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Review

Tuberculosis vaccines: Time to think about the next generation

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ABSTRACT

Efforts over the last 2 decades have led to a rich research and development pipeline of tuberculosis (TB) vaccines. Although none of the candidates has successfully completed the clinical trial pipeline, many are under advanced clinical assessment. These vaccines aim at prevention of active TB, with most of them being considered for preexposure with recent additions for postexposure or multistage administration. A few therapeutic vaccines are under clinical assessment, as well. Preexposure vaccination with the licensed TB vaccine BCG prevents severe forms of TB in children but not in adolescents and adults. The current vaccine pipeline does not include strategies which prevent or eliminate infection with the causative agent *Mycobacterium tuberculosis* (*Mtb*). Rather in a best-case scenario, they are quantitatively superior to BCG in preventing active TB over prolonged periods of time, ideally lifelong in the face of latent *Mtb* infection. Qualitatively superior vaccines should be capable of preventing or eliminating *Mtb* infection, in this way eliminating the risk of TB reactivation. The time is now ripe to exploit radically new strategies to achieve this goal.

1. The disease and the pathogen

Tuberculosis (TB) currently afflicts some 9 million individuals resulting in the death of 1.5 million cases annually [1]. TB thus remains a major scourge amongst all infectious diseases [2,3]. It is caused by the acid-fast bacillus *Mycobacterium tuberculosis* (*Mtb*), an intracellular pathogen, which has developed numerous mechanisms to avoid killing by professional phagocytes, notably, mononuclear phagocytes (MPs) [4,5]. These evasion mechanisms include arrest of phagosome maturation at an early stage [5,6]. The early phagosome provides a niche for the pathogen where it can persist for long periods of time. Activation of MPs increases their antibacterial defense armamentarium thereby reducing the chances for active *Mtb* to persist. The TB bacillus enters the host in a metabolically and replicatively active stage (in short: active stage) [7–10]. To elude immune defense, it transits into a stage of dormancy. The genetic programs in active versus dormant stage differ profoundly [11,12]. Active *Mtb* expresses genetic programs of replication and high metabolic activity. This includes the expression of virulence factors which allow *Mtb* to invade the host, to inactivate or subvert host defense mechanisms and to damage host tissue [7–10]. During its dormant stage, *Mtb* is virtually devoid of genetic programs of metabolism, replication and virulence [11,12]. Dormant *Mtb* express reduced virulence and host-cell damaging activity but at the same time they are a difficult target for immune defense and hence are normally not eliminated. Rather dormant *Mtb* persist in infected healthy individuals, leading to latent *Mtb*-infection (LTBI) [7–10,13]. Once the immune pressure is debilitated, *Mtb* can be resuscitated and return to a stage of metabolic and replicative activity. This is the dominant stage of *Mtb* during active TB disease, transmission and entry into a new host. It is likely that the two populations coexist in TB patients: the small population of dormant *Mtb* represent a clandestine base of persistence that can be resuscitated at later stages once the major population of active *Mtb* have been eliminated by drug therapy. As a corollary, the course of disease and time needed for drug treatment are prolonged [7,8,10]. Reciprocally, in healthy individuals with LTBI a few dormant *Mtb* are resuscitated [9,13,14] and exist in an active stage, as evidenced by the success of preventive, long-term therapy with drugs that only act on metabolic and replicative, but not on dormant, *Mtb* [15,16].

Transition from an active to dormant stage is also reflected in alterations of the expressed antigen profile [9]. Antigens expressed by dormant *Mtb* are termed dormancy antigens [7,9,10]. In a

Abbreviations: Ad35, adenovirus 35; AS, adjuvant system; Ag85A, antigen 85A; BCG, bacille Calmette–Guérin; DTH, delayed-type hypersensitivity; DCs, dendritic cells; GLA, glucopyranosyl lipid A; IFN-γ, interferon-gamma; IGRA, IFN-γ release assays; IL, interleukin; LTBI, latent *Mtb*-infection; hly, listeriolysin; MHC, major histocompatibility complex; MPs, mononuclear phagocytes; MAITs, mucosal-associated invariant T cells; MIP, *Mycobacterium indicus pranii*; *Mtb*, *Mycobacterium tuberculosis*; NK, natural killer; Pfo, perfringolysin; PEST, proline (P), glutamic acid (E), serine (S) and threonine (T); Treg cells, regulatory T cells; TLR, toll-like receptor; TDB, trehalose 6,6′-dibehenate; TB, tuberculosis; TST, tuberculin skin test; TNF, tumor necrosis factor; Th1, type 1 helper; UreC, urease C.

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broader sense, this term is also used for antigens expressed by *Mtb* stressed under nutrient deprivation and effective immune control [9,11]. Current vaccine candidates comprise antigens expressed by active *Mtb* and only recently vaccines, comprising both types of antigens, have been considered [17–21].

2. Immunity, protection and pathology

Because of the intracellular lifestyle of *Mtb*, immunity critically depends on T lymphocytes [4,22]. Following aerosol infection with *Mtb*, alveolar macrophages and interstitial dendritic cells (DCs) engulf the pathogen and transport it to draining lymph nodes [23]. Some *Mtb* also reach the lung parenchyma where they start replicating. In draining lymph nodes, T lymphocytes are specifically stimulated by DCs which present *Mtb* antigens [22–24]. During recirculation, *Mtb*-specific T cells interact with *Mtb*-infected MPs in the lung. Here, they attract and activate additional monocytes and T cells to form a solid granuloma where the pathogen is contained (Fig. 1).

A variety of T-cell populations participate in immunity against TB [4,25]. Of critical importance are the CD4 T cells which produce type 1 cytokines, notably interferon-gamma (IFN-γ), and tumor necrosis factor (TNF). These type 1 helper T cells (Th1 cells) activate effector functions in MPs that control intracellular *Mtb*. Hence, they are critical for protective immunity in TB. In addition, Th17 cells are stimulated which produce interleukin (IL)-17, which primarily attracts and activates neutrophils [26]. It is likely that Th17 cells pave the way for entry of monocytes and Th1 lymphocytes to the site of granuloma formation and hence, contribute to protection against TB at early stages [26,27]. Unrestricted Th17 stimulation, however, causes damage due to exaggerated inflammation evoked by neutrophils and inflammatory monocytes [28–31]. Evidence has been presented that Th2 cells, which produce IL-4 and IL-5, can be stimulated during the course of *Mtb* infection, as well [32]. These cytokines stimulate B lymphocytes to mature into antibody-producing plasma cells [33,34]. Moreover, the Th2 cells primarily participate in control of helminth infections [33,34]. Since Th2 cells counter-regulate Th1 cells, they likely impair protective immunity against TB [33,34].

The CD4 T cells are stimulated by antigenic peptides in the context of gene products of the major histocompatibility complex (MHC) class II, which are derived from the phagosomal compartment [24]. The preferential residence of *Mtb* in the phagosome favors MHC class II processing, although *Mtb* has developed means to impair this pathway [35,36].

CD8 T lymphocytes have been consistently demonstrated in TB [4]. They produce cytolytic molecules, notably, perforins, granulysins and granzymes, which do not only lyse host cells but also kill *Mtb* directly [37]. Thus, CD8 T lymphocytes likely contribute to control of *Mtb* by several means. CD8 T lymphocytes recognize antigenic peptides in the context of MHC class I, which are generally loaded in the cytosolic compartment [24]. MHC class I loading can occur as a result of egression of *Mtb* into the cytosol or leakage of *Mtb* proteins from the phagosome into the cytosol [38]. Moreover, apoptosis of infected MPs and DCs leads to the formation of apoptotic vesicles, which can be engulfed by DCs in the vicinity [39,40].

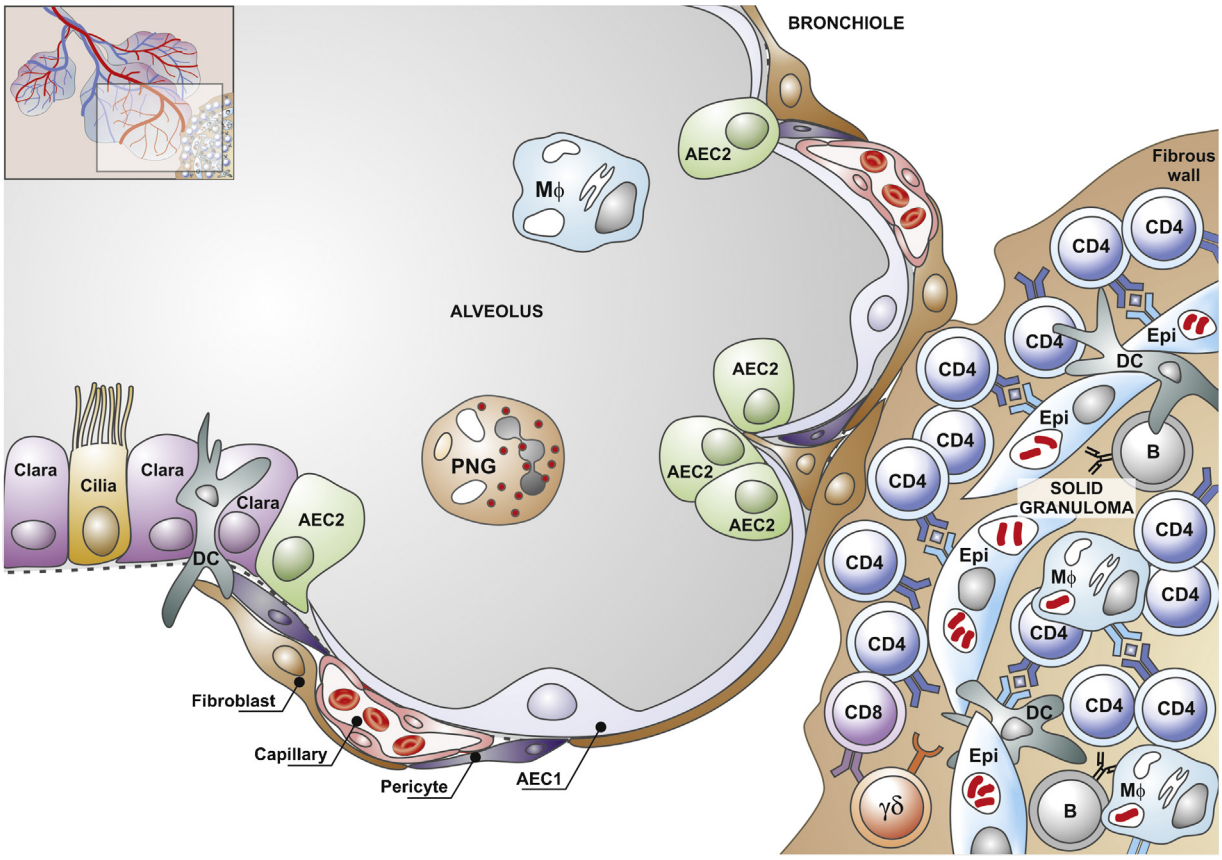

Fig. 1. Containment of *M. tuberculosis* (*Mtb*) in solid granuloma. Latent *Mtb* infection in healthy individuals is characterized by solid granulomas which contain *Mtb*. The figure depicts an alveolus adjacent to a solid granuloma. *Mtb* (red rods) are contained in epithelioid cells and macrophages within the granuloma. The outer layer comprising different subsets of T lymphocytes is surrounded by a fibrous wall. Inside the granuloma, T lymphocytes interact with macrophages and dendritic cells (DCs) to achieve long-lasting containment of *Mtb*. Abbreviations: AEC1, alveolar epithelial cell type 1; AEC2, alveolar epithelial cell type 2; B, B cell; CD, cluster of differentiation; CD4, CD 4 T cell; CD8, CD 8 T cell; DC, dendritic T cell; EPI, epithelial cell; gamma delta, γδ T cell; MΦ, macrophage; PNG, polymorphonuclear neutrophilic granulocyte.

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