USE OF CFP-10- ANTIGEN WITH Fcγ2α IGG FOR VACCINE AGAINST TUBERCULOSIS: EFFECTIVE OR NON-EFFECTIVE?

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ABSTRACT: Tuberculosis (TB), a major public health problem, is a re-emerging challenging through the world. Prevention of this disease is a priority of WHO. Many subunit vaccine have been candidate for vaccination. Evaluating the safety and efficacy of these antigens is the concern of many researchers. This review is discussed efficiency or non-efficiency of CFP-10- antigen with Fcγ2α IgG for vaccine design against tuberculosis.

Keywords: CFP-10, Fcγ2α IgG, Mycobacterium Tuberculosis, Vaccine.

INTRODUCTION
This review is discussed efficiency or non-efficiency of CFP-10- antigen with Fcγ2α IgG for vaccine design against tuberculosis. Tuberculosis (TB), a major public health problem, is a re-emerging challenging through the world (1-2). According to the World Health organization (WHO) estimation, tuberculosis is responsible for three millions deaths and over eight million new cases yearly (3). Absence of operative vaccine and rising of more and more resistant strains like multiple drug resistant (MDR) and a main drug resistant (XDR) make difficulty controlling TB (4). Many successful vaccines have been advanced through trial and error which was developed between 1906 and 1919 by attenuation of the virulent Mycobacterium bovis, but without any immunological consideration such as BCG vaccine (5). So, accessibility to the new operational vaccine against TB is urgently needed to control its spreading. Up until now, around ten vaccine candidates have left the laboratory stage and entered clinical trials (5).

Because of possibly cloning, expressing and producing relatively easily of protein antigens group, most research has probably been devoted to them (6). Likewise, new-generation vaccines goal set up the host immune system can be predicted (7). Such these vaccines can be immune system stimulants, which directly affect cytokine response for example or alternatively, mark the phagosome, or interfere with the host cell cycle. Therefore a live vaccine and secondly follow with a boost of antigen stand the rationale to vaccinate. Trials currently underway in primates and humans may show whether this approach suggests any advantage (5). Candidate molecules has in the recent years concentrated on proteins released from dividing bacteria based on the reasoning that live bacteria generally induce higher levels of protection than killed preparations (8). For a number of years, the components of culture filtrate have been investigated by using narrow-molecular-mass fractions as a guide to identify immunologically active single molecules (8). So, it is important to measure proliferation of T cells after immunization with vaccines when stimulated in vitro with a specific antigen (9). Several recombinant mycobacterial antigens were detected by Young et al. (1985). They screened the mycobacterial recombinant DNA libraries with antibody probes and succeeded to identify some recombinant mycobacterial antigens (10). Testing of these antigens with T-cell lines and clones showed that human T-cells recognized most of them as...
well. In the recent years, the concept of subunit and peptide vaccines has generated a lot of interest due to safety concerns of live vaccines in immune compromised individuals. Subunit vaccine candidates are based on antigens that are recognized by T cells from patients with latent infection or whose tuberculosis has been cured (10). Evaluating the immunogenicity and protective efficacy of secreted proteins encoded by RD1 region is the key for development of subunit and DNA anti tuberculosis vaccines (11).

BCG vaccine lacks the potent secreted T-cell antigens ESAT-6 (6-kilo Dalton early secretory antigen target) and CFP-10 (10-kilo Dalton culture filtrate protein) as a result of deletions. Both, ESAT-6 and CFP-10 antigens, are present in all virulent mycobacteria studied (12). CFP10 was cloned and expressed as a fusion protein in soluble form to be available for diagnostic purpose. This crucial T-cell antigen of M. tuberculosis is encoded by ORF6 of the RD1 immunological region (10). The 10-kDa culture filtrate protein (CFP-10) is a well-characterized, secreted mycobacterial protein that elicits CD8+ T cells in both people and mice following M. Tuberculosis infection (13). CFP-10 is so commonly recognized by T cells from M. tuberculosis-infected people that it is one of the antigens now being used for the immune diagnosis of tuberculosis (13). CFP10 is known to induce strong IFN-γ production, proliferation of T cells and moderate cytotoxic T cell activity in M.tb infected mice as reported by Weldingh et al. (1998) (4).

The family of Fc receptors IgG (FcγRs) provides a prime example of how simultaneous triggering of activating and inhibitory signaling pathways sets thresholds for cell activation and thus generates a well-balanced immune response (14). FcγRs are expressed widely throughout the hematopoietic system and play a major role in the activation of innate immunity by specific high-affinity antibodies produced by the adaptive immune system (14). Fcγ2α not only control innate immune effector cell activation but are also involved in regulating the production and specificity of their ligands (that is, antibodies). Thus, Fcγ2α are involved in regulating a multitude of innate and adaptive immune responses, which makes them attractive targets for the development of novel immunotherapeutic approaches. Although initial studies suggested that certain T-cell subpopulations might express FcγRs, more recent evidence suggests that this is not the case. The question of T-cell expression of FcγRs is, however, best considered to be an open one, as it is notoriously difficult to examine every possible subset or activation state of T cells for FcγR expression. Innate immune effector cells, such as monocytes, macrophages, DCs, basophils and mast cells express activating and inhibitory FcγRs (14).

**CFP-10- ANTIGEN WITH FCγ2A IGG FOR VACCINE**

Culture filtrate proteins (CFPs) are the principal targets of the T-cell response in mice, both at the height of infection and in a state of memory immunity, as well as in humans with active TB (15). Crude Mycobacterium tuberculosis H37Rv culture filtrate protein (CFP) produced by the National Institutes of Health, National Institute of Allergy and Infectious Diseases (Contract N01-AI-75320, kindly donated by Dr. J. Belisle at Colorado State University) was used in the vitro immunological assays (16). Culture filtrate protein (CFP)-10 is secreted in the early or active phase of infection and elicit strong cell mediated immune responses and their use as a cocktail of such antigens may increase the diagnostic sensitivity (17). However, these pre-exposure candidates are designed for prevention of disease and will therefore neither eradicate the pathogen, nor prevent stable infection (5). CFP10 was found to distinguish TB patients from BCG-vaccinated donors and is, together with ESAT-6, an interesting candidate for the diagnosis of TB (8).

Studies in animal models have provided such insights and helped our understanding of the immune response to tuberculosis in human disease. The mouse is relatively more resistant and the guinea pig more sensitive to M. tuberculosis and thus provide clinical pictures of slow and rapid progression respectively of the disease in humans (12). Assessments of the immune responses generated by a DNA vaccine encoding CFP-10 and determine the epitope specificity of the elicited T cells. It would found that the CFP-10 DNA vaccine elicits class I major histocompatibility complex (MHC)-restricted CFP-10 specific CD8 T cells in C3H mice (13). Studies conducted in the past have shown that non-living subunit vaccines in the form of CF of M. Tuberculosis provide protection against viable M. Tuberculosis challenge in animal models of TB (18).

Cellular immune responses, both in the CD4+ and CD8+ T cell subsets, are essential components of an effective immune response against TB (2, 19). It has been demonstrated that T cells responsible for the recall of protective immunity are directed to highly secreted protein fractions in a mouse model of TB. CD4+ T cells produce interferon-γ and several cytokines including interleukin-2, both of which have important role in fighting against tuberculosis (12). Cellular immune responses are critical for the control of Mycobacterium tuberculosis infection. The contribution of CD4+ T cells has been extensively documented, and the increased susceptibility of human immune deficiency virus-infected people to tuberculosis underlines the importance of CD4+ T cells in...
preventing the disease caused by M. tuberculosis. On the other hand, the role of CD8+ T cells in immunity to M. tuberculosis is still being elucidated (13). Several animal models, including normal mice depleted of CD8+ T cells, immune deficient mice reconstituted with immune CD8+ T cells, and knockout (KO) mice that lack CD8+ T cells, have clearly shown that CD8+ T cells are required for optimum control of bacterial replication and host resistance to M. tuberculosis infection (13). Intramuscular immunization with a DNA vaccine encoding CFP10 elicited production of IFN-γ by systemic CD4+ T cells, and one intravenous dose of the CFP10-based DNA vaccine coated with polyethylenimine (PEI) stimulated IFN-γ production by lung CD4+ cells and reduced the pulmonary bacillary burden (20). It could be concluded that CFP10 is a potential vaccine candidate and that coating vaccines with PEI enhances local protective immunity to tuberculosis (20). CFP-10 specific CD8+ cells undergo a rapid expansion and accumulate in the lung and spleen following challenge of immunized mice with aerosolized M.tuberculosis. Protective immunity is induced by CFP-10 DNA vaccination as measured by a CFU reduction in the lung and spleen 4 and 8 weeks after challenge with M. tuberculosis (20). These data demonstrate that CFP-10 is a protective antigen and that CFP-10 specific CD8+ T cells elicited by vaccination are sufficient to mediate protection against tuberculosis (13). The results demonstrated that after protein boosting, immunoglobulin (Ig) G subclass profile skewed to the IgG1 isotype, which indicated a Th2 type immune response (9).

Vaccines containing protein antigens with appropriate adjuvants have been shown to function effectively in animal studies cases. Subunit vaccine such as CFP-10 may be overcome by using suitable adjuvants in trials. Various CFP antigens have been assayed in the presence of distinct adjuvants (DDA) in experimental murine TB (15). These adjuvants include incomplete Freund’s adjuvant (IFA), which was shown to induce protection comparable to that achieved through BCG immunization (17). This protocol resulted in an increased relative ratio of IgG1 and the cytotoxicity of T cells (21). Also, this practice is determinative that whether a DNA vaccine encoding the full-length CFP-10 gene elicits CD8+ T cells specific for CFP-10. The T cells that are primed develop into functional memory T cells, since a dramatic increase in the frequency and absolute number of CFP-10-specific CD8 T cells is observed following challenge with M. tuberculosis (13). By defining the epitope specificity of the T cells elicited by vaccination, it has been demonstrated that CFP-10-specific CD8+ T cells are sufficient to confer protection against tuberculosis (22). The goal would be to increase duration of immunity and improve protection conferred by the prime event (5). Such CFP-10 antigens boosting vaccines might have to be repeatedly administered during an individual’s lifespan with changing antigen composition (5).

**DISCUSSION**

This review shows that CFP-10 is a target of protective immunity. The 10-kDa culture filtrate protein (CFP-10) antigen of T cells is secreted in abundance by Mycobacterium tuberculosis and is frequently recognized by T cells from infected people and it is hypothesized that these proteins are important targets of protective immunity. These data provide important proof for the principle that vaccine strategies that induce stimulation of CD8+ T cells can provide protection against tuberculosis. One, CFP-10, is recognized by CD8+ T cells, and the other, CFP-10, is recognized by CD4+ T cells. Culture filtrate from Mycobacterium tuberculosis contains protective antigens of relevance for the generation of a new antituberculosis vaccine. The advances in CFP-10 DNA and subunit vaccine technology have greatly facilitated the prevention of the etiologic agent of tuberculosis (TB) antigens. This data demonstrates that vaccine-elicited 10-Kilodalton culture filtrate protein specific CD8+ T Cells are sufficient to mediate protection against Mycobacterium tuberculosis infection (13). More recent developments have resulted in more specific and sensitive assays measuring IFN-γ production by CD4+ T lymphocytes against defined Mtb antigens, notably CFP-10 and ESAT-6. These so-called IFN-γ release assays (IGRA) can distinguish Mtb-infected not only from uninfected individuals but also from BCG-vaccinated individuals, because CFP-10 and ESAT-6 are produced by Mtb but not by BCG (23).

**CONCLUSION**

In the present review, the efficiency of novel vaccine, CFP-10 with Fcy2a IgG, of TB was evaluated. It is expected that an ideal anti-TB vaccine should provide consistent and long-term protection in humans, irrespective of the geographical location of use by considering various immune responses through the world. The great obstacle to the development of protein subunit vaccines is the limited availability of new adjuvants capable of eliciting a suitable pattern of immune response. Secondly, M. tuberculosis is known to alter its gene...
expression radically during the course of infection. What effect does it have on the host's immune response, and in such cases would the new vaccines continue to remain protective? (12)

Some little antigens such as CFP-10 need to be complexed with multiple strong T cell adjuvants such as DDAMPL, DDA-MPL-TDM, DDA-MPL-TDB or a Toll-like receptor (TLR3 or TLR9) agonists complexed to cationic liposomes.

And at last but not least, The use of a simple antigen may seem counterintuitive, since it is widely believed that humoral immunity may not be important in mycobacterial infection or disease. However, we do not know this for certain, and immune boosters or vaccination with antigens alone have shown promising effects.

REFERENCES


