The Fusion Multistage Synthetic Peptides as the Best Candidates for New Tuberculosis Vaccine

Sir,

Tuberculosis (TB) is one of the main infectious diseases, caused by *Mycobacterium tuberculosis* complex (MTBC), and it is annually associated with high rate of mortality (1.5 million deaths) in the world. Nowadays, the emergence of multidrug-resistant TB, extensively drug-resistant TB, and human immunodeficiency virus has led to exacerbated concerns about controlling TB.[1] According to the reports, one-third of the world's population are contaminated with *M. tuberculosis* without clinical symptoms.[1,2]

Currently, the TB vaccine (*Mycobacterium bovis* Bacillus Calmette-Guérin [BCG]) is one of the main strategies in controlling and prevention of TB among the population; it provides successful immunity against disseminated and tubercular meningitis in children; however, it has immaterial efficacy in reactivation of latent TB and adult pulmonary TB. According to the literature, the efficacy rate of BCG vaccine in adults is ranged between 0% and 80%.[3,4] Given the important role of vaccination in prevention of the infectious disease, this phenomenon was emphasized in introducing and production of the safety and effective vaccine against TB.[5]

Identification of *M. tuberculosis* antigens and selecting the most appropriate delivery systems for identifying the antigens to stimulate the immune system cells to provide the exclusive response are among the most important prerequisites that should be considered in establishing vaccine candidates.[6,7]

Scientists have made several proposed synthetic vaccines such as recombinant BCG, attenuated mutants of *M. tuberculosis*, DNA vaccines, protein subunit vaccines, and multistage synthetic vaccine.[3,5,6] *M. tuberculosis* bacilli are facultative intracellular bacteria, which promote the cellular immunity, and TH_1 (CD8+) plays a key role in protective immunity for TB disease using the increased tumor necrosis factor alpha, interferon-gamma (IFN-γ), interleukin-2, and activation of macrophage cells.[7]

The multistage synthetic vaccine is one of the best candidate TB vaccines, which is usually associated with the effective immunity response, according to the studies; this vaccine is constructed from immunogenic secretory proteins that include early-stage secretory proteins such as early secretory antigenic target-6 (ESAT-6, *esxA* or Rv3875), culture filtrate protein-10 (CFP-10, *esxB* or Rv3874), and antigen 85 protein family (Ag85B) and secondary-stage secretory protein, such as the heat-shock protein X (*HspX*), which is combined with a peptide domain part for binding to immunity-related cell.[3,6,8] The peptide parts can be a part of immunoglobulin protein, which is attached to Fcγ receptors (FcγR) on antigen-presenting cells (APCs), macrophages, and dendritic cells (DCs); FcγR arbitrate is the specific uptake of antigens of immunity-related cells such as DC, transferring to the cytoplasm, and loaded onto major histocompatibility cells class I that is offered to cytotoxic T-lymphocytes and increases the production of IFN-γ cytokines, which are the active part of cell-mediated immunity for destroying the intracellular pathogens.[3,6,9] Based on the reviewing of the reports, multistage synthetic recombinant proteins such as fusion protein ESAT-6, CFP-10, HspX, and a constant part of immunoglobulin G can promote the effective promoted immunity response in animals and humans during animal-laboratory studies and clinical trials.[3-7,10-12]

The BCG vaccine is a viable attenuated strain of *M. bovis* BCG, which is not able to produce immunological memory cells in humans. Therefore, the researchers have studied for developing the human immune system against *M. tuberculosis* using highly immunodominant *M. tuberculosis*-secreted antigens such as ESAT-6 or Ag85b, which is coded by RD1 locus that is not present in *M. bovis* or *M. bovis* BCG strains. Extended studies on immune-promoting antigens of replicating phase of *M. tuberculosis* have led to introducing the Ag85B and ESAT-6 subunit vaccine, which has recently entered to Phase IIa of clinical trials. Moreover, reactivation of pulmonary TB was one of the important concerns and these subunit vaccines were not able to prevent the reactivation of latent TB. Thus, the suitable construction synthetic peptides should contain the early and latent *M. tuberculosis* antigens such as Mtb10.4-HspX, H56, or ID93, which have come in Phase I of clinical trials. However, the synthetic peptides were rejected from clinical trials due to reactivation of herpetic infection, interference, or dangerous side effects.[3,13]

Immune adjuvants are one of the crucial parts of effective vaccines; this compound was participating in effective antigen processing, introduction to APCs, and modifies the immune response to production of higher amount of antibodies, activation of TH_1 and macrophages to eliminate the dormant *M. tuberculosis* from alveolar macrophages. There are different types of adjuvants such as chitosan, alginate, gamma-polyglutamic acid, dextran, hyaluronic acid, trehalose dimycolate, monophosphoryl lipid A, and dimethyldioctadecylammonium bromide.[3,14]

Protein engineering in this study, including the unfolding or aggregation of multistage proteins, design, and selection of immune-promoting domains, selection of suitable vectors,

postmodification process of transcription and translation, transformation *in vitro*, selection of appropriate recipient cells, animal rights, and ethical limitation of laboratory animals, is costly and needs skilled technicians.[15]

In general, due to inefficacy of the immunity of BCG vaccine against adult TB, it is essential to establish studies for designing a new TB vaccine. Multistage synthetic peptides are one of the best options for developing the effective TB vaccine and the suitable booster for BCG vaccines. Whereas the presence of problems in designing, production and expression of this peptides, the modification and establishing of more studies about of synthetic-peptides can lead to production of an effective new generation of TB vaccine.

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Conflicts of interest

There are no conflicts of interest.

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