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REVIEW ARTICLE

Routing Innate and Adaptive Immune response against *M. tuberculosis* and boosting *Mycobacterium bovis Bacillus* Calmette Güerin (BCG) vaccine immunity through prime boost protocols

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ABSTRACT

Tuberculosis (Tb) is still a global health problem, especially in developing countries. Several factors contribute to this, among them the increasing multidrug resistance strains, the dangerous liaisons with other intracellular pathogens, such as HIV, and more recently, SARS-CoV2 pandemics. There are many aspects that remain to understand the bacterial molecular mechanism of pathogenicity and the immune response induced by the interaction of M. tuberculosis (*MTb*) with the host. The official and current vaccine based on the attenuated *Mycobacterium bovis Bacillus Calmette Guerin* (BCG) is protective against several forms of Tb meningitis and Miliary TB or disseminated disease in young children. However, it fails to protect young and adult individuals. There are several new promising candidates for vaccines to replace or boost BCG-induced immunity. Several evidences exist from humans and mice on the role of the trained innate memory of monocytes and NK cells, on the second encounter with the same mycobacterial pathogen or other respiratory pathogens. This type of immune response is nonspecific and independent of the T and B cells. Thus, BCG vaccination is a double immunogen that activate specific immune responses and is also able to stimulate nonspecific immune responses. Here, it is outlined the host immunity against *MTb*, the potential of BCG vaccination and prime boost protocols for routing innate and adaptive immune responses in TB.

Keywords: *M. tuberculosis*; prime boost protocols; BCG based vaccine

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1. Introduction

Tuberculosis (TB) caused by the intracellular Gram-positive bacteria *Mycobacterium tuberculosis* (*MTb*) is a chronic infectious disease. TB remains a threat and a global health problem because the last year were reported around 11 million new active Tb individuals[1,2]. Most infected individuals will remain asymptomatic, commonly known as latent infection, representing a large reservoir (95%) of pathogenic *Mtb*[3,4]. While only 5% of these latent infected individuals will develop active TB. Moreover, the problem is worsened by the upraising multidrug resistance strains (MDR) and by COVID-19 pandemics, especially in low-income countries[1,2,5]. The only prophylactic treatment against TB is the attenuated *Mycobacterium bovis Bacillus Calmette Güerin* (BCG) vaccine, which protects against Miliary TB, disseminated (TB) associated with meningitis in children. However, it fails to protect young and adult people[6–9].

Intense efforts have been made for the implementation of novel subunits vaccines that can boost BCG-induced immunity, especially

the long-lasting immunological memory, or even can replace it (recombinant BCG or attenuated *Mycobacterium tuberculosis* (TB-VAC)[10–16]. Furthermore, several studies have reported that there is a lack of correlation between CD4+ T cells IFN-γ producers and the protective immunity induced by the BCG, which strongly indicates that there is a missing link in the knowledge and understanding between *Mtb* and the host immune system[17–19].

Upon interaction of *Mtb* with the host, mechanisms of the innate and adaptive immune response are activated in a manner that allows the coexistence of the bacilli and the human host (latent infection)[20–24]. These individuals that remain asymptomatic and vaccinated can also control the bacilli growth by another innate mechanisms, such as autophagy, oxygen/nitrogen reactive species, and apoptosis[25–35].

The interplay of the innate and adaptive immune response represented by APCs, and in particular, the macrophages and the T cellular immune response, is pivotal in the establishment of the *MTb* infection[18,36–38]. Early infection by *Mtb* leads to active and/or latent stages[39,40]. At level of the cellular function of the host immune system, the initial natural crosstalk between *Mtb* and its host involves two principal events: 1) Phagocytosis of *MTb* by antigen presenting cells (APCs, macrophages and dendritic cells)[23,24], resulting in the secretion of selected cytokines that allow clearance, and elimination of *Mtb*[41]; 2) IFN-gamma (IFN-γ), and TNF-alpha(α) induction play a role in *Mtb* mycobacterial growth regulation, granuloma formation, and therefore, connection with adaptive immunity[42–45].

In addition, granuloma formation allows *MTb* survival, and the individuals develop chronic, latent infection. Interestingly, it seems that latent *Mtb* can be intracellular located in diverse kind of cells in tissues with apparent normal histology, in the lungs and other organs[36,39,43,46–48]. The reactivation of *Mtb* infection depends on several factors[49,50]; among them is the host immunocompetence, and immunotherapies (inhibitors of TNF-α) interleukin (IL)-17 and interleukin (IL)-23[51]. In immunocompromised individuals, the reactivation phase is characterized by increased bacterial growth and symptoms of TB[39,40,52]. Whereas in latent infection, the host defense mechanism control *M. tb* infection. A key point is the granuloma formation because it represents the preferred cellular niche of *MTb* for the dormancy stage. It is in this stage of infection that exists an interplay of *Mtb* with the innate and cellular host immunity[39,40]. The knowledge, the elucidation of the mechanism of host-pathogen interaction are involved in the definition of the development and design of vaccines and therapeutic interventions[18,48,53–60] (**Figure 1A**).

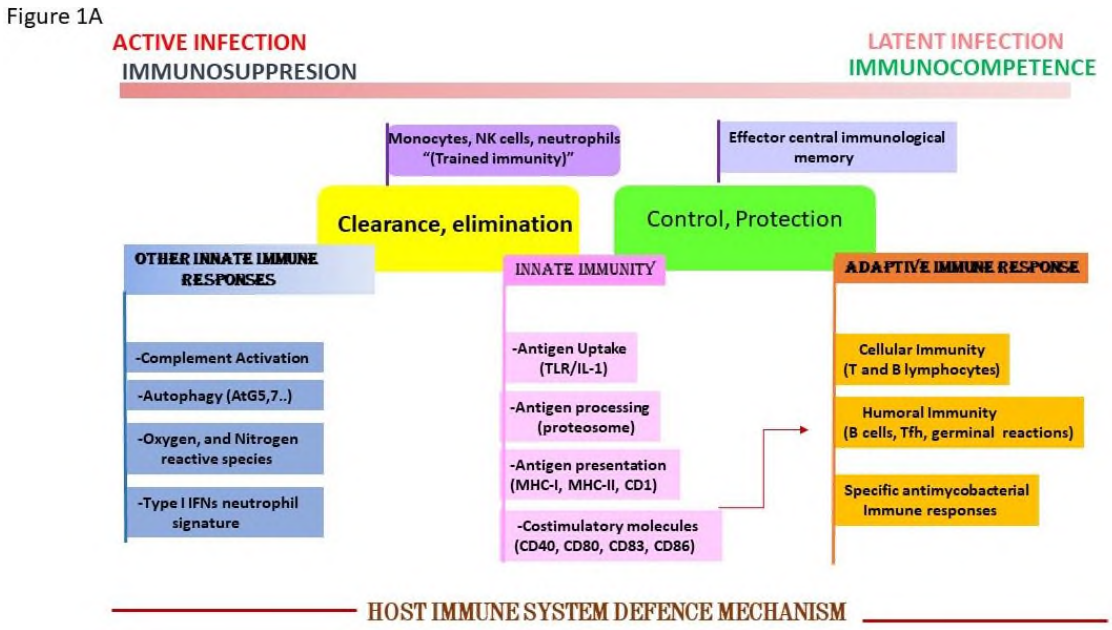

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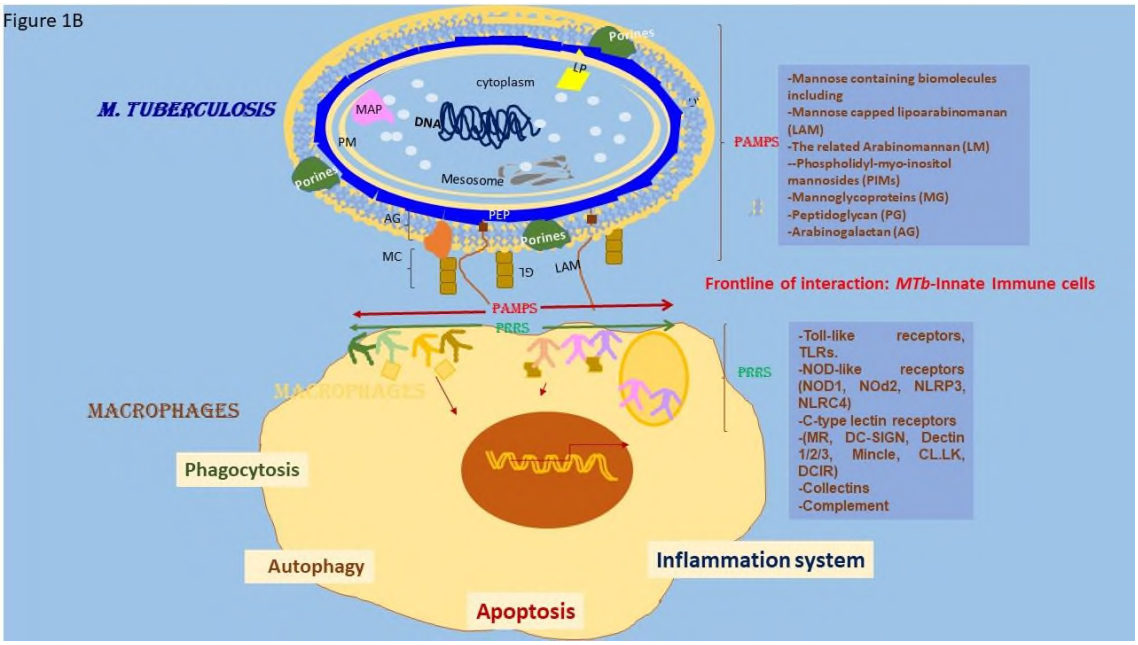
Figure 1. (*Continued*).



(B)

Figure 1. (A) Upon infection with *Mtb*, there are two fates, an individual develops active infection (red) or latent infection (less red), depending on the immunocompetence of the individual. For the clearance and elimination of pathogen (active), innate and no innate mechanisms are activated and are pivotal. In latent infection, the cellular immune response interplay and crosstalk with the innate cells are pivotal. Indeed, this interplay between the immune system and *Mtb*, it has been proposed is part of the coevolution of *Mtb* and humans, dated thousand years ago[61]. Because of this, the eradication of *Mtb i*s a challenge. **(B)** *M. tuberculosis* with the host innate immune cells. The different molecular components of *MTb* (immunodominant antigens of the cell wall as LAM, or mycolic acids, efflux pumps, and or secretion systems) and the innate cells (macrophages, dendritic and epithelial cells) that interact at the front line of local and mucosal sites, leads to activation of several cellular functional outcomes of the host defense like autophagy, reactive oxygen production, phagocytosis, inflammasome activation, activation of NF-kβ (pro-inflammatory cytokines)[62].

M. tuberculosis chemical and structural composition

Mtb is a non-sporulating Gram-positive bacillus, slow-growing intracellular pathogen. Structurally, *MTb* distinguishes by the remarkable composition of its cell wall, which constitutes approximately 60% of the dry weight[63–65]. The *MTb* cell wall is a thick layer of hydrophobic mycolic acids that allow the entry of nutrients[65]. Mycolic acids are distributed as a thick layer at the external portion of the cell wall, while the internal layers of mycobacteria consist of arabinogalactan, phosphatidyl-myo-inositol mannosidase (PIMs), and peptidoglycans[63,64]. Next to the mycolic acid layer, other components include mannose-containing biomolecules, including mannose-capped lipoarabinomannan (Man-LAM), the related lipomannan (LM), and mannoglycoproteins[66]. Mannan and arabinomannan are on the surface forming the outer capsule. Man-LAM, LM, and PIMs, all share a conserved mannosyl-phostidyl-myo-inositol (MPI) domain that presumably anchors the structures into the plasma membrane[67]. Lipids and carbohydrates play crucial roles in *MTb* survival and infection[68], followed by the layer of Peptidoglycan (PG), Arabinogalactan (AG), Trehalose-5-5'-dymicolate (TDM), Mycolic acid (MA) and Muramyl dipeptide (MDP)[65,67] (**Figure 1B**).

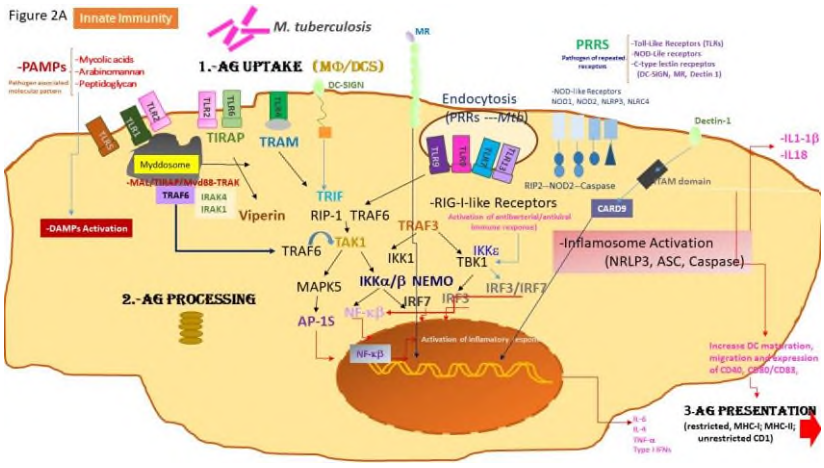
Regarding to Man-LAM[64], it is considered a virulence factor that is on the cell wall surface. LAM is a heterogenous lipoglycan with a characteristic tripartite structure of a carbohydrate core, the MPI anchor and various mannose-capping motifs, characteristic of all pathogenic mycobacteria. In addition, the phosphatidyl-myo-inositol mannosides (PIMs) are divided into two groups dependent on the mannose content, which determines its immunogenic effect[66,68,69]. Also present on the cell surface are the main glycoproteins secreted during growth[63,65] (**Figure 1B**). The components of the *Mtb* cell wall account for interaction with innate cells[38,49,51,69,70]. Thus, for example, the efflux pump system of *Mtb*—another mechanism of the *MTb* immune escape[71–73] is carried out by transporters located on the plasma membrane[72]. Moreover, in the outer layer, the arabinan chain is formed by highly branched AG, and the nonreducing end of the glycan chain is connected to

the mycolic acid (MA)[63,64]. In another hand, the cell membrane has functions in cell growth, communication, and stimulation of the host's immune response[66,68,69].

2. Molecular interaction of *M. tuberculosis* with the innate immune cells

The successful molecular interaction of *MTb* with the host innate immune cells (APCs) results in connection with the adaptive immune system[50,74–77]. Tb is a chronic disease that requires the constant expression of cellular immunity to limit bacterial growth. This results in chronic inflammation which requires regulation. Indeed, inflammatory cytokine systems, as immunomarkers of antimycobacterial protective immunity are potential candidates in vaccine design[48,58,59,61,78–80].

As a complex mixture of antigens, *Mtb*s can induce immune responses in the host[79–81]. It starts with the initial crosstalk and recognition of bacterial molecules expressed on the surface of APCs (macrophages, dendritic cells, epithelial cells) located in the upper airways[40,82,83]. Different PAMPs (pathogens-associated molecular patterns) of *MTb* are recognized in the bacillus cell wall, such as the peptidoglycan, mycolic acids, and arabinogalactan[40,81,84–86]. Diverse PRRS (pattern of recognition receptors) on the APCs surface like Toll-like receptors (TLR2/TLR4, TLR5), C-type lectin-like receptors (Dectin 1, DC-SIGN, MR), RIG-like receptors[83,87–90], and the cytoplasmic receptors TLRS (TLR3, TLR7, TLR9) and NOD-like receptors (NOD1, NOD2, NLRP3, NLRS4). For example, lipopolysaccharide (LPD) and lipoarabinomannan (LAM) in the cell wall of *MTb* are recognized by TLR2/TLR1 or TLR2/TLR6 heterodimers expressed on the membrane of host immune cells, which in turn activate the expression of NF-kβ and cytokines that can further leading to host cell injury[70]. *Mtb* can also interact with other cytosolic PRRS like the Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRS), NOD1. NOD2[91–93], or with the Dectin, Mannose lectin-like receptors (MCS), DC-SIGN (DC-specific intercellular adhesion molecule-3-grabbing nonintegrin)[84,94–101] (**Figure 2A**). The initial molecular signalization through these receptors is to transmit downstream to TIRAP, TRAM, or TRIF[102], Myddosome (formed by Myd88, IRRK1, IRK4), and then activate TRAF6, TAK1, and to MAPK, IKKα/β, NEMO for AP-1S, NF-kβ translocation, resulting in the expression of several genes encoding the inflammatory response mediated IL-6, IL1-β, TNFα, IL4, and chemokines[103–105]. These products attract and recruit immune cells to the site of infection, thus, controlling *MTb* infection[62,93,100,106,107] (**Figure 2A**). Other events that occur is that infected APCs can remain for two weeks, keeping an inflammatory state for clearance and elimination of the pathogens by the production of reactive O2 species and activation of the autophagy system, as well as activation of the proteosome for antigen processing[35,47,60,74,75,77,108–118]. Moreover, maturation, migration of APC, and the expression of the costimulatory molecules are events favored by the initial and successful TLRs signalization pathways and translocation of the NF-κβ.



(A)

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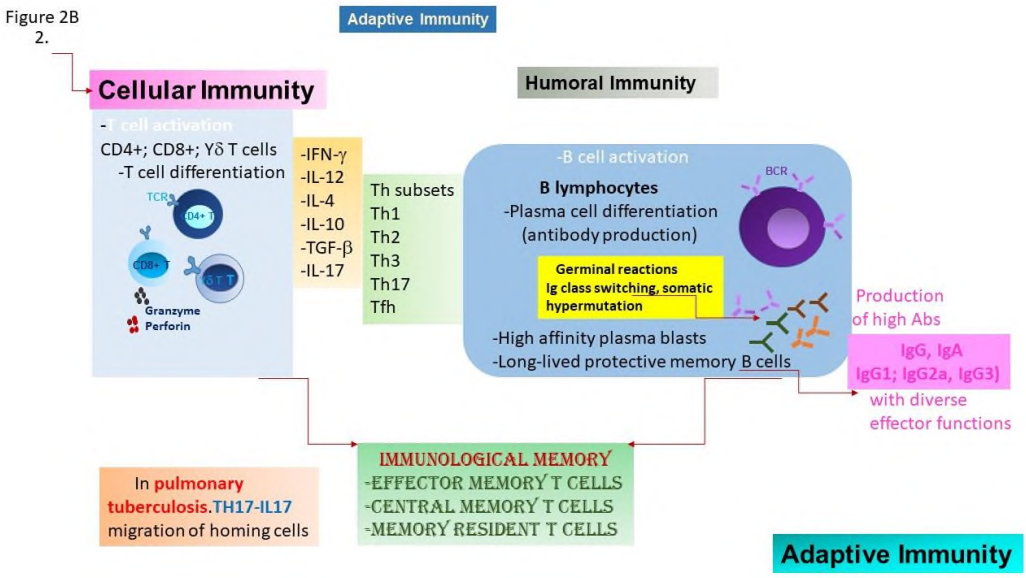

(B)

Figure 2. The induction of the innate **(A)** and adaptive **(B)** immune response by *M. tuberculosis*. For the induction of the innate primary immune response to MTb, an initial recognition and molecular interaction between PAMPs, (pathogens-associated molecular patterns (PAMPS), and the PRRS (pattern of recognition receptors) on host innate cells. It leads to the downstream signalization of different adaptors molecules, and ending with the activation of three main pathways, NF-kβ, MAPK5 and the PIBk/Akt pathways. The translocation of NF-kβ lead to cytokines, chemokines, and expression of costimulatory molecules. This allow the maturation of antigen-presenting cells (APCs) (dendritic cells, macrophages), resulting in further antigen presentation through MHC restricted or unrestricted through CD1, CD1, CD1b, or CD1c cells (CD1 family of glycoproteins are MHC class I-like molecules that present a wide array of self and foreign lipid antigens to T-cell receptors (TCRs) on T-cells)[119,120], connecting, thus with the adaptive immune response. The main actors of this type of cellular immune response are B and T cells are activated and differentiate into more specialized cellular and effector functions. T lymphocytes become helpers of the B cell differentiation for antibody production. Naïve T cells differentiate into different subsets with effector functions such as TH1, TH2, Th3, and TH17 that can exert a protective immune response against *Mtb*.

2.1. *M. tuberculosis* induced adaptive immunity

It is well known and accepted from several studies about preclinical models and clinical studies, that the principal defense against *Mtb* is IFN-γ production from the CD4(+) T cells restricted by MHC-II complex during early infection; while at chronic or late time point CD8(+) T cells restricted by the histocompatibility complex MHC type 1 (MHC-1), producers of granzyme and perforin play a significant role[8,21,22,39]. IFN-γ-producing CD4+ T helper cells (Th1) are required for control of bacterial growth, initiating and maintaining a mononuclear inflammatory response[36,39,43–45,47], other T cell subsets induced by *Mtb* infection play a role in the early stages *Mtb* infection in animal models[26,43,121]. The protective capacities of both types of lymphocyte populations occur through different mechanisms by IFN-γ and TNF-α production, potent activators of macrophages[121]. Furthermore, other innate immune cells such as gamma-delta (γδ) T cells, NK cells, and neutrophils participate actively restricting *MTb* growth. At this point, it is noteworthy to mention that IL-22 produced by NK cells in humans and CD4+ T cells in macaques could limit the growth of *Mtb* in macrophages by enhancing the phagolysosomal fusion and autophagy[47,113,114,116,117,122–125]. Another molecule involved in this process is melatonin (*m3*+ gene), a protein that binds Zinc and whose upregulation could indicate macrophage activation by IFN-γ[126,127]. Besides, interleukin 13 (IL-13), a Th2-type cytokine that inhibits autophagy[26,44,47], can also function to recruit T cell antigen-specific during vaccination to the lumen of the upper airways after *Mtb* challenge[42,45]. Interestingly, the unconventional route by which the pathogens can activate the adaptive immune response, as described recently by Ernst[61] is through an alternative donor un-restricted T cell population, a population of unconventional T cells (mucosal-associated invariant T cells (MAITs), and by gamma- delta (γδ) T cells with TCRc that interact with a set of non-polymorphic antigens such as lipids, including the mycobacterial lipids antigens presented by CD1, CD1b, or CD1c cells[119,120,128–130] (**Figure 2B**). In addition, in vitro and in vivo studies have shown that for the establishment of *MTb* in its

niche (lung granuloma, macrophages), the interplay of the host immune cellular responses is pivotal[28,42-44,45,52] (**Figure 2B**). The polyfunctional activities of CD4(+), CD8(+) T cells, the NKT cells, and γδ T cell, and the cytokines produced, either for maintaining the activated state of macrophages (TNF-a, IL6, IL1β)[131–133] (**Figure 2B**) or for the effector and protective functions as IFN-γ, IL17, IL2p70; IL-23, IL22[28,42–44,45,52] (**Figure 2B**).

The protective role of the TH17 and IL-17 against *MTb* infection

Tb is a chronic disease that require the constant expression of cellular immunity to limit bacterial growth, resulting in chronic inflammation, which requires regulation. IFN-γ-producing CD4+ T helper cells (Th1) control bacterial growth and initiate and maintain a mononuclear inflammatory response. Other T cell subsets induced by *Mtb* infection include subsets that produce IL-17 (TH17)[134].

IL-17 is a potent inflammatory cytokine capable of inducing chemokine expression and recruitment of cells to parenchymal tissue. Indeed, IL-17 is a cytokine produced by T cells in response to IL-23 that may contribute to inflammation[135,136].

In mice, it has been shown that IL-17-producing cells play a role in the early stages of *Mtb* infection[131–133,138–140]. In several experimental settings in preclinical models it has been found that IL17 is produced and correlates with reduced CFUs in lung and in spleen[141]. In naïve mice, as well as during *Mtb* infection, IL-17 production is primarily from gamma delta T cells and other non-CD4(+) CD8 (+) rather than CD4 T cells, which represent a central innate protective response to pulmonary infection[131–133]. Furthermore, signaling via Toll-like receptor (TLR) 2 has an impact on the regulation of p19 (IL-23) expression in response to *Mtb* and on the establishment of TH17 cell response[132,139,142]. IL-17 and IL-22 can induce CXCL13 in mouse primary lung fibroblasts, suggesting that these cytokines are likely involved in B cell follicle formation[143]. The absence of IL-23 expression compromises the long-term immunity to Tb due to reducing expression of CXCL13 in B cell follicles and the reduced ability of T cells to migrate from the vessels and into the lesion. The recall response of the IL-17 producing CD4 (+) T cells population occurred concurrently with expression of the chemokines CXCL19, CXCL10 and CXCL11[143]. Furthermore, TH1 and TH17 responses cross-regulate each other during mycobacterial infection. Tthe absence of memory TH17 cells upon *Mtb* infection results in loss of both the accelerated TH1 response and protection. This may be important for immunopathogenesis consequences not only for TB but also for other mycobacterial infections[138,143–145]. Both IL-17 and TH17 responses to *Mtb* are dependent upon Interleukin (IL-23). Indeed, IL-23 was essential for the accelerated response for early cessation of bacterial growth and establishment of an IL-17-producing CD4(+) T cell population in the lung of mice[136,144,145] (**Figure 2B**).Of note is that IL-1β and IL-6 are crucial for the *MT*b H37Rv induced expansion of IL-17 interferon (IFN)-γ and IL-17 in CD4(+) T cells, and from MDR-Tb and PPD. It seems that the genetic background of the infecting *Mtb* strain on the ex vivo TH17 response influences the IL17 response[138,142,146]. Interestingly, Toll-like receptor (TLR)-2- signaling mediates the expansion of Il-17-IFN-γ cells and the enhancement of latency-associated protein (LAP) expression in CD14 and CD4(+) T cells from MDR-TB, which suggest that the MDR strain promotes IL-17 IFN-γ T cells through a strong TLR-2 dependent TGF-β production by APCs and CD4(+) T cells[145]. Interestingly, in *Mtb* infected mice, measurement of IL17, IL17ra, IL22 and IL23a were not significantly modified as compared to controls. Moreover, neutralization of IL-17A or IL-17F did not affect infection control either. Ongoing clinical studies with IL-17 neutralizing antibodies show high efficacy in patients with psoriasis without increased incidence of TB infection or reactivation. Therefore, both experimental studies in mice and clinical trials in human patients suggest no risk of TB infection or reactivation by therapeutic IL-17 antibodies, unlike by TNF-α. it is also important to consider that repeated BCG vaccination in mice is linked to the production of an intense inflammatory response associated to tissue damage in particular necrosis, principally due to the recruitment, activation and migration of neutrophils[147].

In humans, recent studies have provided insight into the role of IL-17 and IL-17-producing cells at three stages of the *Mtb* infection spectrum (latently TB infected; reactivated, and active). For example, *Mtb*-stimulated CD4(+) T cells from Tb patients secreted lesser IL-17 than did CD4(+) T cells from healthy tuberculin reactors (PPD(+). It has been reported that IL-17 play a key role in host defense against M. tuberculosis. However, it is also known the immunopathogenic role of this cytokine not in Tb but in other autoimmune disease. An example of this, el ongoing clinical studies with IL-17 neutralizing antibodies show high efficacy in patients with psoriasis without increased incidence of TB infection or reactivation. Overall. These results that no risk of TB reactivation by therapeutic treatment of IL-17 as reported by Sequeni et al.[148]. In addition, it has been investigated the role of the IL-17 driven tissue damage in the human lung by IL-17. Biopsies of Tb patients, and cytokine determination in patient bronchoalveolar lavage fluid (BALF) measured by Luminex assays. Other measurements were also analyzed. The results shown that IL-17 drives airway stromal cell-derived MMP-3, which mediates tissue damage in TB, alone or in conjunction with a monocyte-dependent networks in TB[149]. Furthermore, in HIV+ individuals, with latent and active TB a lower induction of IL-17, IL-22, IL-23R, and PD-1(Programmed Death 1), FoxP3+, and IL.10 in response to mycobacterial antigens, (CFP1; ESAT-6)[150]. These data suggest the role of IL-17 and IL-22 in different stages of human TB. In active TB patients, low IL-17 but high IL-4 induction was found. On the contrary, in latent TB patients, high IL-17 and low IL-4 induction[151]. Under this settings, no IL17 driven tissue damage. Furthermore, in BCG vaccinated children a dramatic IL-17, IFN-γ induction were found, suggesting that in adjuvanted subunit Tb vaccine, induction of Th17 cells be promoted.

3. BCG vaccine induced immunity

In general, vaccination aims to link innate and adaptive immune responses. Tb vaccine design and development focus on this. BCG vaccine can induce an anti-mycobacterial immune response after a second encounter with the same pathogen (*Mtb*). Of note is that *MTb* induces non-specific immune responses[152,153]. This last one might be "beneficial for the host upon early infection, and BCG vaccination could eliminate diverse pathogens[154–157]. Moreover, under the settings of BCG vaccination, natural or recombinant BCG vaccine in conjunction with prime-boost protocols could increase clearance and protection against the same pathogen or other respiratory airway pathogens[158,159]. In calves[160], this route leads to a general program of APCs activation, maturation, and migration from the systemic compartment to the mucosal sites. Innate cells such as macrophages, monocytes, and natural killer cells can contribute to the non-specific immune responses and are prone to respond to the external stimulus by expressing recognition patterns of receptors (PRRs) on their surfaces that interact with pathogen-associated molecular patterns (PAMPs)[92,93] or DAMPs (danger-associated molecular patterns)[91,99,160], and thus, downstream transmitting to the nucleus through NFkb, for activating the transcription and expression of cytokines genes. The induction of a pro-inflammatory state is important and necessary for the cellular anti-mycobacterial immune response. (**Figures 2** and **3**)[135,136,161]. This mode of action of the BCG vaccine resembles a double sword: 1) BCG's ability to induce and activate specific innate and adaptive immune systems. 2) The induction of a nonspecific response, now called trained immunity[155,157,158,162]. This type of response might be beneficial to support early clearance of infection to the same pathogen, to other nonrelated respiratory pathogens[163], or even against other chronic diseases (cancer)[164]. Indeed a specific response follows a nonspecific innate immune response (trained immunity) to generate a memory innate-like response independent of T and B cells[162,165,166]. The proposed mechanism of the trained immunity induction is that after a second encounter with the pathogen, there is a molecular interaction of the TLRS and the different PAMPs of the pathogen. A downstream signal is transmitted to the nucleus of the innate cells, resulting in the rearrangements in the pattern of histone methylation and a higher expression of the pro-inflammatory cytokines. Thus, is produced an increased and faster second response toward other nonrelated pathogens, such as SARS-CoV2 or another chronic noninfectious disease[99,154,156–158,167]. Specifically, referring to the trained immunity induced by BCG vaccine, several evidences from the

literature in human and mice have shown that intradermal BCG vaccination induce epigenetic reprogramming in the pattern of histone methylation of regulatory elements of specific pro-inflammatory genes in circulating monocytes, leading to a trained state with the pathogen of the complex of *Mtb* or to another respiratory pathogens, including viruses or chronic diseases[165,166,168] (**Figure 3A**). How does BCG vaccination trigger innate and cellular immune responses at a systemic level in *M. bovis*-immunized mice? It has been proposed that BCG vaccination confers cellular immunity through the establishment of the central role of CD4 (+) T cells[138,143,144,161,162,169]. Indeed, it has been found that a single systemic BCG vaccination induces distinct systemic and mucosal populations of T effector memory (T(EM))(CD4+CD44(hi)CD62(lo) CD27-T cells. These expanded cells concomitantly produce a set of proinflammatory cytokines, such as IFN-γ and TNF-α or IFN-γ, IL-12, and TNF-α to maintain functionality for periods longer than 16 months in BCG-vaccinated and *M. bovis*-immunized mice. Therefore, persistent mucosal populations of T(EM) cells (CD4+CD44(hi)CD62(lo)CD27-T) IFN-γ and TNF-α or IFN-γ, Il-12, and TNF-α are strongly associated with protection and are potential targets for vaccine design to increase the number of relevant antigen-specific T(EM) in the lung may represent a new generation of TB vaccines[169].

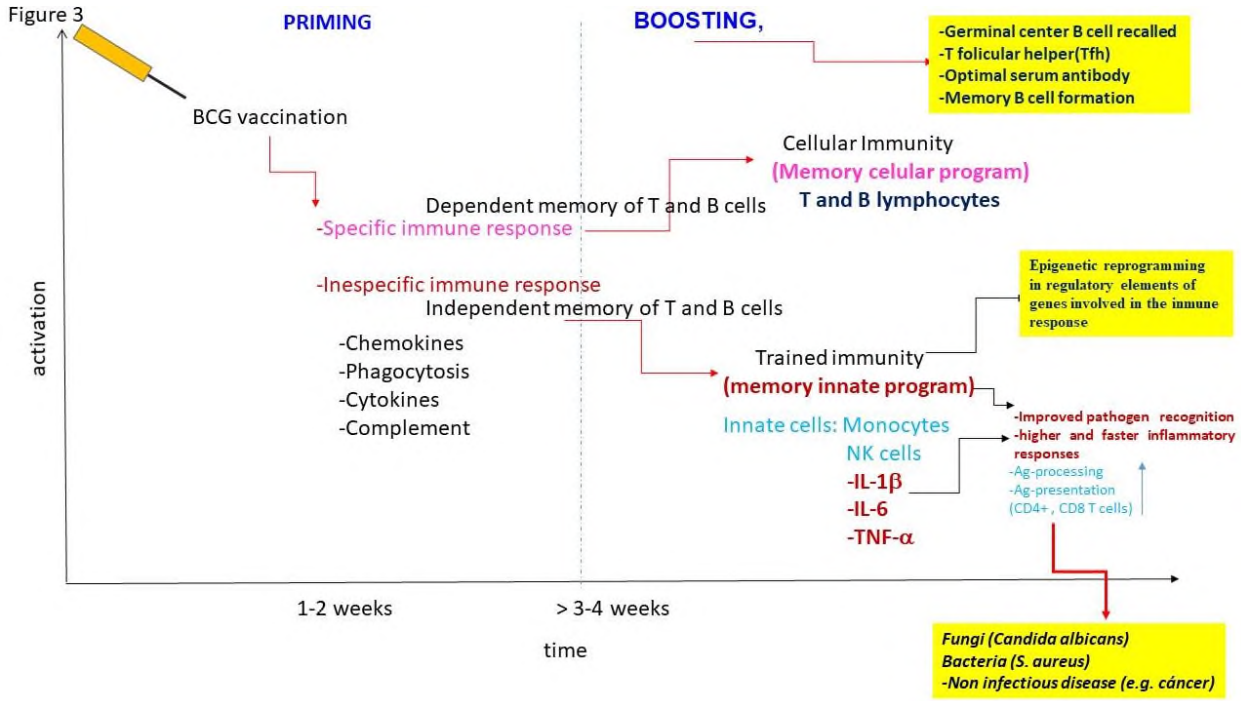

Figure 3. *Mycobacterium bovis Bacillus Calmette Guerin* (BCG) vaccine as an antigen induces innate and specific antimycobacterial cellular immune. One question to resolve is how to boost long-lasting memory and protective responses for young adults. To this end, heterologous prime-boost protocols are a promising strategy for modulating central and effector memory responses and even TH17/IL17 responses. Nowadays, the fact that the BCG vaccine acts as a double sword opens the possibility to improve BCG, either as recombinant or with adjuvant immune dominant antigens, to target innate nonspecific immune responses (trained immunity)[159,162].

BCG vaccine triggers an accelerated interferon-gamma response by CD4(+) T cells in the lung during subsequent *Mtb* infection. Moreover, in preclinical models, BCG vaccination induces IL-17-producing CD4(+) T cells that populate the lung and after *MTb* aerosol challenge, trigger the production of chemokines that recruit CD4(+) T cells producing interferon-gamma, which ultimately restrict bacterial growth[138,143,144]. Furthermore, BCG-induced immune T cells generated from knockout mice IL12- or IL-23 were deficient in IFN-γ production but exhibited a robust IL-17 secretion associated with a degree of protection against pulmonary infection[170]. In addition, studies in mice have shown that IL-17 plays a role not only in the early neutrophil–mediated inflammatory response but also in the T cell-mediated IFN-γ production and granuloma formation in response to pulmonary infection by BCG[161]. IL17 knockout mice produced less IFN-γ

production after one month of BCG vaccination with impaired granuloma formation, suggesting that IL-17 plays a role in the induction of an optimal TH1 response (IL-12, IL23) and optimal expansion of IFN-γ secreting T cells. Thus, in addition to IFN-γ-producing T cells, IL17-producing T cells (TH17) observed during mycobacterial infections contribute to protective immunity[135,136]. In agreement with these data from the literature, the question about how BCG vaccination could be harnessing against *Mtb*? One potential alternative is to augment and promote TLR signalization, NF-κβ translocation to the nucleus, and TH17/IL17 cellular immune responses. Insights into the alternatives to boost BCG-induced immunity, several pieces of evidence have shown that these protocols, either homologous but mostly heterologous, are promising not only to induce protection in terms of reduction of bacterial load in the lung but also can tuning the innate and adaptive immune responses[171–175,177]. In terms of priming to the different innate cells, activation and differentiation of the B and T subsets[176–181]. Under different settings in the animal models, different routes of immunization, different doses of antigen, and other pathogenic mycobacteria have been assessed[182,183]. Prime-boost allows to follow the course of the infection and the host immune response. Heterologous prime-boost provides a powerful tool for TB vaccination strategy to target innate and adaptive immune response at local and mucosal sites[42,159,162,184]. Based on several studies in humans and mice, it has been reported that BCG vaccination, especially after mucosal route of administration, elicits CD8+T cellular immune responses[160,185] (**Figure 3**), and airway tissue-resident memory T cells are enhanced[42,184]. The induction of IL-17 by gamma delta T cells is also promoted[131–133]. In conjunction with these cellular immune responses, other pro-inflammatory cytokines (IFN-γ, IL-4, IL-12, IL-6, IL1-β, TNF-α, TGF-β, IL-10). and chemokines (CXCL9) play a role in the specific and non-specific immune responses, mediated by monocytes, macrophages, and NK cells, after BCG vaccination[144,159,162,185,186].

4. Conclusions

Upon pathogen infection, an initial recognition and molecular interaction between PAMPs, (pathogens-associated molecular patterns (PAMPS), and the PRRS (pattern of recognition receptors) on host innate cells. It leads to the recruitment of different adaptors, such as Myd88(myeloid differentiation primary response protein 88, TRIF (TIR domain. containing adaptor protein inducing IFN-β), TIRAP (TIR domain. containing adaptor protein), and TRAM (TRIF-related adaptor molecule), for signal transmission to downstream molecules resulting s in the activation of three major signaling pathways: NF-kβ, MAPK5 and the PIBk/Akt pathways for the induction and production of inflammatory cytokines. Cytokines, chemokines, and expression of costimulatory molecules allow the maturation of antigen-presenting cells (APCs) (dendritic cells, macrophages), resulting in further antigen presentation through MHC restricted or unrestricted through CD1, leading to the connection with the adaptive immune system. B and T cells are activated and differentiate into more specialized cellular and effector functions. T lymphocytes become helpers of the B cell differentiation for antibody production. Naïve T cells differentiate into different subsets with effector functions such as TH1, TH2, TH3, and TH17. Remarkably T cells become effector and memory T cells (central and peripheric, fundamental against intracellular infectious disease and key in the development of vaccines.

Mycobacterium bovis Bacillus Calmette Guerin (BCG) vaccine as an antigen induces innate and specific antimycobacterial cellular immune. One question to resolve is how to boost long-lasting memory and protective responses for young adults. Several studies in preclinical models have shown that heterologous prime-boost protocols are a promising strategy for modulating central and effector memory responses and specially TH17/IL17 responses. Nowadays, the fact that the BCG vaccine acts as a double sword opens the possibility to improve and boost BCG protective immunity, including long lasting memory response. This can be do it, either as recombinant or with adjuvant immune dominant antigens, to target innate nonspecific immune responses.

5. Remarks and in perspective

Cellular immunity is pivotal against *M. tuberculosis* infection. However, in recent times increasing evidence sustains the potential role of the innate memory called "trained immunity" by monocytes and NK cells. BCG vaccine can induce specific anti mycobacterial responses and nonspecific immune responses against other respiratory pathogens and chronic noninfectious diseases. Thus, trained memory can be effective against a second encounter with the same pathogens, producing higher inflammatory mediators (cytokines, chemokines) that allow a faster response. A remarkable feature of trained immunity, independent of the T and B cellular immune response, is the crosstalk between the innate cells as the first line of defense at the skin and mucosal sites. The perspective is to harness the BCG vaccine's ability to induce specific and nonspecific immune responses. BCG vaccine can be natural or recombinant. The tunning and modulation of the outcome of the innate and cellular response might be through heterologous boosting with any of the immune dominant antigens of *M. tuberculosis* (Ag85B, nHBHA, or a combination of them). These promising strategies can augment specific and nonspecific immunity. Furthermore, a perspective attractive for vaccine design and development based on natural BCG or recombinant BCG is to take advantage of the most recent high throughput technologies such as biomass. Under different experimental settings in preclinical models to approach and dissect the pool of immune markers that correlate with protection following vaccination and boosting with heterologous or homologous antigens such as ESAT-6 (active disease) or late time point of infection (nHBHA, Ag85B) (latent infection), VitD or even arabinomannan or another factor of virulence of *Mtb*. For enhancing and boosting BCG immunity through genetically engineering BCG for targeting innate (augment trained immunity) and cellular immune response (TH1, TH17).

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Conflict of interest

The authors declare no conflict of interest.

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