Immunological Host Responses Against Mycobacterium tuberculosis and M. bovis Infection: A Review

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A B S T R A C T

The immune response against tuberculosis (TB) plays a fundamental role in the outcome of Mycobacterium tuberculosis (Mtb) and M. bovis (Mbs) infection. The host’s innate immune cells such as macrophages, dendritic cells (DCs), neutrophils and natural killer (NK) cells interact with Mtb and Mbs. And as such express a variety of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nod-like receptors (NLRs) and C-type lectin receptors (CLRs). All these receptors have been implicated in the recognition and uptake of Mtb and Mbs by various innate immune defense-associated cellular functions, such as phagocytosis, autophagy, apoptosis and inflammasome activation. In view of this, the present review article provides an updated overview and a better understanding of the cellular and molecular immune mechanisms underlying host-pathogen interactions that could provide a rational basis for the development of effective anti-TB therapeutics and diagnosis of the disease.

Introduction

In the entire history of humankind, it is believed that tuberculosis has killed more people than any other disease. Tuberculosis dates back to at least 4000 BC and was present in ancient Egypt, Greece, Rome and India. In 1882, the microbiologist Robert Koch discovered the tubercle bacillus, at a time when one of every seven deaths in
Europe was caused by TB. The first half of the 20th century estimated that more farm animals died of *M. bovis* than all other infectious diseases combined (Mortaz *et al.*, 2015).

Tuberculosis in cattle is a zoonotic disease caused mainly by *Mycobacterium bovis* (Mbs), although it is reported outbreaks caused by *M. tuberculosis* (Mt) and *M. caprae* in this species. In cattle, the most probable and important route of infection is by inhalation of the bacteria (even by inhalation of a single bacillus in an aerosol droplet). This disease is a significant zoonosis, spread by inhalation of aerosols or the ingestion of unpasteurized milk. In developed countries, eradication programs have reduced or eliminated tuberculosis in cattle and human (disease is now rare); however, reservoirs in wildlife make complete eradication difficult. Bovine tuberculosis is still common in less developed countries, and severe economic losses occur from livestock deaths, chronic disease and trade restrictions. In some situations, this disease may also be a serious threat to endangered species (Korb *et al.*, 2016).

To reduce the economic losses caused by Mt and Mbs, it's very important to possess the molecular knowledge and host interaction of the bacteria. Mt and Mbs, both is an intracellular pathogen and maintains the equilibrium with host immunity by the formation of granuloma, which causes latent infection. It results in non-sterilizing control of infection. But the failure of the host cells to restrain bacterial growth results in granulomatous lesions (with more necrotic macrophage death and increased inflammatory cell recruitment). The latent TB reactivation rate is around 5 to 10%. This reflects that this bacteria has developed a highly intricate mechanism to evade the host innate immunity including cytosolic escape, the restricted production of antimicrobial peptides, blockade of phagosome maturation, apoptosis, inflammasome activation and modulation of autophagy. These strategies developed by Mt also limit the development of adaptive immune responses (Mortaz *et al.*, 2015; Korb *et al.*, 2016 and Goldberg *et al.*, 2014). In this review, we highlighted recent research regarding major innate immune responses, role of signal transduction pathways in the pathogenesis, cells involved in immune response; and acquired immune response and humoral immune response against mycobacteria. This review also focuses on the mechanism of how Mt modulates the host immune response for progressive disease.

**Innate immune response**

The innate response begins after the infection and before the initiation of adaptive immunity. The importance of this kind of response is due to its capacity to neutralize the progression of the infection. In order to protect against infection, the first step is to detect the presence of microorganisms. The body initially do this by recognizing molecules unique to groups of related microorganisms and are not associated with human cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPs. Recognition of PAMPs is performed by germline-encoded receptors expressed mainly on immune cells termed pattern recognition receptors (PRRs). These receptors are on sentinel cells of the innate immune system such as macrophages or dendritic cells (DC), the majority of which are lipid in nature (Lederer *et al.*, 1975; Sinsimer *et al.*, 2008). A variety of PRRs has been shown to recognize mycobacterial PAMPs, such as TLRs, NLRs, CLR, scavenger receptors (for example, MSR1, MARCO and CD36), CD14 receptors, AIM2 and AhR. (Court *et al.*, 2010; Bowdish *et al.*, 2014).

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PRRs cascade multiple signaling in host to launch a variety of innate immune defense functions such as phagocytosis, autophagy, apoptosis and inflammasome activation.

Recognition of mycobacterial lipids by macrophages has been demonstrated via the mannose receptor, complement receptors, scavenger receptors and CD14 (Pugin et al., 1994). Furthermore, various lipids from Mtb have been shown to ligate TLR-2 on human macrophages. DC are known to possess and utilize these same receptors as well as other, structurally related molecules such as the DC specific C-type lectin (DC-SIGN) which have also been heavily implicated in immune recognition of the bacilli (Ehlers, 2010; Geijtenbeek and Gringhuis, 2009).

Many lipids have been implicated in mycobacterial virulence which are not found in other bacterial genera. Lipomannan (LM), lipoarabinomannan (LAM), the phosphatidylinositol mannosides (PIMs), the cord factors trehalose mono and dimycolate (TMM and TDM) and the phthiocerol dimycocerosates (PDIMs) are all surfaces bound mycobacterial lipids capable of modulating innate immunity (Brennan and Draper, 1994).

Recently, newly identified lipids, such as monomycolyl glycerol (MMG), have been shown to modulate host immunity (Andersen et al., 2009) and hypervirulence (Reed et al., 2004). However, little data exist which describe the effect of M. bovis derived lipid on bovine innate cells.

The first step in understanding the mechanisms of recognition of pathogenic bacteria is a solid knowledge of the structure of the cell wall of the microorganism, which is the first structure to come in contact and to be recognized by the cells of the immune system. It has been demonstrated that dectin and TLR4 are playing a role in the induction of IL-17 by TB (Andersen et al., 2009). The cytokine IL-10, which is generally secreted by TH2 cells, affects macrophages by suppressing cytokine production, and thereby down-regulating TH1 cell activity and proliferation, and one study suggests that IL-10 plays a central role in enhancing the survival of Mtb within macrophages (Gupta et al., 2010). It has been shown in a variety of studies that both cytolytic T lymphocytes and IFN-γ-activated macrophages are necessary for conferring protective immunity against Mtb. As a result, these are the immunological pathways that must be focused on in developing an efficacious vaccine to tuberculosis.

The Th1 pathway of the immune response including CTL activation is best stimulated by antigens that have been synthesized and degraded inside the cell and presented on the cell surface with MHC Class I. IFN-γ is an important cytokine for immune protection, but, in excess, it is also a key mediator of immunopathology. Massive activation of macrophages within tubercles by IFN-γ results in the concentrated release of lytic enzymes. These enzymes destroy neighboring healthy cells and create circular regions of necrotic tissue (Urban et al., 2006).

**Cells involved in the immune response**

**Macrophages**

The macrophage is the paradigmatic cell regarding *M. tuberculosis* infection. Indeed, alveolar macrophages have been shown to play an essential role in the elimination of particles that enter the organism through the airways; and have long been considered the first cell population to interact with the tubercle bacillus. More macrophages are
recruited afterward from the bloodstream and are in charge of maintaining the infection in the host (Dannenberg, 1991).

The initial interactions of the bacilli with the macrophage take place through cellular receptors, such as receptors for Fc, complement, mannose, surfactant protein, CD14 and CD43 (Randhawa et al., 2005). Though it is unknown if the bacteria interact with one or more of these receptors during in vivo infection, the results of in vitro experiments suggest that the macrophage response depends on the type of receptor with which the bacteria interact.

Their interaction with Fc receptors increases the production of reactive oxygen intermediates and allows the fusion of the bacteria-containing phagosomes with lysosomes. On the other hand, the interaction of the bacteria with the complement receptor 3 (CR3) prevents the respiratory burst and blocks the maturation of phagosomes harboring the bacteria, thus preventing fusion with lysosomes (LeCabec, 2000).

The interactions of mycobacteria with members of the Toll-like receptor family have been studied for some years. TLR-2 and TLR-4 are activated by several M. tuberculosis components. Among others, the 19-kDa lipoprotein and lipoarabinomannan (LAM) activate macrophages through TLR-2, promoting the production of IL-12 and inducible nitric oxide synthase (iNOS) (Brightbill et al., 1999).

Regardless of the receptor with which the bacteria interact, it has been observed that the cellular cholesterol present in the macrophage cell membrane is an essential molecule for the internalization of the bacteria (Gatfield and Pieters, 2000). It is believed that cellular cholesterol works as a direct anchorage point for the bacterium and stabilizes its interaction with the macrophage membrane. Afterward, the bacterium is efficiently internalized (Pieters, 2001).

Once the bacteria enter the macrophage, they generally locate themselves in the mycobacterial phagosome. This structure derives from the plasma membrane and presents some cell surface receptors. In contrast to normal phagocytosis, during which the phagosomal content is degraded upon fusion with lysosomes, the mycobacteria block this process. This inhibition depends on an active process induced by viable mycobacteria since dead bacilli can be easily found in lysosomal compartments.

Besides having a different morphology, the vacuoles in which the bacteria reside present early endosomal compartment markers instead of the characteristic late endosomes (Hasan et al., 1997). In addition, these mycobacterial phagosomes retain early markers, such as Rab5 and Rab14 GTPases, and do not acquire the late Rab7 molecule; a finding which is also consistent with a blockage of the maturation process from early to late endosome (Kyei et al., 2006).

Another characteristic of the mycobacterial phagosome is its limited acidification. Normally, material transported through an endosomal route finds an acidic medium due to the action of the vesicular proton-pump adenosine triphosphatase (V-ATPase) in the late endosome. It is suggested that such reduced acidification is the result of a low or zero concentration of V-ATPase in the mycobacterial phagosome.

A more recently described property is that this mycobacterial phagosome cannot physically associate with iNOS (Miller et al., 2004). The inability of the mycobacterial phagosome to mature has been attributed to the active retention of a protein present in phagosomes,
known as tryptophan aspartate coat protein (TACO), which was elegantly demonstrated by Ferric et al., When these authors infected TACO-deficient cells, the maturation of mycobacterial phagosomes was not arrested and therefore these cells were able to eliminate bacilli by fusion of phagosomes with lysosomes.

It is also worth noting that TACO binds itself to the plasmatic membrane of macrophages through cholesterol, which also plays an essential role in mycobacterial uptake by macrophages. These events show both molecules to be importantly associated in the mycobacterial mechanisms for survival (Gatfield and Pieters, 2000).

The inhibition of phagosome maturation by mycobacteria may be reverted by cytokines, such as interferon-gamma (IFN-γ) and TNF-α, which also stimulate microbicidal mechanisms, including the production of reactive oxygen and nitrogen intermediates (Chan et al., 1992).

The protective role of nitrogen intermediates has been demonstrated in different murine models (Flynn et al., 1998), and a similar function has been suggested for these molecules in human TB (Nicholson et al., 1996).

In contrast, the role played by the reactive oxygen intermediates during infection has not been completely explained, though it is known that hydrogen peroxide produced by macrophages activated by cytokines has a mycobactericidal activity (Walter and Lowrie, 1981).

Also, it has been found that the tubercle bacillus presents molecules, such as LAM and phenolic glycolipid I, which work as oxygen radical scavenger molecules (Chan et al., 1991). This understanding may allow the development of novel approaches to control TB via modulation of macrophage phenotype, form, metabolism and function.

Dendritic cells are clearly involved in the protective immune response to M. tuberculosis infection. As explained above, when M. tuberculosis bacilli are inhaled and phagocytosed by the pulmonary macrophages, they remain, and even replicate, within the cell phagosome. Dendritic cells recruited from blood, and probably also from lung tissues, may play a role in protective immunity since they are found in increased numbers in TB lesions (Pedroza-Gonzalez et al., 2004; Garcia-Romo et al., 2004).

Dendritic cells recognize, capture and process antigens, thus being able to present them in the context of major histocompatibility complex (MHC) molecules, as well as through CD1 (Gumperz and Brenner, 2001). Dendritic cells bind antigens via C-type lectin receptors and Fcγ/Fce receptors and internalize them by endocytosis. M. tuberculosis endocytosis is carried out through known C-type lectin receptors, such as dendritic cell-specific intercellular-adhesion-molecule-grabbing non-integrin (DC-SIGN) (Tailleux et al., 2003).

This molecule interacts with mannose capped-LAM, a component of the mycobacterial cell wall (Geijtenbeek et al., 2003; Figdor et al., 2002). In addition, peripheral blood dendritic cells and immature dendritic cells derived from monocytes express TLR-2 and TLR-4 (Kadowaki et al., 2001), two Toll-like receptors with which mycobacteria seem to interact.

Thus, it can be assumed that a protective host response may be induced through these signals. Additional signals generated by the association of mannose capped-LAM to DC-SIGN induce IL-10 production (Geijtenbeek
et al., 2003), while the union of a 19 kDa *M. tuberculosis* lipoprotein to TLR-2 induces production of IL-12, TNF-α, and IL-6 (Means et al., 2001).

Once the antigens have been captured and internalized, dendritic cells become mature (indicated by phenotypical and functional changes) and efficiently migrate to peripheral lymph nodes. There is evidence of in vivo *M. tuberculosis* and BCG transport from lung tissues to the lymph nodes inside infected dendritic cells (Dieu et al., 1998).

This migration of infected dendritic cells requires the expression of the chemokine receptor 7 (CCR7) on their surface, which makes them sensitive to chemokines (CC) CCL19 and CCL21 (Kriehuber et al., 2001; Bhatt et al., 2004). It is important to mention that maturation of dendritic cells is not only accompanied by an increased synthesis of MHC class I and II, but also by the expression of co-stimulating molecules, such as CD80 and CD86 and the production of IL-12 (Steinmann, 2001). The internalization of *M. tuberculosis* into human and murine dendritic cells has been observed in several in vitro (Bodnar et al., 2001; Giacomini et al., 2001; Hanekom et al., 2002) and in vivo (Jiao et al., 2002; Pedroza- Gonzalez et al., 2004; Garcia-Romo et al., 2004) studies.

Reportedly, when dendritic cells derived from monocytes are infected with *M. tuberculosis*, their ability to present lipidic antigens is impaired and thus the expression of CD1 decreases (Stenger et al., 1998). Components of the mycobacterial cell wall were also shown to inhibit the phenotypical maturation of dendritic cells induced by lipopolysaccharides. Different lineages of *M. tuberculosis* may vary in the degree by which they affect the dendritic cells. In particular, the enhanced virulence ascribed to Beijing strains might well be related to their inability to stimulate dendritic cell maturation (Lopez et al., 2003).

In a protective immune response, dendritic cells induce maturation of T cells towards a T helper 1 (Th1) profile by secreting cytokines, such as IL-12, IL-18, IL-23, and probably IFN-α and β, but not IFN-γ (Wozniak et al., 2006; Kadowaki et al., 2001). Th1 cells expand in response to the BCG antigens presented by the dendritic cells in the lymphoid nodules and migrate toward infection sites, such as the lung tissue, where they liberate IFN-γ, thus activating local macrophages that control bacilli replication (Humphreys et al., 2006). Besides, it has been shown that DCs undergo cell death after infection with Mtb in vitro, just as macrophages, and could help by this way the protection of the host against TB (Ryan et al., 2011).

**Neutrophil leukocytes**

Even though macrophages are considered the main targets for infection by *Mycobacterium spp.*, it has been recently proposed that other cell populations can also be infected by mycobacteria and therefore may be important in the development of the disease. Neutrophils are the first cells to infiltrate the lungs after Mtb infection and are the most abundant cell type appearing in the bronchoalveolar lavage and the sputum and triggers inflammatory signals.

Using the murine experimental model, the role played by neutrophils in TB is controversial. These cells have been detected at the beginning of infection as well as several days after infection (Pedrosa et al., 2000; Fulton et al., 2002) and were thought to have an important role in the control of mycobacterial growth. Indeed, if neutrophils are eliminated before infection, mycobacterial growth increases in the lungs of
experimentally infected animals; and conversely, if mice are treated with an agent that increases neutrophils, the bacillary growth rate decreases (Appelberg et al., 1995; Fulton et al., 2002).

However, when the microbicidal ability of neutrophils against mycobacteria was analyzed, controversial results were obtained. There are reports of neutrophils being able to kill mycobacteria (Jones et al., 1990) and other reports where this phenomenon was not observed (Denis, 1991). Nevertheless, it is believed that the function of neutrophils goes beyond their microbicidal ability. Therefore, these cells are thought to contribute to the control of infection through the production of chemokines, the induction of granuloma formation and the transference of their own microbicidal molecules to infected macrophages (Tan et al., 2006).

On the other hand, neutrophils have recently been ascribed a role in the development of the pathology, rather than the protection of the host. TB susceptible animals were found to have a larger and longer accumulation of neutrophils in TB lesions compared to TB resistant animals (Eruslanov et al., 2005). It is evident from the various studies that Mtb actively manipulates Neutrophils. For example, Mtb induces neutrophil necrosis and prevents apoptosis dependent on region of difference 1 (RD-1)-encoded virulence factors (Corleis B, et al., 2012).

More recently it was demonstrated that, ESAT-6 protein, secreted by a type VII secretion system (ESX) encoded by RD1 in Mtb, induce an intracellular Ca\(^{2+}\) overload followed by necrosis and the formation of neutrophil extracellular traps (NET) characterized by extruded DNA and myeloperoxidase (Francis RJ, et al., 2014). Furthermore, neutrophils are involved in the induction of adaptive immunity and are critical for granuloma cavitation during Mtb infection (Blomgran R, et al., 2011 and Ong CW, et al., 2015). More work is needed to identify additional mycobacterial effectors of neutrophil necrosis, so that it can be determine whether pharmacologic intervention targeting neutrophil necrosis could alter uncontrolled inflammation and immunopathology during Mtb infection.

**Mast cells**

Mast cells are effector cells with a relevant role in allergic reactions and are also critical for the development of a T helper 2 (Th2) response (Galli et al., 1999; Williams and Galli, 2000). They are found in the mucosa of the respiratory, gastrointestinal, and urinary tracts and can also be observed in the vicinity of blood and lymph vessels. These cells express a receptor with a high affinity for IgE (FcεRI) and therefore this immunoglobulin is bound to their membrane.

Upon the union of the antigen to the active sites of FcεRI-bound IgE, mast cells liberate several molecules, including preformed mediators and mediators, synthesized de novo (Williams and Galli, 2000). Among the preformed mediators contained in mast cell granules are histamine, tryptase, chymase, carboxypeptidase, and heparin, while mediators synthesized de novo include leukotriene C4, prostaglandin D2, platelet-activating factor (PAF), tumor necrosis factor-alpha (TNF-α), transforming growth factor (TGF-β), fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor (VEGF), and interleukins IL-4, IL-5 and IL-8 (Sayama et al., 2002).

Besides this interaction between IgE and the antigen, other agents can induce the activation of mast cells and the liberation of cytokines and other mediators. Due to their strategic distribution within the lung, mast cells have a
fundamental role in the defense of the host against mycobacteria. An early study showed an increased number of mast cells and their degranulation in the lungs of animals experimentally infected with *M. tuberculosis* (Ratnam et al., 1977).

Munoz et al., (2003) demonstrated that there is an interaction between mast cells and *M. tuberculosis* through the CD48 molecule. This interaction triggers the release of preformed mediators, such as histamine and β-hexosaminidase, and the liberation of *de novo* synthesized cytokines, such as IL-6 and TNF-α, which are involved respectively in the activation of neutrophils and the maintenance of the integrity of the granuloma.

The secretory proteins *Mycobacterium tuberculosis* complex secreted antigen (MTSA-10) and 6-kiloDalton (kDa) early secretory antigenic target (ESAT-6) contribute to the activation not only of macrophages and dendritic cells but also of mast cells for the liberation of their pro-inflammatory mediators (Trajkovic, 2004).

**Natural killer cells**

Natural killer cells play a very important role in the development of the innate immune response. Their main function has been associated with the development of cytotoxicity to target cells and they are among the first cell populations to produce IFN-γ during the immune response. For a long time, the study of this cell population was focused on their role in viral and tumoral diseases. More recently, however, increasing interest has arisen in their eventual function in several bacterial infections.

The number of natural killer cells was shown to increase in the lungs of C57BL/6 mice during the first 21 days after aerosol infection with *M. tuberculosis* complex strains. This cell expansion was associated with an increased expression of activation and maturation markers and IFN-γ production. However, the depletion of natural killer cells had no influence on the lung's bacterial load, indicating that although these cells become activated during the early response in pulmonary TB, they are not essential for host resistance (Junqueira-Kipnis et al., 2003).

Natural killer cells also play an important role in human TB by regulating different aspects of the immune response. Human natural killer cells have been shown to have enhanced cytotoxicity for macrophages infected with *M. tuberculosis*. They also optimize the ability of CD8+ T lymphocytes to produce IFN-γ and to lyse *M. tuberculosis* infected cells, thus joining innate to adaptive immune responses (Vankayalapati et al., 2004).

**CD1d-restricted natural killer T cells**

These are a unique subset of human natural killer T cells characterized by the expression of an invariant V alpha 24 T cell receptor that recognizes the nonclassical antigen-presenting molecule CD1d. The activity of CD1d-restricted killer cells is notably enhanced by the marine glycolipid alpha-galactosylceramide derived from sponges. Once activated by alpha-galactosylceramide, CD1d-restricted natural killer T cells contribute to human host defense against *M. tuberculosis* infection.

Human monocyte-derived macrophages expressing CD1d can induce effector functions of natural killer T cells against cells infected with *M. tuberculosis* when activated with alpha-galactosylceramide. These functions include IFN-γ secretion, proliferation, lytic activity, and anti-mycobacterial activity; this latter via the antimicrobial peptide granulysin, which damages the mycobacterial surface. There is further support of the potential interaction of
natural killer T cells with CD1d-expressing cells at the site of disease since CD1d can be readily detected in granulomas (Gansert et al., 2003). Such a role has not been proved in M. tuberculosis infected mice. Rather, natural killer T cells have been shown to play a detrimental role, at least in the late phase of mouse experimental infection (Sugawara et al., 2002).

Epithelial cells

Alveolar macrophages have been considered for a long time to be the first cell population to interact with M. tuberculosis. However, the number of epithelial cells in the alveoli is 30 times higher than the number of macrophages and thus, the likelihood that they are the first cells exposed to the infecting bacilli is similarly higher. The first indication of the involvement of epithelial cells in M. tuberculosis infection was derived from a study where the presence of mycobacterial DNA was detected in necropsy specimens from people who had died from diseases other than TB.

In that study, M. tuberculosis DNA was detected in macrophages, type II pneumocytes, fibroblasts, and endothelial cells (Hernandez-Pando et al., 2000). In addition, several in vitro studies have characterized the interaction between epithelial cells and M. tuberculosis. These cells can host M. tuberculosis bacilli and allow their replication (Bermudez and Goodman, 1996).

Moreover, epithelial cells are able to establish an initial pro-inflammatory environment by secreting IL-8 and inducing the production of nitric oxide (NO) (Roy et al., 2004). Obviously, in vivo experiments are necessary to better understand the role played by alveolar epithelial cells in M. tuberculosis infection.

Defensins in Innate Response

A conspicuous element of the innate immune response against microorganisms is a group of small endogenous antimicrobial peptides known as defensins (Diamond et al., 1998). These cationic peptides, consisting of approximately 30 to 50 amino acids, are present in myeloid and epithelial cells of all animal species. They were shown to display antibacterial (Gabay et al., 1989), antifungal (Selsted et al., 1985), and antiviral (Daher et al., 1986) activities. These molecules are classified as alpha, beta, and theta defensins based on the position of cysteine residues and the number of disulfur bonds (Bals et al., 2000). In phagocytic cells, defensins represent the main microorganism destruction components independent of oxygen metabolism (Miyakawa et al., 1996). Allegedly, these peptides break the membrane of several microorganisms and some of them are even able to pass through the cytoplasmic membrane and enter the infected cell (Ganz, 2003; Rivas-Santiago et al., 2006).

Defensins were first described in guinea pig and rabbit neutrophils (Zeya and Spitznagel, 1963). There is no report of human monocytes and macrophages having defensins, although neutrophils have been reported to have four known human neutrophil defensins peptides, of which three (HNP-1, HNP-2 and HNP-3) were found to be active against Mycobacterium avium-intracellulare and M. tuberculosis (Miyakawa et al., 1996). In vitro, the human alpha-defensins present in human neutrophils directly attract CD4+/CD45RA+ T cells, CD8+ cells, and dendritic cells. The expression of human beta-defensin 1 is constitutive in epithelial cells but the expression of human beta-defensins 2 and 3 is inducible by IL-1, TNF-α, and by Toll-like receptor recognition of bacteria and fungi (Kaiser and Diamond, 2000).
Mice infected with *M. tuberculosis* express murine beta-defensins mBD-3 and mBD-4. In the first stages of infection, the epithelial cells of the respiratory tract express both defensins, which correlates to the early control of bacterial proliferation. However, their expression decreases as the disease progresses. In the latent infection model, mBD-3 and MBD-4 are continuously expressed, but their expression is suppressed if the infection is reactivated (Rivas-Santiago et al., 2006).

*M. tuberculosis* infected mice that have been treated with the defensin peptide HNP-1 show a reduction of bacterial load in the lungs, liver, and spleen (Sharma et al., 2001). This observation suggests that defensins could represent important components of the innate response mechanisms against *M. tuberculosis* and could be used as new therapeutic tools.

**Role of signal transduction pathways in the pathogenesis of Mtb**

**Role of Toll-Like Receptors (TLRs) in Pathogenesis of Mtb**

Toll-like receptors (TLRs) play a critical role in both innate resistance and the initiation of adaptive immunity to infectious agents (Doyle and Neill, 2006). So far fifteen functional TLRs have been identified in mammals, and they are playing an important role in specific recognition of pathogen-associated molecules. Upon ligand binding to the receptors, TLRs initiate a cascade of events leading to the transcription of NF-κB-dependent genes, mostly inflammatory genes (Gupta et al., 2010).

TLRs recognize pathogen-associated molecular patterns (PAMPs) or endogenous inflammation-associated molecules. TLRs recognize distinct molecular structures on microbes, and, in several cases, different sets of TLRs have been associated with the response to different classes of microorganisms.

Upon inhalation, Mtb travels to the lung where it infects resident alveolar macrophages. This initial infection leads to an innate immune response, which includes stimulation of TLRs that recognize pathogens and are located on the plasma membrane and within endosomes of host cells. Emerging of data indicated that Mtb is specifically recognized by TLRs 2, 4, and 9. TLR activation upregulates transcription of proinflammatory cytokines IL-1β, TNF-α, and IL-6, which are essential for the recruitment of immune cells to the site of infection and controlling Mtb infection (Doyle and Neill, 2006).

Recent studies in mice with inactivated TLR genes showed that TLR2 is important in controlling and surviving the Mtb infection (Lee et al., 2009). However, some observations suggested that TLR4 is also important for the survival of Mtb infection (Doyle and Neill, 2006).

In this regard, human studies show that polymorphisms of TLR2 or TLR4 may result in increased susceptibility to microbial infections, possibly by changing the balance of Th1/Th2 response. Now it became clear that changes in TLR expression might represent useful markers of the immunological status of patients and their contacts. Thus, TLR8 plays a key role in damping inflammation and tissue damage in *M. tuberculosis* infection (Lee et al., 2009).

**Role of Inflammasomes Signaling in Mtb**

In addition to TLR recognition, a newly discovered class of intracellular danger-sensing proteins, the nucleotide-binding domain, leucine-rich repeats containing
family proteins known as NLRs, sense pathogens and pathogen products in the cell cytoplasm. With more than twenty members, the NLRs function in host protection against a broad range of danger signals. Several NLRs function in immunity through the formation of a multiprotein complex known as an inflammasome (Ting et al., 2008).

IL-1β induces the release of GMCSF which leads to the activation and increased survival of monocytes/macrophages and enhanced oxidative burst in the lungs; thus, maintaining and prolonging inflammatory reactions, IL-1β is secreted by activation of inflammasome signaling which is triggered by signal transduction via TLRs and purinergic receptors. Apoptosis-associated speck-like protein, containing a caspase recruit domain (ASC) and procaspase 1, forms a multimeric cytosolic molecular complex known as the NALP3 proinflammatory cytokine regulation can be critical to the long-term survival of Mtb infection (Shin et al., 2010).

**Acquired immune response against mycobacteria**

In contrast to innate mechanisms, the specific or adaptive immune response requires the specific recognition of foreign antigens. The innate immune system has a profound influence on the type of acquired immune mechanisms generated, and *vice versa*, the specific immune response executes several of its effector functions via the activation of components of the innate immunity. Specific immune responses can be divided into cell-mediated mechanisms, which include T-cell activation and effector mechanisms, and the humoral immune response, consisting of B-cell maturation and antibody production.

Both mechanisms are not mutually exclusive, and T helper cells are required for antibody maturation, isotype switching and memory. B cells also function as antigen-presenting cells by activating T cells in a specifically driven manner.

*M. tuberculosis* is the most conspicuous example of an intracellular bacterium that persists for long periods within the host, causing a latent infection, namely a chronic asymptomatic infection without tissue damage. This is best illustrated by the fact that two billion people worldwide are infected with *M. tuberculosis*, but more than 90 % of them remain healthy and free of clinical disease and the tubercle bacilli remain within them in a state of dormancy.

Therefore, although the host cell-mediated immunity is enough to control the progression of the disease, it fails to exert sterile eradication and hence, those two billion infected persons suffer the latent form of TB (Collins and Kaufmann, 2002).

As for other intracellular infections, the primary protective immune response is cell-mediated rather than antibody-mediated. *M. tuberculosis* resides inside the macrophage and is relatively resistant to microbicidal mechanisms that efficiently eliminate other phagocytosed bacteria. This is due in part to the ability of the tubercle bacilli to hinder macrophage activation by IFN-γ and IL-12. Several studies have confirmed the critical importance of these cytokines in both human and mice *M. tuberculosis* infection. In addition, deficiencies in IL-12 or IFN-γ, or their receptors, render the individual more susceptible to mycobacterial infections (Alcais et al., 2005). For the last 20 years, it has been assumed that the induction of a Th1-type immune response affords the host the greatest protective capacity. Despite the fact that there are hundreds of studies published on TB immunity, still, there is a lack of information regarding important issues, such as the role of lung antigen-presenting cells in
vivo during pulmonary TB (Pedroza-Gonzalez et al., 2004). This type of information would allow a better understanding of the induction of specific immune responses against M. tuberculosis, and therefore the development of tools that could control the disease more effectively.

**Humoral Immune Response**

Because of their intracellular location, it is frequently assumed that tubercle bacilli are not exposed to antibody and therefore this type of immune response is non-protective. However, during the initial steps of infection, antibodies alone or in conjunction with the proper cytokines may provide important functions, such as prevention of entry of bacteria at mucosal surfaces. Even though the issue remains controversial, the role of antibodies in intracellular bacterial infections has gained renewed attention.

Lately, their participation in the control of acute infections, such as chlamydial respiratory infection (Skelding et al., 2006), and chronic infections produced by Actinomycetes, including M. tuberculosis (Salinas and Rivera, 2004; Williams et al., 2004; Reljic, 2006), was explored. Antibodies can be exploited in two ways in the clinical management and control of TB: as serological diagnostic tools; and as active participants in protection. Serological methods have been regarded for a long time as attractive tools for the rapid diagnosis of TB due to their simplicity, rapidity, and low cost. As early as 1898, Arloing showed that sera from TB patients could agglutinate tubercle bacilli (Daniel and Debanne, 1987). With the introduction of the enzyme-linked immunosorbent assay in the 70s, interest was renewed, and several groups of investigators committed themselves to find an optimum antigen for TB serodiagnosis.

At that time, complex antigens were used in most cases, such as whole bacteria, culture filtrates, bacterial extracts, tuberculins and their purified derivates (PPD). More recently, individual purified antigens have also been assayed, including proteins, lipopolysaccharides and glycolipids, i.e., Ag 85, 38-kDa protein, LAM or diacylthrehaloses. To date, however, no test has shown sufficiently high sensitivity and specificity values for diagnostic purposes (Singh et al., 2003; Raqib et al., 2003; Lopez-Marin et al., 2003).

As for their use in protection against TB, antibodies could enhance immunity through many mechanisms including neutralization of toxins, opsonization, complement activation, promotion of cytokine release, antibody-dependent cytotoxicity, and enhanced antigen presentation. In this sense, data from several laboratories indicate that anti-mycobacterial antibodies play an important role in various stages of the host response to TB infection (Costello et al., 1992; Teitelbaum et al., 1998; Hoft et al., 1999; Hoft et al., 2002; Williams et al., 2004; De Valliere et al., 2005).

In particular, De Valliere et al., (2005) showed that specific antibodies increased the internalization and killing of BCG by neutrophils and monocytes/macrophages. Moreover, antibody-coated BCG bacilli were more effectively processed and presented by dendritic cells for stimulation of CD4+ and CD8+ T-cell responses. This enhanced anti-mycobacterial activity of phagocytes by antibody-coated bacilli is extremely important in the context of mucosal immunity.

IgG and IgA antibody classes have been shown to be present in the mucosal secretions of the human lower respiratory tract (Boyton and Openshaw, 2002). The specific mycobacterial targets for antibody-mediated enhanced interiorization and/or killing are not
known, but surface antigens such as LAM or proteins expressed under stress conditions, such as alpha-crystallin protein, may be relevant. In an experiment where 17 recombinant mycobacterial protein antigens, native Ag85 complex, LAM, and \textit{M. tuberculosis} lysate were used to detect antibody responses induced by BCG vaccination, only LAM-reactive serum IgG responses were significantly increased in both BCG vaccinated individuals and active TB patients. As expected, oral BCG vaccination leads to a significant increase in LAM-reactive secretory IgA (Brown \textit{et al.}, 2003).

A new approach toward protection against TB, using passive inoculation with IgA antibodies, was tested in an experimental mouse model of TB lung infection (Williams \textit{et al.}, 2004). Intranasal inoculation of mice with an IgA monoclonal antibody against alpha-crystallin protein reduced the \textit{M. tuberculosis} colony up to 10-fold, forming units (cfu) in the lungs nine days after either aerosol or intra-nasal challenge.

Both monomeric and polymeric IgA reduced cfu to the same extent, suggesting that the antibody may target the Fc alpha receptor (Fc-\(\alpha R\)) rather than polymeric immunoglobulin receptor (poly-IgR) in infected lung macrophages. As expected, protection was of short duration, probably due to the rapid degradation of the intranasally-applied IgA.

More recently, in a follow-up of this study (Reljic \textit{et al.}, 2006) the duration of protection was extended by inoculation of IFN-\(\gamma\) three days before infection, and further co-inoculation with IgA at different time points (2 h, 2 and 7 days) after aerosol infection with \textit{M. tuberculosis} H37Rv. Instead of a 10-fold reduction in cfu, a 17-fold reduction was observed, as well as lower granulomatous infiltration of the lungs. Thus, the combined administration of IFN-\(\gamma\) and IgA shows promise as a prophylactic treatment of immunodeficient patients or as an adjunct to chemotherapy.

Taken all together, these findings suggest an urgent need to reassess the role of antibody responses in TB. In particular, the mechanism involved in antibody-mediated enhancement of innate and cell-mediated immunity should be addressed, in order to analyze whether these mechanisms could be exploited to develop better TB vaccines or to design alternative immunotherapeutic tools.

**Cellular Immune Response**

Since the tubercle bacilli reside inside a compartment within the macrophage, their antigens are presented by MHC class II molecules to CD4+ T lymphocytes. These cells play an important role in the protective response against \textit{M. tuberculosis} and, when they are absent, the growth of the bacilli cannot be controlled (Caruso \textit{et al.}, 1999). This is the case in patients with immunodeficiency, such as that caused by HIV infection in humans.

The main function of CD4+ T cells is the production of cytokines including IFN-\(\gamma\), which activates macrophages and promotes bacilli destruction. Recently, another function has been ascribed to these cells, i.e., helping to develop the CD8+ T cell-mediated response (Serbina \textit{et al.}, 2001). In the same way, CD4+ T cells may participate in the induction of apoptosis of infected cells and the subsequent reduction of bacterial viability through the CD95 Fas ligand system. The participation of CD8+ T cells in the control of the infection is well recognized. Mice deficient in molecules such as CD8\(\alpha\), transporter associated with antigen processing (TAP), and perforin, were shown to be more susceptible to \textit{M. tuberculosis} infection than animals that produced these molecules (Behar
et al., 1999). The mechanisms used by these cells for the control of TB seem to be mainly cytokine production and bacterial lysis.

In the lungs of infected mice, CD8+ T cells showed to be able to secrete IFN-γ through activation of the T-cell receptor or by interaction with infected dendritic cells (Serbina and Flynn, 1999). Once again, the function performed by this IFN-γ is the activation of the macrophage and the promotion of bacterial destruction. In addition, CD8+ T cells proved to be efficient in lysing infected cells and in reducing the number of intracellular bacteria (Stenger et al., 1997). The mechanisms of control of the bacterial load seem to be associated with granular exocytosis involving perforin and granzymes. Still, granulysin, which is found in CD8+ T granules, is the molecule responsible for killing the bacterium (Stenger et al., 1998).

**Gamma/delta T cells**

Previously, the CD4-CD8- T cells, known as γδ T cells, were considered to play a low-profile role in the immune response. They were believed to proliferate only in response to non-peptidic antigens (Schoel et al., 1994). As they were found in early lesions, they were thought to react to infected macrophages only through the production of IFN-γ (Ferrick, 1995). In the last few years, however, γδ T cells proved to be relevant for the regulation of the immune response. High levels of γδ T cells are usually found in the peripheral blood of TB affections (Ito et al., 1992). Ex vivo, γδ T cells from human TB patients display a lytic activity that is independent of the MHC. While the lytic activity of CD4+ and CD8+ T cells decreases gradually as the disease becomes more severe, γδ T cells increase their activity, lysing target cells infected with *M. tuberculosis* through the Fas-FasL mechanism and the perforin pathway (Barrera, 2003).

In a murine model of TB infection, γδ T cells were shown to contribute to the elimination of *M. tuberculosis* and to have an anti-inflammatory effect. Indeed, when these cells are eliminated by genetic manipulation or by using a specific monoclonal antibody, inflammatory damage is accelerated in the lungs of mice infected with *M. tuberculosis* (D.Souza et al., 1997). In addition, γδ T cells produce IL-17 during early infection, which probably promotes the flow of cells towards infection sites.

This IL-17 secretion may be produced in response to IL-23 secretion by dendritic cells infected with *M. tuberculosis* (Lockhart et al., 2006). The role of γδ T cells in protective immunity is not limited to cytokine secretion (such as IL-17 and IFN-γ) and cytotoxic activity. These cells also behave as antigen-presenting cells. Like dendritic cells, they can process and efficiently present antigens and give the co-stimulating signals needed to induce the proliferation of αβ T cells (Brandes et al., 2005). As noted, γδ T cells act as a link between the innate immune response and the adaptive immune response, although other roles played by these cells still remain unknown.

**The immune response related to progressive disease:**

**Mechanisms of Immunopathology**

In the early 90s, some researchers reported an increased expression of Th2 cytokines, especially IL-4, in patients with advanced pulmonary TB (Schauf et al., 1993; Sanchez et al., 1994). Later, other authors failed to detect IL-4 and the issue remained controversial (Lin et al., 1996). More recent data indicate that these failures could be attributed to technical problems (Rook et al., 2004), and now there is substantial evidence that demonstrates a Th2 response in human
TB (Seah et al., 2000; Marchant et al., 2001; Leinhardt et al., 2002). Interestingly, IL-4 levels tend to be higher in patients living close to the Equator, possibly as a consequence of simultaneous infection with helminths and/or higher mycobacterium inoculums (Malhotra, 1999). Indeed, TB patients have several IL-4-dependent manifestations, including high IgE antimycobacterial antibodies, antibodies against cardiolipin (Fisher et al., 2002) and high expression of DC-SIGN in dendritic cells (Relloso et al., 2002). IL-4 has been detected in TB lung lesions by in-situ hybridization (Fenhalls et al., 2000).

Also, IL-4 messenger ribonucleic acid (mRNA) and T-cells containing IL-4 are increased in pulmonary TB. This high IL-4 expression correlates significantly with serum IgE, serum soluble CD-30, and also with the extent of cavitation (Seah et al., 2000; Lienhardt et al., 2002). It has been demonstrated that CD8+ cells are another source of IL-4, and this correlates with cavitation. The presence of IL-4 in the late stages of the disease has a direct pathogenic role because it downregulates the protective Th1 responses (Biedermann et al., 2001).

Similar abnormalities are also observed in the lungs of Balb/c mice, which have been experimentally infected via the trachea with a high dose of M. tuberculosis H37Rv (Hernandez-Pando et al., 1996; Hernandez-Pando et al., 1998). In this model, there is an initial phase of partial resistance dominated by Th1 cytokines plus activated macrophages that produce TNF-α and express iNOS. The phase of progressive disease starts after one month of infection. This late phase is characterized by a drop in the number of cells expressing INF-γ, IL-2, TNF-α, and iNOS, progressive pneumonia, extensive interstitial fibrosis, high bacillary counts and very high levels of IL-4 and TGF-β, produced by a distinctive type of macrophage with numerous cytoplasmic vacuoles (foamy macrophages).

It is important to point out that this animal model resembles the disease in developing countries, where the infecting dose is usually high and the progressive disease tends to show a high IL-4 response (Rook et al., 2004; Flynn, 2006; Singh et al., 2017a).

Thus, during early infection (first month) there is a predominance of Th1 cells, while during progressive disease a mixed Th1/Th2 pattern exists in this animal model.

In the Balb/c model of progressive pulmonary TB, the mixed Th1/Th2 cytokine pattern is associated with the pathology and reduced protection (Rook and Hernandez-Pando, 1996). When pre-sensitized with 107 cfu of Mycobacterium vaccae, saprophytic, highly immunogenic mycobacteria, mice infected with M. tuberculosis mount a strong Th1 response and are partially protected. In sharp contrast, when pre-immunized with a higher dose of the same mycobacterial preparation (109 cfu), mice develop a response with a mixed Th1/Th2 pattern that leads to increased severity of infection with the disease, and death (Hernandez-Pando and Rook, 1994; Hernandez-Pando et al., 1997; Singh et al., 2017b Singh et al., 2018).

Thus, pre-exposure to saprophytic mycobacteria can determine either resistance or susceptibility to M. tuberculosis infection, and the effect seems to be dose-dependent. The nature, route, and dose of mycobacterial exposure depend on where and how an individual lives because mycobacteria are not part of the usual commensal flora. This variable priming of anti-mycobacterial responses by saprophytes can either protect or predispose to infection, and might well be responsible for the uneven efficacy of BCG vaccination in different parts of the world (Rook et al., 2005).
Thus, activated macrophages are efficient producers of pro-inflammatory cytokines, such as TNF-α, and contribute to the control of the infection, while vacuolated macrophages are severely infected cells and efficient producers of anti-inflammatory cytokines that enable bacilli growth, such as TGF-β.

Various symptoms of TB, such as fever, weight loss, and tissue damage, resemble the pathological effects of TNF-α. Evidence that such symptoms may be produced by this cytokine has come from experiments with thalidomide, a compound that decreases the half-life of TNF-α mRNA (Moreira et al., 1993). TB patients treated with this drug show rapid symptomatic relief and weight gain (Kaplan, 1994).

Thus, TNF-α has paradoxical participation in the immune-pathology of TB: it plays an essential role in protection but may also be a significant factor in its pathology. This ambiguous activity of TNF-α might be defined on-site in the light of the predominant cytokine pattern, Th1 or Th2. In fact, the sensitivity of a given inflammatory site to TNF-α is dependent on the cytokine profile of the prevailing CD4+ T cells. This ambiguous effect of TNF-α was also observed in Balb/c mice immunized with different doses of M. vaccae two months before challenge with fully pathogenic M. tuberculosis.

They have concluded that the TNF-α was released into a relatively pure Th1-mediated inflammatory site, where it may act merely as a supplementary macrophage activating cytokine. But, when released into a mixed Th1/Th2 site with high IL-4 concentration, it causes damage (Hernandez-Pando, 1997). These observations were confirmed in a further study using the Balb/c model of progressive pulmonary TB (Hernandez-Pando et al., 2004). It is apparent that the immune response to bovine tuberculosis is multifaceted and that diagnostic parameters are likely to perform differentially as the disease progresses.

Various studies have contributed to our understanding of bovine tuberculosis in the context of findings of studies of tuberculosis in humans and laboratory animal models. Analysis and extrapolation of data from other species have the potential to expand our understanding of the pathogenesis of the disease in cattle. The distribution of lesions in affected cattle, humans and laboratory animals illustrates the primacy of the respiratory tract as the portal of infection and raises questions about the role of the upper respiratory tract surface, tonsil and dorsal lung regions in disease pathogenesis and transmission.

The mechanisms behind significant pathological processes such as necrosis, apoptosis and liquefaction, occurring within lesions, should be further explored and their potential practical significance assessed in the context of herd disease dynamics and vaccine development. Furthermore, the concepts of latency and disease reactivation considered significant factors in perpetuating tuberculosis in human populations should be investigated in the context of the bovine disease. However, the accumulation of new detailed information on immune responses continues to provide benefits in the logical design of a new diagnostic approach.

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