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Review

Immunity towards tuberculosis infection: A review

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Immune response represents the initial arm of host defense against Koch's bacillus. This review describes and discusses current knowledge of the host's immune response to *Mycobacterium tuberculosis* infection. To improve the diagnosis of tuberculosis, more rapid diagnostic techniques have been investigated in recent years, such as mediators, receptors and activators of immunity, gamma-interferon, tumor necrosis factor-alpha, reactive nitrogen intermediates, T cells, and natural killer. We consider it a first priority to implement programs of education for the development of a strategy to prevent tuberculosis. It is recommended to implement an immunotherapy treatment following chemotherapy to prevent reactivation of the bacillus due to the presence of latent bacilli in tissues.

Key words: Immune response, prevention, control, reactivation, nitric oxide, interferon, latent infection, granuloma, *Mycobacterium*.

INTRODUCTION

Tuberculosis (TB) has been and remains a major global health problem. TB is a pandemic and is amongst the top 10 killer infectious diseases, second only to human immunodeficiency virus (HIV) (Jain et al., 2012). It has extensively affected millions of people world-wide. It causes bad health among millions of people each year (WHO, 2013). TB is primarily a pulmonary infectious disease (Wang et al., 2013). It affects especially young adults and therefore has a high impact on the socio-economic status of a country (Zakham et al., 2012).

In Africa, the study of TB is complicated by the parallel epidemic of HIV because co-infection is common. This makes it necessary to consider HIV infection, especially in high HIV prevalent areas (Morris et al., 2011). HIV is a prerequisite condition for the acquisition of TB. The latest estimates included in this report are that there were 8.6 million new TB cases in 2012 and 1.3 million TB deaths worldwide. The number of TB deaths is unacceptably high given that most are preventable if people can access health care for diagnosis and right treatment is provided. Short-course regimens of first-line drugs (isoniazid, pyrazinamide, ethambutol, and rifampin) that can cure

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around 90% of cases have been available for decades (WHO, 2013). Factors such as the high prevalence of HIV-infected patients, the emergence of multidrug-resistant (MDR) bacteria, and outbreaks involving MDR strains in hospitals have decreased the efficacy of anti-TB drugs (Limoncu et al., 2011). Region of the Americas reported 219,000 cases of TB, 9,800 of which were children (OPS/OMS, 2012). Only in Mexico, there were 19,703 new cases of TB in all its forms and all groups of age (Secretaría de Salud, 2014). Also it was reported that in Mexico, there are 40,000 cases of active TB, and around 2500 cases have strains that are MDR (González-Duarte et al., 2011).

The etiological agent of TB is the group of mycobacteria known as *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, which comprises *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*, and *M. bovis*. Each member of the TB complex is pathogenic to different hosts, *M. tuberculosis* is pathogenic for humans while *M. bovis* is usually pathogenic to animals (cattle) (Alli et al., 2011; Boisson-Dupuis et al., 2011). Within infected macrophages, the construction of the recombinant BCG (BCGi) has been analyzed and its intracellular bioactivity. BCGi is a potential novel recombinant vaccine against TB. Although this BCGi is a potential vaccine candidate against *M. tuberculosis*, it could also be a good tool for further research on the mechanisms of gene 1 (*lpr1*) against *M. tuberculosis in vivo.* It limits gene multiplication of *M. tuberculosis* and switches the cell death pathway of the infected macrophages from necrosis to apoptosis (Wang et al., 2013). Control of TB requires the generation of antigen-specific T-cell responses, activation of infected macrophages and formation of granulomatous lesions to wall off infected macrophages and prevent dissemination of the bacilli. This cellular immune response to intracellular pathogens comprises a spectrum of T-cell subpopulations characterized by distinct cytokine secretion profiles and cell surface marker phenotypes. Three main subsets are recognized and can be identified on the basis of T-cell cytokine profiles: effector T cells that secrete only interferon *gamma* (IFN-γ), effector-memory T cells that secrete both IFN-γ and interleukin-2 (IL-2) and central-memory T cells that secrete only IL-2 (Sester et al., 2011).

Immunological control of *M. tuberculosis* is dependent on Th cell (Th1); Th1-type immune response is necessary for protection against mycobacterial pathogens. These facultative intracellular pathogens reside in mononuclear cells, which allow them to escape the immune response of the host. Therefore, there is a crucial requirement for a coordinated cellular immune response to control the infection (Hovav et al., 2003). Latent TB infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB. The vast majorities of infected persons have no signs or symptoms of TB but are at risk of developing active TB disease (WHO, 2015). Actually,isoniazid preventative therapy is a widely used intervention for treatment of LTBI, particularly in patients at high risk for reactivation (Denholm et al., 2014). One third of the world's population is estimated to be latently infected with *M. tuberculosis* (Lamberti et al., 2014). Nearly one-third of the world's population is infected with TB, and that 95% of these have the infection in this asymptomatic, noncontagious, latent form (Semba et al., 2010). Moreover, there exist recurrent factors of risk like age, stress, undernourishment, alcoholism, cancer, smoking (Semba et al., 2010), and recurrent infections that can cause the resistance, being in the reactivation of the LTBI and the development of the disease (Bouchonnet et al., 2002). Relative risk factors for developing active TB are silicosis, diabetes mellitus (Ocal et al., 2009), chronic renal failure and hemodialysis, gastrectomy, jujenoileal bypass, renal and cardiac transplant and carcinoma of head and neck. Malnutrition markedly increases mortality among both TB and HIV/AIDS patients (Semba et al., 2010), HIV infection and malnutrition lower immunity, increases the risk of reactivation of TB and primary progressive disease. TB is a droplet infection and about 1-2% of close contacts develop active TB disease while 31 to 36 percent will have LTBI; and among the latter 3 to 5% will develop TB within 2 years of infection (Iqbal et al., 2012). The growth of steam cells in the bone marrow is the basis for cellular immunity. Currently, several factors can be studied that produce specific cytokines, which are indicators of the degree of immune response that the host present towards infection caused by *Mycobacterium.* This can determine the presence of latent bacillus, giving the opportunity for timely treatment before the disease is active. *M. tuberculosis* is able to evade or survive the host defense mechanisms. The present review describes and discusses current knowledge of the host immune response to infection caused by *M. tuberculosis*, emphasizing the function of macrophages, T cells, cytokines and chemokines in relation to the protective immune response.

ANTIMYCOBACTERIAL EFFECTOR FUNCTIONS OF MACROPHAGES

The capacity of the macrophages to resist microorganisms depends on their state of activation. The alveolar macrophages constitute the initial defense against the mycobacteria. The phagocytes in alveolar macrophages can be invaded by the cytolytic bacteria that survive and multiply intracellularly (Saukkonen et al., 2002). Only the macrophages, dendritic cells (DCs) and the B cells are recognized like antigen-presenting cells (APC), but other types of cells can work like APC in special conditions (Takamatsu et al., 2002). The DCs are the most powerful APC (Ismaili et al., 2002). The interaction

between the macrophages infected and T cells involve proinflammatory and regulating cytokines, starting with the destruction of organisms infected with *M. tuberculosis*. Nevertheless, a few bacteria survive, prevailing the LTBI. The neutrophils are considered like precursors towards the innate immunity (Fulton et al., 2002). The bacillus exerts little influence on the basic function of the cells of the host, limiting the presentation of the antigen, suppressing the response of the lymphocyte, inducing mediating proinflammatory and immunosupressors and the activation of the macrophages mediated by IFN-γ (Rhoades et al., 2003). The released catecholamines as a response to stress can act like activators of macrophages in the antimycobacterial activity; this is by stimulation of 2β-adrenergic at the level of peroxinitrite produced by the infected macrophages (Weatherby et al., 2003). The *M. tuberculosis* is a pathogen that multiplies in the alveolar macrophages, but in most of the cases it causes bacteriostasis where the pathogen is in a non-replicating state (dormant), latent and resistant to drugs. In depressed immune systems, the pathogen multiplies, and allows TB activation; in most of the cases, people have had LTBI for years or decades (Daniel et al., 2004). Finally, in the alveolar spaces the bacillus can reproduce unhindered, far away from the granuloma. The concentrations of protective cytokines, mainly IFN-γ, are low in the alveolar spaces.

GAMMA-INTERFERON (IFN-γ)

The introduction of interferon-γ release assays (IGRA) are transforming diagnosis of LTBI and improving diagnostic evaluation of patients with active TB (Sester et al., 2011). IFN-γ is a pleiotropic cytokine that plays an essential role in both the innate and adaptive phases of an immune response. In addition, the subsequent activation of lysis of infected APC is crucial to the induction of antimycobacterial immunity. Furthermore, the importance of IFN-γ in antimycobacterial immune responses was demonstrated in IFN-γ gene knockout mice, which do not survive challenge with *M. tuberculosis* or even the avirulent vaccine strain *M. bovis* BCG. Humans genetically defective in production of IFN-γ or the IFN-γ receptor also show increased susceptibility to mycobacterial infection, suggesting a central role of this cytokine in host defense (Hope et al., 2002). Additional IFN-γ in macrophages, DCs, CD4+ T cells have been identified, and even in plasma cells. The IFN-γ is the main activator of macrophages infected, produced by natural killer (NK) and Th1. The tumor necrosis factor-alpha (TNF-α) and IFN-γ activate the microbicide mechanisms in macrophages infected necessary for the control of the infection. After the dimerization induced by binding of the IFN-γ in the R2 chain, the macrophages are recruited in the interior of the complex. The main factor that regulates the production of IFN-γ by Th1 and NK cells is the IL-12; it is a heterodimeric cytokine, that consists of a chain p40 and it is secreted by the macrophages activated and DCs (Roseeuw et al., 2003). The IFN-γ level in pleural fluid is increased in patients with TB; the estimation of the IFN-γ is an excellent strategy of diagnosis for the TB (Sharma and Banga, 2004). To analyze immune response parameters that allow distinction between patients with active TB and non-active states, a rapid 6 h-whole blood assay for intracellular cytokine staining of IFN-γ and IL-2 by flow-cytometry was used to measure and compare antigen-stimulated T-cell cytokine profiles in patients with active untreated TB and patients who had been successfully treated. A threshold in IFN-γ/IL-2 dual positive CD4 T cells has been established to distinguish active disease from successfully treated disease; whole blood is stimulated with purified protein derivatives (PPD), early secreted antigenic target 6-kDa antigen (ESAT-6) and culture filtrate protein 10 (CFP-10), and antigen-specific set of differentiation (CD4) T cells co-expressing CD69, IFN-γ and/or IL-2 (Sester et al., 2011). Also, a recombinant vaccine was developed and prepared from non-pathogenic *M. smegmatis* (rMS), a purified recombinant *M. smegmatis* that expresses a fusion of ESAT-6 and CFP10 and evaluated immune responses and protective effect in mice (Zhang et al., 2010). Cellular immunity against ESAT6-CFP10 was assessed by two different assays: ELISPOT and target cell killing assay. T cells were isolated from each group of mice and the frequency of ESAT6-CFP10 cells was determined by evaluating specific IFN-γ secretion after incubation with peptide-loaded APC. Major Histocompatibility Complex (MHC-II) peptides $ESAT6_{1–15}$ and $CFP10_{32–39}$ were used to evaluate CD4+ cells and MHC-I peptide $CFP10_{11–25}$ was used for CD8+ cells. Only T cells from the rMS-e6c10 group recognized $ESAT6_{1–15}$ and $CFP10_{32–39}$. The magnitude of this response to MHC-I $CFP10_{11–25}$ was about half the magnitude of the response to MHC class II-restricted CFP10 (Zhang et al., 2010); rM.S-e6c10 induced a significantly higher cellular immunity response than did the BCG vaccine and had a protection efficacy similar to that of BCG in MTB-challenged mice. This recombinant *M. smegmatis* holds promise as a TB vaccine and warrants further evaluation; this suggests a more intense cellular immunity response is induced by the fusion protein. The whole blood approach has the potential to differentiate active from treated or LTBI on an individual patient basis within one working day. The assay simultaneously measures IFN-γ and IL-2 at the single cell level which is neither possible by IFN-γ ELISpot nor by ELISA; the two platforms are used in the current commercially available IGRAs (Sester et al., 2011).

TUMOR NECROSIS FACTOR-*ALPHA* (TNF-α)

Cytokines like the TNF-α and the IFN-γ activate microbial

mechanisms in macrophages infected (Lagranderie et al., 2003). The infection of the alveolar macrophages induces the liberation of multiple factors, including early inflammatory cytokines like TNF-α and IL-β that have an autocrine effect activator which promotes the group of leukocytes (Saukkonen et al., 2002). The cytotoxicity that leads to the apoptosis is induced by *M. tuberculosis* in primary macrophages *in vitro;* this is mediated by TNF. These macrophages resist cytotoxicity TNF, and are the first indicator of death when one is infected with attenuated strain of *M. tuberculosis* and their allies mycobacterials. The alveolar macrophages infected with attenuated strain or avirulents of *M. tuberculosis* suffer apoptosis due to the TNF-α of a dependent way. This is in contrast with the infection caused by the virulent mycobacterial strain, which induces little or null apoptosis. The apoptosis of macrophage of the host not only eliminates the growth of the niche of *M. tuberculosis*, but also activates the microbicide mechanism (Riendeau and Kornfeld, 2003).

REACTIVE NITROGEN INTERMEDIATES (RNI)

IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF-α activate the macrophages, in order to resist the growth of intracellular pathogens and to increase antimicrobial molecule production, including nitric oxide (NO) and reactive oxygen intermediates (ROI). Nitrate reductase assay (NRA) is based on the property of *M. tuberculosis* to reduce nitrate to nitrite, which is revealed as a color change of the culture media, using the Griess method (Musa et al., 2005). NO is readily produced by *Mycobacterium*-induced peripheral blood mononuclear cells (PBMC) from *Mycobacterium bovis*-infected cattle. NO responses play an important role in organism and host defense. In recent reports, inflammatory responses increase NO levels through increased expression of an inducible form of NOS (iNOS) in inflammatory cells such as macrophages. Macrophages play an important role in the first and essential line of defense against mycobacterial disease (Martinez-Romero et al., 2013). An increase in NO concentrations has been obtained in the supernatants of mononuclear cell cultures stimulated with lipopolysaccharide (LPS) and 1,25-dihydroxyvitaminD3 (Martinez-Romero et al., 2013). It plays an important role in calcium metabolism; in alveolar macrophages in granulomas, it has a protective effect against oxidative injuries from the NO burst from granulomatous macrophages. Abnormalities in calcium homeostasis have been reported in patients with TB, and the relationship of these abnormalities with vitamin D status is unclear (Semba et al., 2010).

The addition of epinephrine to peritoneum macrophages inhibits their capacity to resist the growth of *Mycobacterium*, half way by the 2-adrenérgico receptor, which correlates with a diminution in the production of NO (Weatherby et al., 2003). The production of NO is essential for the intracellular death of the tubercle bacillus in the macrophages, since it acts like a microbial agent (Waters et al., 2003). IFN-γ and the TNF-α are associated with the answer of NO (Buddle et al., 2002; Waters, et al., 2003). The antibody in lymphocyte supernatants (ALS) method is a rapid diagnostic for the identification of adult patients with active pulmonary TB. This method was validated in the diagnosis of pulmonary TB among well-characterized patients with symptomatic respiratory diseases and healthy controls. The use of higher PBMCs concentration in a smaller volume of culture media in the micro-ALS method allowed for increased concentration of released antibodies in the supernatant, thus permitting a shorter period of cell culture and increased detection. The micro-ALS method also has the potential to identify borderline TB cases that might otherwise be missed due to lower production of specific antibodies by low cell numbers (Rekha et al., 2011).

T CELLS (T CELLS CD4 AND T CELLS CD8)

The development of the cellular immunity acquired by cooperating T cell (Th1) is characterized by the production of cytokines: IL-12, IFN-γ, TNF-α, and by the inflammation granulomatous of macrophage in the tissue (Biet et al., 2002). In order to fight against the TB, the development of the mediated immune response by cytotoxic Th1 CD4+ and T CD8+ of the IFN-γ (Tollefsen et al., 2003) is essential. The development of anergy and reduction in the number of T cells CD4+ in patients with viral diseases contribute to the susceptibility to TB (Bouchonnet et al., 2002). In the cases of HIV the answer of the host to *M. tuberculosis* is associated with an increase in the activation of alveolar macrophages (Gold et al., 2004). The protection from TB is mediated by T cells, CD4+ and CD8+, not by antibodies (Young et al., 2002). Additionally, Mycobacterium *vaccae*, and the PPD of *M. tuberculosis* suppress the allergy and asthma in mice (Hattori et al., 2002). LTBI has historically been diagnosed with a tuberculin skin test (TST) (Mahomed et al., 2011; Alvarez et al., 2014). Actually, the QuantiFERON TB Gold (In-tube method) (QFT-G) (Cellestis Limited, Carnegie, Victoria, Australia) is one such commercially available assay which has been adopted by many countries as an alternative to TST or as part of a two-step approach which uses both tests: a TST is done first and those with positive test result have QuantiFERON done. QFT-G uses ESAT-6, CFP10 and antigen 7.7 of *M. tuberculosis* as stimuli to determine if T cells in whole blood are sensitized to such antigens, thus indicating prior exposure and/or evidence of LTBI (Simsek et al., 2010; Mahomed et al., 2011; Alvarez et al., 2014). IGRA and TST have been used to examine the risk factors of *M. tuberculosis* infection for the purpose of

identifying those at highest risk of infection. Those risk factors included parents' place of birth, number of siblings, distance between siblings (next younger and next older), birth order and mother's age when the child was born, ethnicity, sibling relations, number of household residents and maternal level of education (Soborg et al., 2011). LTBI is the form of TB which never shows signs and is without any symptoms (Iqbal et al., 2012). In addition, the sensitivity and specificity of TST, QFT-G, and T-SPOT.TB was compared in diagnosing LTBI and active TB. As a result IFN-γ tests could be useful in diagnosing LTBI and chemo-prophylaxis, as the false negativity of the TST was higher compared to both QFT-G and T-SPOT.TB; TST in routine clinical use for identifying active TB and LTBI (Simsek et al., 2010; Verhagen et al., 2013; Ting et al., 2014). QFT-2G and TST test responses were used in patients with active TB disease. It is a feasible supportive diagnostic method compared to the TST for adult patients, but excluding patients ≤ 9 years old; however, both the QFT-2G and TST may be performed for patients with active TB disease ≤ 9 years old (Kobashi et al., 2009). In lung tissue, several processes related to calcium homeostasis are thought to contribute to *M. tuberculosis* persistence and the aggregation of macrophages in granulomas; *M. tuberculosis* inhibits a calcium-dependent phagolysosome formation pathway which leads to the prevention of maturation of *M. tuberculosis*-containing phagosomes that form phagolysosomes. Possibly, altered expression of these genes in TB patients reflects *M. tuberculosis*-mediated changes in calcium metabolism in lung tissue that can be measured in peripheral whole blood (Verhagen et al., 2013).

The airway hypersensitivity-responsiveness was measured after exhibition to BCG, and the cells in the washing fluid to bronchialveolar was counted, whose cytokines were detected by ELISA (Li et al., 2006). The control of infection is mediated by *M. tuberculosis*-specific CD4+ and CD8+ T cells way to the secretion of IFN-γ and other Th1 cytokines that activate anti-mycobacterial mechanisms of infected macrophages (Shi et al., 2003). The function of T lymphocytes CD4+ effectors and memory has been analyzed to understand the effects of CD85/ILR-1/ILT2 and CD152 (CTLA-4) in the proliferation of T lymphocyte and production of cytokines in responding to the antigens. It has been demonstrated that these inhibiting receptors exert a dual function in the proliferation of T lymphocyte and that they modulate the production of the cytokines when the bonds are blocked or crossed (Saverino et al., 2002). The infection in mice with a virulent strain of intracellular pathogen facultative *Mycobacterium* has same result in progressive, slow disease, possibly ending in death 40 weeks after the infection. This process also has been associated with a decrement of the attributed immune function to the increase in the apoptosis of T cells and to the diminution in the production of protective cytokine IFN-γ (Mannering and Cheers, 2002). The IFN-α/β can regulate the production of dependent IL-12 of IFN-γ, and damages the Th1 answer in mice infected with *M. tuberculosis*. IL-12 is a heterodimeric cytokine composed of two subunits, p35 and p40, which are encoded by the IL12A and IL12B genes, respectively (Morris et al., 2011).

There are also some indications of which IFN-α/β can exert negative effects on the bacteriostatic activity. The exhibition of IFN-α/β contributes strongly to the mycobacterial replication in human macrophages, besides harming its capacity to control the growth of the BCG of *M. bovis* (Bouchonnet et al., 2002). The immunity can be shown by the answer to some population of cells T including CD4+ αβ, CD8+ and T cells γδ (Baldwin et al., 2002). The T cells γδ require APC for the recognition of the antigen, and specific activation. In T cells γ/δ cultivated bovine, soluble antigens appear before changing their phenotype *in vitro*, express proteins of surface associated with the presentation of antigens and present soluble antigens way MHC class II. A sub-population of circulating cells T γ/δ of pig is able to act like APC (Takamatsu et al., 2002). In the activation of T cells γ/δ of bovine they are possibly fixed by three routes: i. Production of IFN-γ demonstrated by flow cytometry by smear cell; ii. progression within the phase of replication of DNA of the cellular cycle by incorporation of nucleotides marked by radiation; iii direct progression by fixation of mitosis by succinimidilcarboxy fluorescein ester (Baldwin et al., 2002). The patients with typical deficiency of IFN-γ recessive R1 chain autosome have a total loss of IFN-γ sensitivity, and usually die during childhood by the dissemination of the mycobacterial infection (Horwitz et al., 2003). The control of the chronic and acute infection of *M. tuberculosis* in mice is done by employee of cells T CD4. Whereas cells T CD4 are the primary source of the markers of cellular surface CD40L, its importance resides in the optimal production of cells T and in the control of the infection in aerosol (Lazarevic et al., 2003). The expression of the CD80 by accessory cells of human and mouse is important in the induction of cytotoxic T cells CD4+ (Rhodes et al., 2003).

NATURAL KILLER (NK)

NK cells are bone marrow derived lymphocytes, distinct from T and B cells. These cells play roles in immunological processes, which are capable of lysing certain tumor cells without prior sensitization. NK cells represent a population of lymphocytes, which could mediate the innate protection against *M. tuberculosis.* They are applied in the immune response early in virus and intracellular pathogens, taking place in IFN-γ. They destroy the specific cells target, and express surfaces of ligand able to initiate the apoptosis (Hope et al., 2002). This apoptosis induced by primary *M. tuberculosis* in primary macrophages *in vitro* is mediated by TNF.

Additionally, the alveolar primary macrophages are not a homogenous population of cells, whose production of cytokines varies between the donors. The apoptosis does not come from a synchronous way, which requires the accomplishment of complicated experiments to interpret it (Riendeau and Kornfeld, 2003). NK, CD8+, and CD4+ Th1 cells are the most potent, but not the only sources of IFNγ. Cytokines type 1 employees of the immunity are important in the defense of the human host against the intracellular pathogens (Lagranderie et al., 2003). Actin and timosin regulate the growth and cellular differentiation in an overregulation of timosin β-10 in ribonucleic acid-messenger (mRNA) like another consequence of the infection. The apoptosis of the macrophages can be bound to the overexpression of timosin β-10. The mycobacterial species that induce the apoptosis lead to an increase in the condensation of the chromatin and fragmentation of the DNA (Gutierrez-Pabello et al, 2002).

Lymphocytes T CD 4+ take part in the beginning of the allergic inflammation aerial route, the production of cytokines T like Th2, the grouping of eosinophils towards the aerial routes, and the subsequent activation (Lagranderie et al., 2003). HIV accelerates TB because it reduces the number of CD4+ cells. The scattered infection caused by *Mycobacterium* is common in patients with HIV with < 50 T/mm^3 cells CD4+. There is a strong correlation between the replication of HIV and the production of proinflammatory cytokines in the lungs of patients with TB (Gold et al., 2004). It has been determined that the cytokine model mRNA could therefore indicate any superiority of Th-2 or the mediated inmmunosupression by the IL-10 (Westenbrink et al., 2005); and it has been confirmed that immunity towards *Mycobacterium* is predominantly cellular (Avgustin et al., 2005). Th cells mature from a precursory state Th0 to Th1 phenotype or Th2 (Dovedi et al., 2005). TB is a granulomatous disorder, and cellular immune response plays a role in the defense mechanism, in which cells T CD4+ expand in the pleural TB, where they dominate the Th1 cells and are sufficiently activated to produce cytokines Th1 (Okamoto et al., 2005). The concentrations of cytokines that induce IFN-γ like IL-12 and Il-18, chemokines IFN-γ and IFN-γ are elevated in the pleural TB, which is malignant pleuritis. In addition, one knows that IL-12 induces the Th1 response in non-differentiated cells T CD4+ and this supports the dominion of the Th1 cells (Okamoto et al., 2005). IL-12 is a heterodimer connected to disulfur. This is released of the APC (macrophages and DCs) by the *Mycobacterium* and is important for the development of protective immunity against TB. The deficient animals in IL-12 show an increased susceptibility to *M. tuberculosis* infection and a decrement in the IFN-γ production. The vaccination against M. *tuberculosis* requires the activation of Th1 cells to induce the expression of IL-12 and IFN-γ (Cho et al., 2005). Actually, it is reported that IL12B gene expression is a major inducer of IFN-γ and IL12-p40 is required for IFN-γ-induced protection from *M. tuberculosis*. IL12-p40 subunit also increases production of IFN-γ by covalently linking to the p19 subunit of yet another cytokine, IL23 (Morris et al., 2011).

Cytokines IFN-γ and IL-2 which are present in the response to Th1 were observed in tinkles after the BCG treatment (Nadler et al., 2003). The predominant function of the Th1 cells co-activates the cytotoxic cells T (CD8+), which are characterized by their production of cytokine prototype proinflammatory Il-12 and IFN-γ (Dovedi et al., 2005). It has been determined that DCs can capture a series of infectious agents and present/display their antigens to lymphocytes T; the DCs express, among other receivers, specific DC ICAM3 and no-integrin receiver (Dc-sign), the lectin type C, which contains lectin type C, in the dependent mannose calcium outside (Naarding et al., 2005).

MEDIATORS, RECEPTORS AND ACTIVATORS OF IMMUNITY

Between the Th1 cytokines induced by infection BCG, the IFN-γ has the main function of activating half-full immunity by cells. IFN-γ is a strong mediator and suppressor of Th2 activity; BCG allows IFN-γ production, and aids to solve atypical symptoms. With the pre-immunization and inactivated BCG, IFN-γ production is induced by IL-18 in sinergic with IL-12. BCG of *M. bovis* induces an immune response Th1 type on the infection of the macrophages of the host (Biet et al., 2002). The use of BCG treatment for patients with cancer of bladder induces massive amounts of IFN-γ urine, along with other cytokines of Th1; whereas high levels of cytokines Th2 type are produced in patients with difficulty in responding to BCG. It has been demonstrated that in the infection treated with BCG, it suppresses the development of Th2 response in the lungs of models murino, where eosinophilia is induced by air (Biet et al., 2002). The immunodeficiency of receptor 1 of IFN-γ is rare; it is susceptible in a wide rank of pathogenic and nonpathogenic mycobacteria (Horwitz et al., 2003). IFN-γ receptor, composed of the IFN-γR1 and IFN-γR2 chains, is present in many lymphoid and nonlimphoid cells; when deficiency of this receptor is observed, it increases susceptibility to microbial pathogens.

The alveolar macrophages stimulate disbalance of cytokines Th2 in patients with asthma. The production of soluble factors by the macrophages and DCs includes the inflammatory cytokines IL-1, IL-6 and TNF-α, or cytokines regulating like IL-10, IL-12 and IL-18. IL-10 is an immunosuppressor and antiinflammatory cytokine that is applied in the regulation of the immune response. Monocytes, lymphocytes, Th and keratinocites protect IL-10 (Jacobs et al., 2002; Julian et al., 2004). It was observed that intranasal confers greater immunogenicity

than the route subcutaneous against pulmonary TB (Chen et al., 2004). The activation of NK cells for IFN-γ secretion is largely dependent on IL-12 and IL-18. Moreover, DCs are a major source of these cytokines. Additionally, only APC is capable of inducing responses in naive T lymphocytes. Because of this, DCs are likely to be central to the induction of antimycobacterial immune responses (Hope et al., 2002). In addition to NK, NKT cells, which share many properties with NK cells, also have features common to the T-cell lineage, such as expression of T-cell receptors besides CD4+ or CD8+. There cells are able to produce large quantities of IFN-γ, which require the presence of IL-12. Furthermore, they may be also being important in innate responses to pathogens (Hope et al., 2002).

IL-10 is an immune mediator which regulates events *in vivo* and suggests that the reinforcements for the mediators, in the inhibition of cytokines, can be of therapeutic value (Nadler et al., 2003). The infections of BCG of *M. bovis* in deficient patients of receptor 1 of the IL-12 demonstrate the deficiency of the receptor of IL-12 (Lichtenauer-Kaligis et al., 2003). However, in BCG-vaccinated and *M. bovis*-infected cattle, the secretion of IFN-γ by CD4+ besides CD8+ T cells has been demonstrated as an important element of the response to mycobacterial challenge (Hope et al., 2002).

IL-23 has a subunit p40 like IL-12, which is united to one second unique chain, p19. Similarly, the receptor for IL-23 consists of a subunit IL-12R β1, in a complex with a member recently identified as the homopoietin receiving family. IL-12 and IL-23 have similar functions, although are non-identical- including in the stimulation of IFN-γ production (Lagranderie et al., 2003; Lichtenauer -Kaligis et al., 2003). IL12 is a heterodimeric cytokine composed of two subunits, p35 and p40, which are encoded by the IL12A and IL12B genes, respectively. IL12B gene expression is a major inducer of IFNγ, and IL12-p40 is required for IFNγ-induced protection from *M. tuberculosis*. IL12-p40 subunit also increases production of IFNγ by covalently linking to the p19 subunit of yet another cytokine, IL23 (Morris et al., 2011). The stimulation of anti-CD3, of T cells of the lungs explains the production of great amounts of IL-5 (Julian et al., 2004). There is a strong correlation between the replication of HIV and the increase in the production of proinflammatory cytokines (IL-6, IL-1, TNF-α and IL-8) in the lungs of the patients with TB (Gold et al., 2004).

The Toll-like receptors (TLR2) is homologous receptor of IL-12 that, like CD14 requires serum components like LPB for their signalling (Yang et al., 1998). Within the process of the cascade of activation of the TLRs they become jumbled diverse kinases that activate the nuclear factor of transcription (NF-kB); and other factors of transcription to control the proinflammatory effectors either are directly cytotoxic to invade the organism or induce a greater sustained defense than can involve numerous types of immune cells and cytokines (Beutler, 2004). The signalling of receiver TLR constitutes the essential connection between the innate immunity and the adaptive immunity and has a greater influence on the polarization of Th1/Th2 (Hoebe et al., 2004; Iwasaki and Medzhitov, 2004).

Additionally, TLRs and the innate immune response, forward edge of defenses against the microorganisms involve not only the cells with primary immune function such as, the macrophages, neutrophils, DCs, and but also types of cells that seem to show greater monitoring, such as the endothelial cells of the blood vessels and epithelial cells in the intestine; in all the cases, the family of the TLRs receptors is the main sensorial apparatus that recognizes the pathogen-associated molecular patterns of an ample variety of pathogens. TLRs are not only the receivers that the patrons recognize, the intracellular proteins who play an important role, particularly in the defense against the virus; nevertheless, the primary responsibility for the detection of the pathogen falls directly on the TLRs (Doherty and Arditi, 2005).

Drug-resistant TB has highlighted the need for discussion of ethical questions about TB diagnosis and treatment. Drug resistance is a human-made phenomenon. It is caused by lack of patients' adherence to drug taking and/or physicians' failure in prescription making. The global burden of TB is also partly explained by the lack of industries' motivation to develop new TB drugs and diagnostics (Selgelid and Reichman, 2011). In addition, today, the Stop TB partnership is beginning a new chapter of its existence. By moving the secretariat's hosting arrangements to a United Nations Agency specialized in providing administrative services, the partnership can focus its attention and activities on coordinating the global effort against TB and strengthen its advocacy work. The move will make it clear to WHO and the partnership will work both in their respective areas and in collaboration to accelerate the fight against TB. It will allow both institutions to maximize their respective mandates and comparative advantages (WHO-UNOPS, 2014). For example, in Malawi there are significant deficiencies in the diagnostic management of pulmonary TB (PTB) suspects, but this suggests that opportunities exist for improving diagnosis and care (Gawa et al., 2011).

Th1 immune response has critical importance, because it has led to the evolution of multiple mechanisms for the induction and regulation of Th1 cells. The superficial receptors of T cells recognize that the antigen has more surface marker that informs the T lymphocyte that is making contact with another cell. These cellular markers belong to a molecule group known like MHC. The treatment of LTBI is considered a main step to halt the process of conversion to active TB. Clinicians need to improve on their performance of diagnosing and managing TB suspects, clinical decision rule to improve isolation policy. The capacity of health care workers

needs to be strengthened by organizing refresher training on TB diagnosis, treatment and control to foster better management of TB suspects. Improved diagnostic strategies could make a difference to a more rapid and improved TB diagnosis. However, global and national TB targets are unachievable without combining this approach with action on the social determinants of health. To increase the quality of life of the patients with PTB, we think that it is necessary to provide information to the patients about the disease, to ensure the patients are cared for and treated by healthcare professionals specialized in this area; to offer proper information and support to the patients and their families to prevent the infection termed latent infection; to make all healthcare professionals be aware of the factors influencing the patients' quality of life. Further studies are necessary to determine the importance of cytokines responses in cases with TB. The social determinants of health are the key to global TB control.

Conclusion

It is necessary to implement an immunotherapy treatment following chemotherapy in order to prevent reactivation of the bacillus due to the presence of latent bacilli in tissues. Many researchers working with environmental bacteria have made numerous, decisive contributions in this area that has been of critical importance. But, there is need to make more investigation about the development, differentiation, and critical activation of cells in the immune system. Clearly, high RNI, IFN-γ, TNF-α, cells T CD4+, IL-2, IL-12 levels are associated with increased Th1-mediated immune response and can help to study many antitubercular treatments and vaccines production. RNI diagnosis can provide new clues about the different clinical outcomes after *Mycobacterium* infection.

Conflict of interests

The author(s) did not declare any conflict of interest.

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