Antigens for DNA Vaccines Against Tuberculosis

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Introduction

Tuberculosis (TB) is a major global disease caused by a bacterial pathogen and it has existed in the world since antiquity. It is suggested that TB has killed maximum number of people in the world, when compared with other diseases caused by microbial agents [1]. According to the most recent data published by the World Health Organization (WHO), TB was the leading cause of human deaths from a single pathogen, ranking above HIV/AIDS. According to the WHO report, 10.4 million people became diseased, and 1.7 million people died from TB in 2016 [2]. Among the factors contributing to continued carnage due to TB include the non-availability of an effective vaccine that can consistently provide protection in all countries of the world and different manifestations of TB [3]. The currently available vaccine, i.e. Mycobacterium bovis BCG is inconsistent in providing protection against TB in different parts of the world [4]. Hence, work is in progress to develop alternative vaccines based on whole organisms and subunit vaccines, including DNA vaccines [5].

DNA vaccines against bacterial diseases have a backbone of plasmid DNA of bacterial origin, promoters of viral origin for expressing the cloned genes in mammalian cells and contain genes for immunogenic proteins of pathogens. The DNA is delivered into the mammalian recipients and taken up by the host cells, which will express the specific proteins from the corresponding pathogen-specific DNA/gene [6]. Since the proteins of pathogens are foreign for the mammalian recipients, they act as immunogen to induce pathogen-specific immune responses, after appropriate processing and presentation by antigen presenting cells [7]. If the ensuing immune responses are appropriate, the recipients immunized with DNA vaccines will be protected against the disease upon a subsequent challenge with the viable pathogen [8]. Furthermore, DNA vaccines may also have a therapeutic potential if they shift the immune response in already diseased subjects from pathological to protective type [9].

The first experimental DNA vaccine against TB was developed by Lowrie et al. in 1994 by cloning the cross-reactive mycobacterial antigen HSP65 in a plasmid [10]. The recombinant plasmid-based DNA vaccines expressing HSP65 have been shown to provide protection against M. tuberculosis challenge in preventive studies in mice [11], and have also shown therapeutic potential in mouse and monkey models of TB [12,13]. A number of DNA vaccines providing protection against TB in animal models have been developed using other cross-reactive antigens of M. tuberculosis, e.g. Ag85A and Ag85 B, etc. [14,15].

However, any vaccine based on cross-reactive antigens may not be successful in humans presensitized to these antigens through exposure to environmental mycobacteria or vaccination with BCG because such presensitizations may down-modulate the immunologic behavior of cross-reactive antigens present in the vaccines and mask their efficacy [16]. An example of this mechanism operating in mice has been demonstrated in case of adenovirus based Ag85A (Ad85A) vaccine which failed to provide protection against M. tuberculosis challenge in mice presensitized with an environmental Mycobacterium, i.e. M. abscessus [17]. Furthermore, boosting the effectiveness of BCG vaccine in humans did not succeed by using viral vector-based Ag85A vaccine (MVA85A) probably due to the use of a cross-reactive antigen [18]. Therefore, studies have been conducted to identify M. tuberculosis-specific proteins that can be used as antigens for developing DNA vaccines against TB.

The research to identify M. tuberculosis-specific antigens as candidates for new vaccines has led to the identification of ESAT-6, CFP10 and PE35 as major M. tuberculosis-specific antigens [19-21]. The induction of cellular and protective immune responses was observed after vaccination of animals with recombinant plasmid DNA and other vaccine constructs containing genes for ESAT-6 and CFP10 [22-25]. However, ESAT-6 and CFP10 are widely used for diagnostic applications in TB [26,27], and hence these antigens are not suited for TB vaccine development because their diagnostic potential will be compromised. Therefore, further studies were carried out with PE35 as the antigen for DNA vaccine development. It was shown that protective Th1-type cellular immune responses were induced in mice immunized with a PE35-based DNA vaccine construct (pUMCV6-PE35) [28,29]. However, non-protective and pathologic Th2-type and anti-inflammatory responses were not detected [30]. This DNA vaccine construct also induced antigen-specific antibody responses [31]. These results suggest the potential of pUMCV6-PE35 as a new candidate DNA vaccine against TB.

As compared to single antigen-based DNA vaccines, the multivalent vaccines based on cross-reactive antigens appear to be more effective in providing protection against TB in animals due to the induction of broader immune response [32-34]. Therefore, further studies should be conducted to identify additional M. tuberculosis-specific antigens, clone them in DNA vaccine vectors and test their safety and efficacy in animal models of TB. Once successful multivalent DNA vaccine constructs are identified in animal studies, such candidates may be appropriate to evaluate in humans for safety and efficacy both in BCG-vaccinated and non-vaccinated subjects without facing the problems with cross-reactive antigens either from BCG or environmental mycobacteria.

Conclusion

A number of DNA vaccines, based on cross-reactive antigens of M. tuberculosis, have been constructed and tested for efficacy in prophylaxis and therapy of TB in various animal models. However, due to the cross reactivity of antigens with the currently used vaccine M. bovis BCG and environmental mycobacteria, the efficacy of these vaccine in humans is doubtful. To overcome the problem of antigenic
cross reactivity, monovalent antigen DNA vaccines containing single 
*M. tuberculosis*-specific antigens have been constructed and tested in 
animal models of TB. However, to induce broader and more effective 
immune responses, multivalent DNA vaccines expressing several 
*M. tuberculosis*-specific antigens should be constructed and evaluated for 
efficacy against TB in animals and humans.

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References

tuberculosis. Text Book of Biochemistry, Biotechnology, Allied and 
Molecular Medicine (4th Edn.) PHI Learning Private Limited, Delhi, 
India. pp: 1347-1353.
Tuberculosis vaccines: Opportunities and challenges. Respirology.
6. Williams JA (2013) Vector design for improved DNA vaccine efficacy, 
safety and production. Vaccines 1: 225-249.
7. Sharma AK, Khuller GK (2001) DNA vaccines: Future strategies and 
HIV vaccines in rhesus macaque models. Expert Rev Vaccines 16: 
973-985.
DNA vaccines for human papillomavirus and associated diseases. Hum 
Gene Ther.
vaccine against tuberculosis. Vaccine 12: 1537-1540.
Therapy of tuberculosis in mice by DNA vaccination. Nature 400: 
269-271.
Preclinical study and clinical trial of a novel therapeutic vaccine against 
85 complex as a powerful Mycobacterium tuberculosis immunogen: 
Biology, immune-pathogenicity, applications in diagnosis, and vaccine 
therapeutic effects of a Mycobacterium tuberculosis rv2190c DNA 
vaccine in mice. BMC Immunol 18: 11.
16. Prakash O (2014) How to avoid the impact of environmental 
microbea tuberculosis towards the efficacy of BCG vaccination against 
effects on protection against Mycobacterium tuberculosis after immunization with Ad85A. Vaccine 31: 1086-1093.
(2013) Safety and efficacy of MVA85A, a new tuberculosis vaccine, in 
infants previously vaccinated with BCG: A randomised, placebo-
19. Mustafa AS (2013) In silico analysis and experimental validation of 
Mycobacterium tuberculosis-specific proteins and peptides of 
Mycobacterium tuberculosis for immunological diagnosis and vaccine 
development. Med Princ Pract 14:3-51.
20. Mustafa AS (2013) Diagnostic and vaccine potentials of ESAT-6 family 
proteins encoded by M. tuberculosis genomic regions absent in M. bovis 
BCG. J Mycobac Dis 3:129.
antigens/peptides in tuberculin skin testing for the diagnosis of 
DNA vaccine encoding Mycobacterium tuberculosis ESAT-6 and FL 
proteins against Mycobacterium tuberculosis challenge in mice. J Biomed 
to recombinant Mycobacterium bovis BCG constructs expressing major 
antigens of region of difference I of Mycobacterium tuberculosis. Clin 
Vaccine Immunol 20: 1230-1237.
against Mycobacterium tuberculosis-specific proteins PE35 and CFP10 in 
mice immunized with recombinant Mycobacterium vaccae. Saudi Med 
J 35: 350-359.
Mycobacterium tuberculosis proteins as tested by delayed-type 
diagnostic and vaccine potential from genomic regions of difference of 
27. Mustafa AS (2012) Proteins and peptides encoded by M. tuberculosis-
specific genomic regions for immunological diagnosis of tuberculosis. J 
Mycobac Dis 2: 114.
expressing Mycobacterium tuberculosis-specific genes induce immune 
29. Mustafa AS (2016) Immune responses to candidate vaccine antigens 
delivered through naked plasmid and mycobacterial vectors. Open Conf 
mice induced by M. tuberculosis PE35-DNA vaccine construct. Scand J 
Immunol 74: 554-60.
immunized with region of difference DNA vaccine constructs of 
using chemotherapy and immunotherapy with the combined DNA 
vaccine encoding Ag85B, MPT-64 and MPT-83. Gene Ther 15: 653-659.
multivalent tuberculosis vaccine confers protection in a mouse model of 
34. Villarreal DO, Walters J, Laddy DJ, Yan J, Weiner DB (2014) Multivalent 
TB vaccines targeting the ess gene family generate potent and broad cell-
mediated immune responses superior to BCG. Hum Vacc Immunother 
10: 2188-2198.