Vaccine against tuberculosis: a view

Tuberculosis (TB), a disease caused by Mycobacterium tuberculosis, continues to be a big health problem (WHO, 2013), particularly given the emergence of multidrug-resistant, extensively drug-resistant and totally drug-resistant strains of M. tuberculosis, which makes it more difficult to treat the infected individuals (Velayati et al., 2009; Falzon et al., 2011; Zignol et al., 2012). Moreover, the global epidemic of human immunodeficiency virus (HIV)/AIDS has added to the load of TB patients, further worsening the problem (Harries et al., 2010). According to a WHO report of 2013, TB afflicted about 8.6 million individuals and it caused death in more than 1.3 million cases in that year (WHO, 2013), indicating that it is a major scourge amongst infectious diseases. Chemotherapy of active TB saved the lives of many millions of patients, but extending it to chemoprophylaxis of latently infected subjects has not been implemented due to the excessive cost that would be involved. Hence, the availability of an effective vaccine could prove to be an affordable tool, with a major impact on the TB epidemic and thereby on the global elimination of the disease. Therefore, a search for the development of an effective vaccine has attracted a great deal of attention over the years. Thus far, Bacille Calmette–Guérin (BCG) remains the only licensed vaccine which has been used worldwide (Colditz et al., 1994; Zwerling et al., 2011). Its administration soon after birth can prevent severe forms of childhood TB. However, there is general agreement that BCG confers insufficient protection against TB in adolescents and adults. Currently, several candidate prophylactic vaccines have reached clinical trials (Kaufmann, 2013), but as yet, no new approved vaccine is available for immunoprophylactic use in the population. A major challenge for developing more efficacious vaccines against TB is the incomplete understanding of the mechanism of immunity and the mechanisms of immune evasion and subversion by M. tuberculosis.

Immunity in a host has two ‘subtypes’: innate immunity (natural immunity) and adaptive immunity (acquired immunity). On entry of M. tuberculosis into the host, the innate immunity recognizes the invading agent and tends to protect the host as a first line of defence. Subsequently, adaptive immunity is generated. Moreover, innate and adaptive immunities mutually shape and enrich each other (Yoshikai, 2006; Cooper, 2009; del Mar Casal & Casal, 2011). After exposure to M. tuberculosis, the majority (90–95 %) of the infected individuals do not develop symptomatic TB and normally remain with a latent TB infection (LTBI), indicating that such infected persons either develop or have protective immunity. On the other hand, about 5–10 % of the infected people develop symptomatic disease (Jereb, et al., 2003; Andrews et al., 2012) and primarily vaccination is required for this group of individuals. Conventionally, it is acknowledged that cell-mediated immunity (CMI) involving IFN-γ-producing CD4+ T-helper lymphocytes (Th1) plays a predominant role in protecting the host against M. tuberculosis infection (Yoshikai, 2006; Cooper, 2009; del Mar Casal & Casal, 2011). Further, it is known that antigen processing and presentation are carried out by antigen presenting cells ([APCs], primarily monocytes/macrophages and dendritic cells] to stimulate naïve CD4+ T-cells. The stimulated naïve T-cells can then be polarized by APCs (through the secretion of cytokines such as IL-12) to become Th1 cells which are involved in generation of CMI (Trombetta & Mellman, 2005; Jensen, 2007). Briefly, after confronting a pathogen, the APCs ingest the pathogen and cause proteolytic degradation of the pathogen-derived protein antigens. The resulting antigenic peptide fragments bind to the major histocompatibility complex (MHC)-II molecules and thereafter are presented to naïve CD4+ T-cells for their stimulation. Subsequently, the stimulated T-cells lead to activation and polarization towards Th1 cells which further progress towards proliferation and production of a series of cytokines, including tumour necrosis factor-α and IFN-γ. Both of these cytokines reinforce the antimicrobial activity of monocytes/macrophages and dendritic cells (Yoshikai, 2006; Cooper, 2009; del Mar Casal & Casal, 2011).

With a successful vaccine, the induced protective immune response results in the generation of long-lasting memory cells that circulate through tissues and lymphoid organs via the thoracic duct and blood. The memory cells thus produced are involved in immune surveillance for the invading pathogens. On subsequent infection with the pathogen, the memory cells are stimulated quickly and strongly by the pathogen due to the presence of antigens shared between both the vaccine and the pathogen. This quick and stronger secondary immune response is considered to be protective if the disease-causing agent is destroyed (Lanzavecchia & Sallusto, 2005) and thereby prevents the occurrence of symptoms and disease in the vaccinated immune host. In principle, following immunization with candidate anti-TB vaccines (Kaufmann et al., 2010; Kaufmann, 2013), Th1 memory cells against antigens shared between candidate vaccines and M. tuberculosis are supposed to be generated. However, on subsequent infection with M. tuberculosis, the relevant mycobacterial antigens need to be processed and presented by APCs to Th1 memory cells for their stimulation and subsequent proliferation. On successful presentation of antigen, stimulation of memory cells may lead to generation of a protective secondary immune response against invading M. tuberculosis. However, M. tuberculosis is known to have evolved diverse strategies to evade and subvert the anti-mycobacterial, antigen processing and antigen presenting activities of APCs (Wolf et al., 2007; Scherr et al., 2009; Gupta et al., 2012; Tung et al., 2013). Thus, due to
eventual perturbation in antigen presentation, the shared mycobacterial antigens present in *M. tuberculosis* may fail to stimulate vaccine-induced memory Th1 cells for generation of a secondary immune response. Such an occurrence raises intriguing questions as to the efficacy of an anti-TB vaccine working through Th1 cells.

Keeping in view the aforementioned information regarding interaction between the host and *M. tuberculosis*, it is hypothesized that despite generating Th1 memory cells against shared *M. tuberculosis* antigens, the novel candidate vaccines against TB (Kaufmann *et al.*, 2010; Kaufmann, 2013) may still not protect the host prone to develop TB. Due to the evasive and subversive behaviour of *M. tuberculosis*, the APCs may fail to present *M. tuberculosis*-derived antigens (on subsequent infection after vaccination) to trigger the Th1 memory cells to generate a powerful secondary cell-mediated immune response to protect the host. Thus, the *M. tuberculosis* bacilli may still grow elusively in the host causing active disease. Alternatively, it is possible that in individuals prone to having TB, (i) the effector T-cells may fail to produce relevant types or adequate amounts of cytokines after triggering of the memory cells by invading *M. tuberculosis*, or that (ii) despite abundant amounts of T-cell-derived macrophage-stimulating cytokines, the infected macrophages may not be capable of killing the intracellular *M. tuberculosis* organisms.

In conclusion, it is argued that despite inducing potent Th1 memory, anti-TB vaccines may not be protective against TB. This view is supported by the known inconsistent efficacy of BCG vaccination (Andersen & Doherty, 2005), the uncertainties regarding candidate vaccines (Kaufmann *et al.*, 2010; Kaufmann, 2013) and the recent failure of a phase 2b TB vaccine trial in infants (Tameris *et al.*, 2013). In all the foregoing approaches, generation of Th1-mediated protective immunity was the major aim to make the vaccines effective. What could be the remedy when Th1-mediated immunity fails? Probably, the answer may be sought by exploring alternative approaches, involving CD8+ T-cells, natural killer T-cells and γδ T-cells (Yoshikai, 2006; Barnes *et al.*, 2009; Cooper, 2009) for generation of protective immunity by candidate vaccines. The reasons supporting this suggestion are that: (i) these cells are understood to contribute towards protection against *M. tuberculosis*; also, (ii) these cells do not require antigen presentation in association with MHC-II molecules. However, these still rely on antigen presentation in association with MHC-I or CD1, which could also be affected by *M. tuberculosis* (Baena & Porcelli, 2009). Regarding antibodies, there are several pieces of evidence indicating their contribution towards protection against TB (Ackhar & Casadevall, 2013). However, their role in protecting against TB is controversial, as yet. Nevertheless, with vaccination, antibodies can be generated prior to infection, and for production of antibodies, processing and presentation of *M. tuberculosis* antigens are not required. Moreover, there is evidence that antibodies can affect downstream processing and presentation of antigens for generation of CMI. Therefore, the humoral response may help in preventing infection and is worth considering for developing an anti-TB vaccine. Thus, a combined approach, involving multiple antigens targeting multiple cells, deserves attention for further research for developing an anti-TB vaccine. Probably, such a formulation may lead to a better alternative anti-TB vaccine by providing a greater ability for the host to recognize a wider range of *M. tuberculosis* antigens.

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