Mycobacterial Diseases
ISSN: 2161-1068

Mustafa, Mycobact Dis 2018, 8:1
DOI: 10.4172/2161-1068.1000255

Short Communication Open Access

Antigens for DNA Vaccines Against Tuberculosis

Abu Salim Mustafa*

Faculty of Medicine, Department of Microbiology, Kuwait University, Safat 1310, Kuwait

***Corresponding author:** Abu Salim Mustafa, Faculty of Medicine, Department of Microbiology, Kuwait University, Safat 1310, Kuwait, Tel: 24986505; Fax: 5332719; E-mail: abusalim@hsc.edu.kw

Received date: February 04, 2018; **Accepted date:** February 19, 2018; **Published date:** February 26, 2018

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 ensued 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 adeno virus 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.

Acknowledgments

The study was supported by Kuwait University Research Sector grant RM01/13.

References

1. Daniel TM (2006) The history of tuberculosis. Respir Med 100: 1862-1870.
2. WHO Report (2017) Global tuberculosis report.
3. Mustafa AS (2012) What's new in the development of tuberculosis vaccines. Med Princ Pract 21: 195-196.
4. Mustafa AS (2016) BCG pros and cons and new/improved vaccines for tuberculosis. Text Book of Biochemistry, Biotechnology, Allied and Molecular Medicine (4th Edn.) PHI Learning Private Limited, Delhi, India. pp: 1347-1353.
5. Zhu B, Dockrell HM, Ottenhoff THM, Evans TG, Zhang Y (2018) 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 relevance to intracellular pathogens. Immunol Cell Biol 79: 537-546.
8. Chea LS, Amara RR (2017) Immunogenicity and efficacy of DNA/MVA HIV vaccines in rhesus macaque models. Expert Rev Vaccines 16: 973-985.
9. Cheng MA, Farmer E, Huang C, Lin J, Hung CF, et al. (2018) Therapeutic DNA vaccines for human papillomavirus and associated diseases. Hum Gene Ther.
10. Lowrie DB, Tascon RE, Colston MJ, Silva CL (1994) Towards a DNA vaccine against tuberculosis. Vaccine 12: 1537-1540.
11. Tascon RE, Colston MJ, Ragno S, Stavropoulos E, Gregory D, et al. (1996) Vaccination against tuberculosis by DNA injection. Nat Med 2: 888-892.
12. Lowrie DB, Tascon RE, Bonato VL, Lima VM, Faccioli LH, et al. (1999) Therapy of tuberculosis in mice by DNA vaccination. Nature 400: 269-271.
13. Okada M, Kita Y, Hashimoto S, Nakatani H, Nishimastu S, et al. (2017) Preclinical study and clinical trial of a novel therapeutic vaccine against multi-drug resistant tuberculosis. Hum Vaccin Immunother 13: 298-305.
14. Karbalaei Zadeh Babaki M, Soleimanpour S, Rezaee SA (2017) Antigen 85 complex as a powerful Mycobacterium tuberculosis immunogen: Biology, immune-pathogenicity, applications in diagnosis, and vaccine design. Microb Pathog 112: 20-29.
15. Liang Y, Zhang X, Bai X, Xiao L, Wang X, et al. (2017) Immunogenicity and 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 mycobacteria towards the efficacy of BCG vaccination against tuberculosis? Int J Mycobacteriol 3: 1-4.
17. Beverley P, Ronan E, Lee L, Arnold I, Bolinger B, et al. (2013) Environmental effects on protection against Mycobacterium tuberculosis after immunization with Ad85A. Vaccine 31: 1086-1093.
18. Tameris MD, Hatherill M, Landry BS, Scriba TJ, Snowden MA, et al. (2013) Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: A randomised, placebo-controlled phase 2b trial. Lancet 381: 1021-1028.
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 1:43-51.
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.
21. Mustafa AS (2014) The future of Mycobacterium tuberculosis-specific antigens/peptides in tuberculin skin testing for the diagnosis of tuberculosis. J Mycobac Dis 4:3.
22. Jiang Q, Zhang J, Chen X, Xia M, Lu Y, et al. (2013) A novel recombinant DNA vaccine encoding Mycobacterium tuberculosis ESAT-6 and FL protects against Mycobacterium tuberculosis challenge in mice. J Biomed Res 27: 406-420.
23. Shaban K, Amoudy HA, Mustafa AS (2013) Cellular immune responses to recombinant Mycobacterium bovis BCG constructs expressing major antigens of region of difference 1 of Mycobacterium tuberculosis. Clin Vaccine Immunol 20: 1230-1237.
24. Amoudy HA, Ebrahimi BH, Mustafa AS (2014) Immune responses against Mycobacterium tuberculosis-specific proteins PE35 and CFP10 in mice immunized with recombinant Mycobacterium vaccae. Saudi Med J 35: 350-359.
25. Hanif SN, Al-Attiyah R and Mustafa AS (2010) Species-specific antigenic Mycobacterium tuberculosis proteins as tested by delayed-type hypersensitivity response. Int J Tuberc Lung Dis 14: 489-494.
26. Mustafa AS (2010) Cell mediated immunity assays identify proteins of diagnostic and vaccine potential from genomic regions of difference of Mycobacterium tuberculosis. Kuwait Med J 42: 98-105.
27. Mustafa AS (2012) Proteins and peptides encoded by M. tuberculosis-specific genomic regions for immunological diagnosis of tuberculosis. J Mycobac Dis 2: 114.
28. Hanif SNM, Al-Attiyah R, Mustafa AS (2010) DNA vaccine constructs expressing Mycobacterium tuberculosis-specific genes induce immune responses. Scand J Immunol 72: 408-415.
29. Mustafa AS (2016) Immune responses to candidate vaccine antigens delivered through naked plasmid and mycobacterial vectors. Open Conf Proc J 7: 153-199.
30. Hanif SN, Al-Attiyah R, Mustafa AS (2011) Cellular immune responses in mice induced by M. tuberculosis PE35-DNA vaccine construct. Scand J Immunol 74: 554-60.
31. Hanif SNM, Mustafa AS (2017) Humoral immune responses in mice immunized with region of difference DNA vaccine constructs of pUMVC6 and pUMVC7. Int J Mycobacteriol 6: 281-288.
32. Yu DH, Hu XD, Cai H (2008) Efficient tuberculosis treatment in mice using chemotherapy and immunotherapy with the combined DNA vaccine encoding Ag85B, MPT-64 and MPT-83. Gene Ther 15: 652-659.
33. Griffiths KL, Villarreal DO, Weiner DB, Khader SA (2016) A novel multivalent tuberculosis vaccine confers protection in a mouse model of tuberculosis. Hum Vaccin Immunother 12: 2649-2653.
34. Villarreal DO, Walters J, Laddy DJ, Yan J, Weiner DB (2014) Multivalent TB vaccines targeting the esx gene family generate potent and broad cell-mediated immune responses superior to BCG. Hum Vaccin Immunother 10: 2188-2198.