN\text{-}\Upsilon^+Th1$ cells. Over the years, BCG (an inducer of $CD4^+IFN\text{-}\Upsilon^+Th1$ cells mediated immunity) has been used widely, safely and acceptably for immunisation of human beings [8]. However, immunity conferred by BCG is limited in protecting the vaccinees. Hence, emphasis is being laid on developing either some strategy(ies) for improving the performance BCG or for developing better alternate(s) of BCG [3].

Generation of Tregs Against Mycobacteria and their Down Modulation by Immunization with MVA85A Antigen to Boost the Efficacy of BCG

T regulatory cells, the type of $CD4^+$ T helper cells, take part in causing immuno-tolerance to maintain immunological homeostasis in the body. Since, Tregs are known to suppress the $CD4^+IFN\text{-}\Upsilon^+Th1$ cells mediated immunity, down modulation at the level of Tregs has remained one of the emerging approaches for improving through/up regulating the $CD4^+IFN\text{-}\Upsilon^+Th1$ mediated efficacy of vaccines. In this context, it is worth mentioning that mycobacteria including,

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Mycobacterium tuberculosis [9] and environmental mycobacteria like *Mycobacterium vaccae* and *Mycobacterium chelonae* [10,11] have been reported to be inducers of Tregs. It is likely, that exposure of an individual to such mycobacteria could give rise to Tregs in the host and subsequent immunisation of such individuals (exposed to mycobacteria) with BCG could stimulate these already sensitized Tregs for their further proliferation. More-over, BCG itself is also known to be an inducer of Tregs [12]. Thus, a pool of Tregs could be created which eventually may dampen the immunogenicity of BCG due to shifting of the immune-balance in favour of Tregs rather than towards $CD4^+IFN\text{-}\Upsilon^+Th1$ cells. Therefore, negative manipulation at the level of Tregs appears to be an attractive strategy to boost the BCG generated $CD4^+IFN\text{-}\Upsilon^+Th1$ mediated immunity against MTB infection [12]. Such an approach where priming with BCG followed by boosting with Tregs down regulating but $CD4^+IFN\text{-}\Upsilon^+Th1$ stimulating MTB derived heterologous recombinant antigen MVA85A antigen, a has been explored in the past [13,14]. However, this strategy following the principle of down modulation at the level of Tregs to up regulate the $CD4^+IFN\text{-}\Upsilon^+Th1$ mediated immunity has failed in providing improved protection against TB despite of generation of robust and durable $CD4^+IFN\text{-}\Upsilon^+Th1$ mediated immune response against MTB. This indicates that down modulating strategy at the level of Tregs could improve only the immunogenic behaviour of BCG rather than its protective efficacy.

Explaining the Phenomenon for Poor Performance of the Strategy: Priming by BCG Followed by Immunisation with Boosting Antigen

Basically, for a vaccine to be effective, re-stimulation, [by the pathogen derived antigen(s)], of the vaccine generated memory cells is a pre-requisite for their further proliferation leading to formation of effector cells [15]. The poor protective efficacy of the strategy where priming with BCG is followed by boosting with heterologous MTB antigen could be attributed to the failure towards killing of the invading MTB by antigen presenting cells (macrophages/dendritic cells etc.) in the vaccinees. This in turn could result in no/insufficient presentation, in combination with major histocompatibility complex-II, of MTB derived antigens. As a result thereof, re-stimulation of vaccine generated memory $CD4^+Th1$ cells might not occur to produce effector cells for generation of cytokines (IFN-γ and TNF-α etc.) to promote antimicrobial activity in APCs to kill invading MTB in the host [16]. This, eventually, could lead to failure in protecting the host despite of successful immunisation.

Conclusion

Negative regulation at the level of Tregs might enhance the immunogenic behaviour but not the protective efficacy of $CD4^+IFN\text{-}\Upsilon^+Th1$ cell inducing vaccine against TB. Likewise, down modulation at the level(s) of other immuno-regulatory mechanism(s) (e.g. myeloid derived suppressor cells, immune-checkpoints etc.) involved towards down modulation of CD4+Th1 cells [17] might also not potentiate the efficacy of $CD4^+IFN\text{-}\Upsilon^+Th1$ cell inducing anti TB vaccine(s). Thus, developing efficient anti TB vaccine(s) is still a big challenge for scientific community. Hence, investigations on novel strategy(ies) for designing vaccine(s) and for their modes of immunisation are highly needed to develop vaccine(s) for better protection against TB.

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