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REVIEW

Role of cytokines and other factors involved in the *Mycobacterium tuberculosis* infection

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Abstract

Mycobacterium tuberculosis (*Mtb*) is a pathogen that is widely distributed geographically and continues to be a major threat to world health. Bacterial virulence factors, nutritional state, host genetic condition and immune response play an important role in the evolution of the infection. The genetically diverse *Mtb* strains from different lineages have been shown to induce variable immune system response. The modern and ancient lineages strains induce different cytokines patterns. The immunity to *Mtb* depends on Th1-cell activity [interferon-γ (IFN-γ), interleukin-12 (IL-12) and tumor necrosis factor-α (TNF-α)]. IL-1β directly kills *Mtb* in murine and human macrophages. IL-6 is a requirement in host resistance to *Mtb* infection. IFN-γ, TNF-α, IL-12 and IL-17 are participants in Mycobacterium-induced granuloma formation. Other regulating proteins as IL-27 and IL-10 can prevent extensive immunopathology. CXCL 8 enhances the capacity of the neutrophil to kill *Mtb*. CXCL13 and CCL19 have been identified as participants in the formation of granuloma and control the *Mtb* infection. Treg cells are increased in patients with active tuberculosis (TB) but decrease with anti-TB treatment. The increment of these cells causes down-regulation of adaptive immune response facilitating the persistence of the bacterial infection. Predominance of Th2 phenotype cytokines increases the severity of TB. The evolution of the *Mtb* infection will depend of the cytokines network and of the influence of other factors aforementioned.

Key words: *Mycobacterium tuberculosis*, Strains; Virulence; Host genetic; Immune response; T lymphocytes; Cytokines

Core tip: Cytokines are proteins that can alter the behavior or properties of the cell itself or of another cell. These proteins are involved in the immunopathology of different diseases. Study of the cytokines in *Mycobacterium tuberculosis* infection is very important. They participate in the establishment, persistence and

evolution of the infection. The intricate complexity of these regulating proteins stimulate the investigation to the search of more effective treatments that permit the eradication of a disease as tuberculosis which is one of the leading causes of mortality and morbidity worldwide despite efforts made by the scientific community.

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*) is one of the leading causes of mortality and morbidity in different age groups throughout the world, especially in developing countries. The World Health Organization reported an incidence of 8.6 million cases of TB globally. Most of the estimated number of cases occurred in South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India and China alone accounted for 26% and 12% of total cases, respectively. An estimated 1.1 million (13%) of the 8.6 million people who developed TB were HIV-positive. About 75% of these cases were in the African Region[1]. The latent form of *Mtb,* that represent one-third of the global population, can reactivate years after a primary infection when host immunity declines[2]. In Venezuela the TB prevalence in Warao children was 3190/100.000[3].

Mtb enters the body almost exclusively by the airway (95%). *Mtb* is usually located in the lungs, causing pulmonary TB, but in a variable proportion, can spread through the blood and it produces extra pulmonary tuberculosis, with involvement of the lymph nodes, pleura, genitourinary system, meninges and peritoneum[4].

Pulmonary TB is the main clinical form of the disease and is classified into primary and post-primary (or reactivation). The primary pulmonary TB is due to initial infection with tuberculous bacillus. The location of the primary focus is sub pleural in the mid lung segment. In these primary foci infiltration of lymphocytes, monocytes (MNs) and macrophages (MAs) occur. MAs engulf the bacilli and reach the hilar and mediastinal lymph nodes and occasionally supraclavicular or retroperitoneal causing lymphadenopathy. The injuries of the parenchyma and lymph nodes are resolved spontaneously with calcifications radiographically visible. The post-primary TB is due to endogenous reactivation of the bacillus present in residual foci located in the pulmonary apexes, kidney and/or adrenal glands, which were controlled at the time and remained dormant for many years[4].

Investigations appoint that TB pathogenesis can be divided in four events: inhalation of *Mtb*, inflammatory cell recruitment, control of mycobacteria proliferation and post primary *TB.* Mycobacteria persistence is associated to failure in the immune vigilance; reactivation of the disease, nearby bronchial damage and spreading of the *Mtb* to other areas of the lungs[4-9]. It has been shown that whereas 90% of infected individuals will remain latently infected without clinical symptom, 10% of the individuals infected with *Mtb* will develop active disease[10].

In developing TB, many factors participate, such as: (1) virulence of *Mtb* strain; (2) Mechanisms of *Mtb* Evasion; (3) Host genetic; (4) the coexistence environmental factors such as poverty, malnutrition and overcrowding, facilitate infection; and (5) immune response[11,12].

In this review, we discuss all the factors related with immune response and the participation of cells and regulating proteins in the *Mtb* infection. Also, overall information about the pathological-mechanisms inherent to the behavior of cytokines which allow explaining the clinical manifestations, the evolution of the disease and the resistance to drugs among other aspects, represent a substantial contribution to the knowledge of TB.

IMMUNE RESPONSE, FUNCTION OF THE CELLS AND CYTOKINES PARTICIPANTS IN THE *MYCOBACTERIUM TUBERCULOSIS* INFECTION

Immune response

Many models of animals have been utilized for the study and understanding of TB, such as: Mice[13], rabbits[14], guinea pigs[15], and Nonhuman Primates[16,17]. In addition, studies *in vivo* e *in vitro* in human have provided important insights.

These investigations and other have shown that the balance between host immunity and bacterial evasion strategies among other factors determine the control *in vivo* of *Mtb*. Innate and adaptive immune responses are important for the eradication of the microorganism Figure 1. Pathogen recognition receptors, Toll-like receptors, Nucleotide Oligomerization Domain (NOD)-like receptors, and C-type lectins, have all been implicated in recognition of mycobacteria and in the initiation of the cytokines response. Adaptive immunity is triggered when the bacterial infection eludes the innate defense mechanisms[18]. Gallegos *et al*[19] and Urdahl *et al*[20] have suggested that TB bacterium reside in an immune-privileged site during the earliest stages of infection. Mycobacteria invade the host's pulmonary alveoli, where adaptive immunity is activated. *Mtb* is initially phagocytized by macrophages, where the bacterium is able to survive[21]. Infected macrophages secrete Tumor necrosis factor-α (TNF-α) to recruit CD4+ and CD8+ T cells to the site of infection[22] where they realize effector functions. In turn, cytokines as Interferon-γ (IFN-γ) cause the activation of macrophages[23]. Bacteria are mainly killed by activated macrophages and by cytotoxic

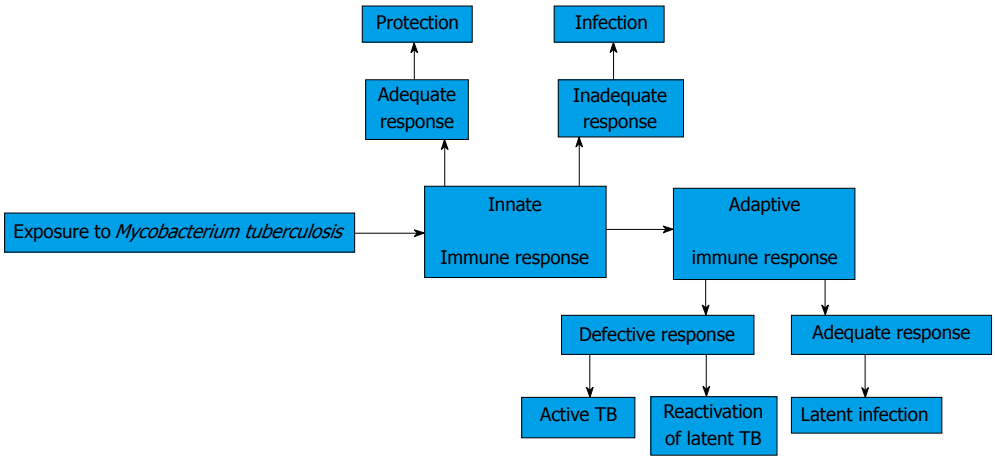

Figure 1 Innate and adaptive immune responses in the *Mycobacterium tuberculosis* infection. TB: Tuberculosis.

functions of activated CD4+ and CD8+ T cells or by TNF-α induced apoptosis of infected macrophages. The balance between pro-inflammatory and anti-inflammatory cytokines regulates the effectiveness of the immune response and tissue damage. Recent studies have demonstrated a role for B lymphocytes towards protection against mycobacterial infections[24]. These lymphocytes form evident aggregates in the lungs of tuberculous humans, non-human primates and mice, which show features of germinal center B cells. These cells can regulate the T cell response, cytokine production and the level of granulomatous reaction[25].

Granulomas form when an intracellular pathogen or its constituents cannot be totally eliminated. These consist of a central core of infected macrophages. The core can include multinucleated giant cells surrounded by epithelial cells. Other cell types are recruited such as: DCs, lymphocytes and fibroblasts. The collagen as element of extracellular matrix integrates the granuloma. This circumscribes the infectious process and also affects immunopathologically sites, where located[26,27].

Matrix metalloproteinases-9 (MMP-9) from epithelial cells initiates recruitment of monocytes to the developing granuloma. During reactivation, granulomas become caseating and necrotic, and the increment of MMP-1 secretion from macrophages allows the degradation of collagen and tissue destruction, which culminates in *Mtb* released into the airways. Experimental studies have revealed the importance of metalloproteinases. Mice treated with an inhibitor of MMPs delayed the formation of granuloma or these were smaller with more collagen. The exact mechanisms by which this balance is achieved, and how it breaks down are unknown. After many years, the organisms emerge from latency to develop post primary tuberculosis that produces cavities in the lungs where the proliferation of large numbers of bacteria occurs and the cough that the patients present facilitate transmission to new hosts[26,27].

Function of the cells

Many cells take place in the immune response in the *Mtb* infection. Also, the regulating proteins that secrete these cells form a complex network that traduces pathological change in cells and tissues. All this determines an active and latent form of the infection which depends of the evolution in time[4].

Phagocytic cells

Neutrophils are among the earliest cells to migrate to the site of *Mtb* infection and evidence exists that these phagocytes participate in the granulomatous reaction[28,29]. Increased neutrophil infiltration has been associated with excessive lung pathology and with poor bacillary control in genetically susceptible mice[30,31]. It has been proposed that neutrophilia is indicative of failed Th1 immunity in response to the use and challenge with aerosol *Mtb*[32]. There is also evidence suggesting that interaction of *Mtb* with neutrophils increment DCs migration to the draining lymph nodes thereby promoting the initiation of adaptive immune response in an aerogenic tuberculous infection[33].

Researchers have evaluated the significance of neutrophils in the protection against *Mtb* and conflicting results have yielded[28,30,34-39]. The role of these professional phagocytes in TB is yet to be clearly defined. However, the roles of neutrophils in development of immune response to *Mtb* could depend on the characteristics of the site of immunological reaction and the level of neutrophilia, as well as other immune system factors[40].

Mtb-induced neutrophil extracellular traps (NETs) were found to be reactive oxygen species and phagocytosis dependent. NETs binding heat shock protein 72 (Hsp72) or recombinant Hsp72 were able to trigger cytokine release from macrophages. NETs can participate in the innate response and influence the immune regulation[41].

The macrophages are activated for many stimuli in the course of an immune reaction and are important in the innate and adaptive immune response. Special attention has been given to macrophages and dendritic cells during the *Mtb* infection. In the pathogenesis of TB,

macrophages are the first-line of defense as the TB bacilli enter the airways[42-45]. *Mtb* has several mechanisms for persisting in human tissues[46-48]. The necrosis of *Mtb*-infected macrophages is considered as the dominant form of cell death instead of apoptosis[47,49,50].

Mtb also promotes its replication by inhibiting the apoptosis of infected macrophages[51]. Apoptosis-associated biomarkers, rather than inflammatory cytokines, are independent factors in predicting active TB. Among the apoptosis-associated biomarkers, Decoy receptor 3 (DcR3) seems to be the most associated with immune cells[52-54]. It has the potential to discriminate between latent and active TB. If 99% of active TB cases can be identified by DcR3 plus PGE2, these both will be useful as a screening criterion[55].

Researchers have demonstrated that *Mtb* suppresses the pyroptosis by macrophages, and possibly in dendritic cells. Pyroptosis is a cell death that is accompanied by the release of pro- inflammatory cytokines from the dying cells and attracts an innate response to the site of infection. This mechanism is different to apoptosis and necrosis[56].

A study has demonstrated that culture conditions can promote or limit replication of the bacteria in macrophages. Also, the cytokines had different effects depending on: the cell period (differentiation or activation), time (early or late) of exposure, concentration of the cytokines, and the magnitude of the microbial challenge. The authors had demonstrated that 40% human plasma, under 5%-10% oxygen, and the involvement of granulocyte macrophage colony-stimulating factor (GM-CSF), TNF-α, followed by IFN-γ, limit the replication of the bacteria in macrophages. However, if fetal bovine serum is used, 20% oxygen, GM-CSF, higher concentrations of regulating proteins, and there is premature exposure of IFN-γ, the control of the infection by phagocytic cells is lost. Even, GM-CSF and/or TNF-α contributed with the most successful cellular differentiation, whereas IFN-γ and TNF-α allowed for the best activation. The new culture method will favor the study of antimicrobial mechanisms of human macrophages[57].

Mature dendritic cells (mDCs) are antigen presenting cells. DCs capture Ags of *Mtb* and transport it to the lymph nodes for T cell priming and T helper type 1 polarization because they are important secretors of Interleukin-12 (IL-12) after bacterial stimulation. In contrast, macrophages realize their microbicidal function in the granuloma because they are more efficient in killing intracellular *Mtb*[58,59] and for the maintenance of the Th1 polarity. The IL-12-secreting DCs are considered as the bridge between innate and adaptive immunity in TB, with important implications for DCs-based vaccine designed strategies[60,61]. However; the increment of Cortisol affects significantly the functions of *Mtb*-induced DCs. It has demonstrated a cross-regulation between adrenal steroids and the function of antigen-presenting cells in TB[62].

B lymphocytes

B cells contribute to adaptive immunity by secreting antibodies. Studies have shown that the administration of an *Mtb* high dose in aerosol[63] or intravenous[64] provoke in B cell-deficient mice higher bacterial loads compared to control mice. However, low dose does not alter lung bacterial burden[65-68].

The lungs of *Mtb*-infected B cell-deficient mice display exacerbated inflammation, with enhanced neutrophil recruitment[63]. Experimental evidence suggests that humoral immunity plays a role in the regulation of the Th1 response in TB[69]. It has recently been reported that a subset of B cells (CD19+, CD1d+, CD5+) in the blood of humans with tuberculous infection can suppress pro-inflammatory Th17 phenotype[70].

The lung neutrophilia and enhanced Th17 response seen in *Mtb*-infected B cell-deficient mice could be reversed by passive immune serum therapy, increasing the possibility that immunoglobulins may contribute to the regulation of some immune system cells. Researchers have demonstrated that B cells are required for the development of optimal protective anti-TB immunity upon BCG vaccination by regulating the IL-17/neutrophilic response[40]. The presence of antibody to Ag85 in the sera of TB patients has been associated with a good prognosis[71]. However, studies of B cell immunodeficiency in both humans[72,73] and mice[66,67] have questioned whether these lymphocytes impart a protective effect against *Mtb*.

Investigators based in their results appoint that the participation of B lymphocytes in tuberculous infection is phase-specific. These cells participant in the granuloma formation during the acute infection maintain the local response against *Mtb* and prevent reactivation of the disease during its evolution[29,63,74].

A more recent study has demonstrated that when antibodies interact with stimulatory FCγ receptors of the antigen presenting cells enhance the Th1 response (Predominance of IFN-γ) which controls the infection. Interaction of the antibodies with inhibitory FCγ receptors compromises the anti-bacterial immunity (Predominance of IL-10)[24].There exist immunopathological differences in each case[69]. Other researchers have revealed that the immunity to *Mtb* can be modulated by B cells "in an organ specific manner" with the participation of cytokine production and macrophage activation[75] (Figure 2).

T lymphocytes

Armed effector T cells are crucial to almost all adaptive immune response. Alterations of the Th cells functions conduce to inefficient clearance of pathogens and can cause inflammation and autoimmunity[76].

The reasons for the impaired *Mtb*-specific T cell function in active tuberculosis remain controversial. Patients with mutations in Th-1 cytokine signaling pathways such as IFN-γ and IL-12 (a p40 and p35 heterodimer) are susceptible to overwhelming infection with *Mtb*[77,78]. Impaired Th1 lymphocyte response in *HIV* infection also produces ineffective immunity to *Mtb*[79]. Several observations suggest that the Th2 cytokines, IL-4 and IL-10, are associated with LTB infection, reactivation

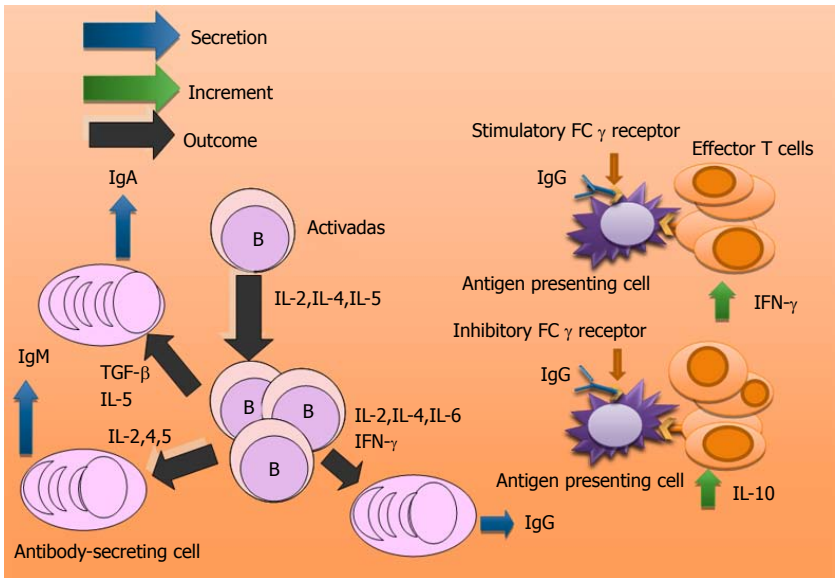

Figure 2 Cytokines involved in antibody secretion in the *Mycobacterium tuberculosis* infection. Interaction of IgG with stimulatory or inhibitor receptors and the secretion of cytokines. TGF-β: Transforming growth factor-beta; IL: Interleukin; IFN-γ:Interferon-γ.

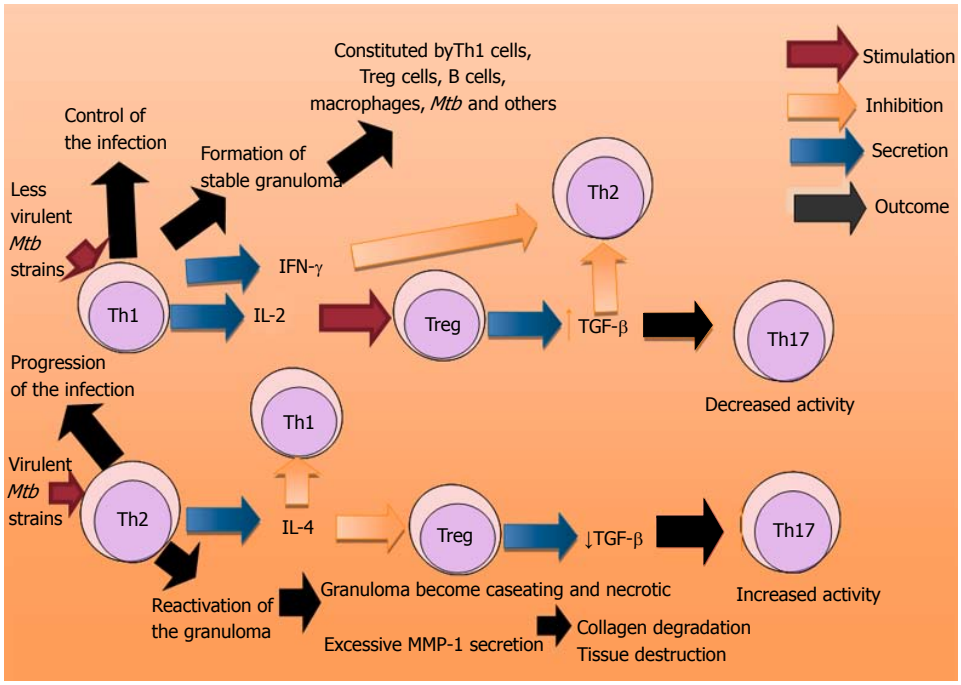

Figure 3 Participation of Th1, Th2, Th17 and T reg phenotypes in the evolution of the *Mycobacterium tuberculosis* infection. TGF-β: Transforming growth factor-beta; IL: Interleukin; IFN-γ: Interferon-γ.

and advanced TB[80,81].

Patients with extrapulmonary disease have immune responses *in vitro* suggestive of Th1 response, whereas patients with miliary/disseminated disease have a suggestive Th2 response[82]. There are several lines of evidence suggesting that overexpression of Th2 cytokines increases the severity of TB, including observations that virulent *Mtb* strains preferentially induce Th2 cytokines expression, whereas less virulent strains induce Th1 cytokines, including IFN-γ and TNF-α[83-85] (Figure 3). There are many factors that can change the immune response in different pathologies, such as: the etiological agent and its immunogenicity, evasion mechanisms of the pathogen, the type of pathology, the phase of the clinical entity, concurrent infections and infestations, the host genetic condition and the sufficiency or insufficiency of the immune system among others[86] (Figure 4). Thereon, authors express that coincident hookworm infection exerts a profound inhibitory effect on protective Th1 and Th17 response in latent TB and may predispose toward the development of active TB in humans[87].

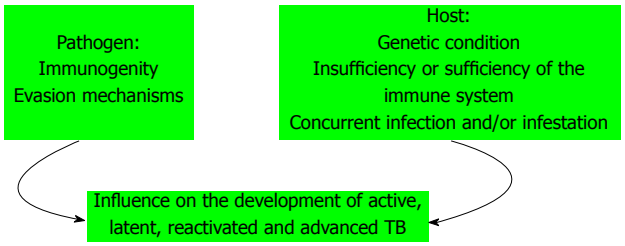

Figure 4 Factors involved in the evolution of *Mycobacterium tuberculosis* infection. TB: Tuberculosis.

In the antigenic presentation the function of MHC class II molecules is to present peptides generated in the intracellular vesicles of B cells, macrophages, and other antigen-presenting cells to CD4 T cells. CD4+ T cells are required for the control of intracellular *Mtb*. The depletion of CD4 T cells increases in quantitative form the bacterial burden associated with MHC II (+/+) cells but not MHC II (-/-) cells[88].

There is no doubt that immunity to *Mtb* depends on Th1-cell activity (IFN-γ and IL-12 and the production of tumoral necrosis factor-α), but Th1 immunity alone is not sufficient to protect the host from *Mtb* infection, development of the disease, or dissemination[8]. For other authors, active TB is characterized by a profound and prolonged suppression of *Mtb*-specific T cell responses, as evidenced by decreased production of the Th1 phenotype cytokines as IL-2 and IFN-γ[89-93]. Overproduction of immunosuppressive cytokines (IL-10 and Transforming growth factor-β) by mononuclear phagocytes has been implicated in decreased T cell function during TB[94-97]. Other studies are controversial with respect to IFN-γ serum levels. These reported in active TB levels significantly higher than in patients during anti- TB therapy, in patients after treatment, in contact and in healthy control. Also, they observed the increment of IL-10, IL-6 and decrease of IL-4[98].

The predominance of Th1 phenotype plays a relevant role in immunity to TB in children. The children are more prone to developing extrapulmonary manifestations of TB than adults. Pediatric TB is characterized by diminished Th1, Th2 and Th17 phenotype cytokines, which favor the development of neurologic TB, suggesting a crucial role for these cytokines in protection against pediatric tuberculosis. Among children with extrapulmonary TB, those with neurologic involvement exhibited a more significantly diminished Ag-driven IFN-γ and IL-17 production[99].

Investigations have implicated Regulatory T cells (Treg) in the pathogenesis of *Mtb* infection. The induced Treg cells (iTreg) are differentiated from naïve T cells in the presence of Transforming growth factor β following T cell receptor (TCR) stimulation. These cells produce large amounts of IL-10 and Transforming growth factor-β[100,101]. Unlike Th1, Th2 or Th17 cells, iTreg displays immune-suppressive activity with minimal antigen specificity[102]. Tregs are increased in the peripheral blood of active TB patients compared with *M. bovis* BCG vaccinated healthy donors. This agrees with recent reports in humans[103] and in the murine TB model[104,105]. It has been demonstrated that Treg cells proliferate and accumulate at sites of infection, and have the capacity to suppress immune responses[105]. Circulating Treg cells in the peripheral blood declined progressively by anti-TB treatment[106].

During the initial T cell response to *Mtb* infection, the pathogen induces the expansions of Treg cells that delay the onset of adaptive immunity, suggesting that *Mtb* has sequestered Treg to allow that the bacterium replicate endlessly in the lungs until T cells finally arrive[107]. The increase of these cells causes down-regulation of adaptive immune response facilitating the persistence of bacterial infections. The induction of Treg by *Mtb* can be an evasive mechanism of the bacterium that permits its replication[108]. Studies have appreciated in active TB infection high levels of circulating Treg cells which inhibit the Th1 response but not the Th17, facilitating the bacterial replication and tissue damage. The presence of persisting immune activation and high frequencies of Treg lymphocytes may reflect immune dysregulation that predisposes individuals to clinical tuberculosis, specifically to extrapulmonary TB[109,110].

CD8 +T cells secrete preformed perforins and granzimes that act over the target cells to die via apoptosis. A study has demonstrated reduced numbers of CTLs expressing low levels of perforin and granulysin, correlated with an elevated frequency of FoxP3+ Treg cells inside of the granulomas. Also, there are high levels of transforming growth factor-β that produce active immunosuppression at the local infection site. These results suggest that an imbalance in the proportion of effector T cells to Treg cells, present at the site of infection, may contribute to the establishment of TB infection[111]. A recent study has identified a mycobacterial protein and peptide recognized by γδ T cells isolated from pulmonary tuberculosis patients. The activated γδ T cells exhibited cytolytic effector function against BCG-infected cells and played a role in the recruitment and activation of other immune cells involved in the antibacterial response[112].

Studies reveal that cytokines network is formed with the participation of the regulating proteins and different subset of cells to achieve control, persistence and severity of TB (Figure 3).

Natural killer cells

Natural killer cells (NK) are important components of innate immune system and mediate resistance against intracellular pathogens. Their cytotoxicity is modulated by a wide variety of cell surface receptors. Both inhibitory and activating receptors encoded by killer immunoglobulin-like receptors (*KIR*) genes bind to HLA ligands to control the activation NK. Not much is known about KIR genes and their influence on the pathogenesis with *Mtb* infection. Activating genes KIR2DS1, KIR2DS5 and inhibitory genes KIR3DL1,

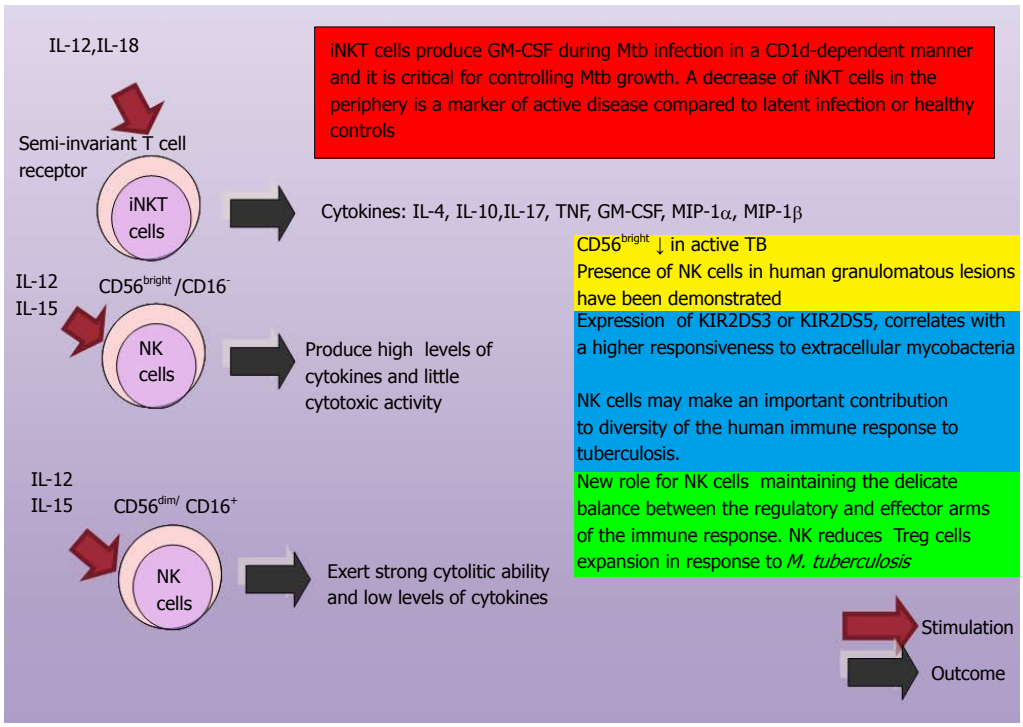

Figure 5 Participation of invariant natural killer T and natural killer cells in the control of *Mycobacterium tuberculosis* infection. iNKT: Invariant natural killer T; CD: Clusters of differentiation; MIP: Macrophage inflammatory protein; GM-CSF: Granulocyte macrophage colony-stimulating factor; TB: Tuberculosis; NK: Natural killer; IL: Interleukin.

KIR2DL3 conferred susceptibility towards TB either individually or in haplotype combinations[113]. A study demonstrated that the aerosol infection with *Mtb*, permit the expansion of the NK cell within the lungs, the expression of markers of activation, and the production of IFN-γ and perforin. These authors appoint that the depletion of NK cells did not affected the bacterial load. Redundant biological actions may be involved[114].

Before, was thought that the memory-like responses were limited to adaptive immunity. Recently, has been demonstrated that NK cells have the capacity for memory-like responses. Three steps have been proposed in the participation of NK cells for the control of infectious processes: initial infection, resolution of inflammation and new inflammatory challenge. An *in vivo* adoptive transfer system was used to determine the NK cell immune memory property. Cytokines secreted by macrophages and dendritic cells induced the production of IFN-γ by NK cells. IFN-γ active CPAs and the naive NK cells transform into memory like NK cells which will be prepared for a new infection and an effective control of the intracellular pathogens such as *Mtb*[115-117]. Investigations have demonstrated that human CD45RO$^+$ NK cells from pleural fluid cells (PFCs) of tuberculous patients express a "memory-like" phenotype that may have an important role in the defense against infection by *Mtb*[118] (Figure 5).

Osteoclasts

Virulent *Mtb* strains that infect multinuclear osteoclasts present an intracellular rapid growth and an osteolytic response, rather than inflammation. Also, highly-fused multinucleated osteoclasts incapacitated the production of cytokines and chemokines[119]. A study reveals that *Mtb* produces a protein called chaperonin Cpn60.1 which stimulates the human and murine monocytes cytokines sintesis. Also, it is a potent inhibitor of osteoclastogenesis both *in vitro* and *in vivo* and is considered a potential cure for osteoporosis[120].

CYTOKINES AND THEIR PARTICIPATION IN THE ANTIBACTERIAL IMMUNE RESPONSE

Cytokines are proteins that participate in regulating the immune system in physiological entities such as pregnancy[121] and other pathologies: bacterial[86,108], viral[122,123], parasitic[124,125], allergic[126,127], rheumatologic[128,129] and neoplastic[130,131], and in deficiencies of Vitamin A and iron[132-134]. Their synergistic, antagonistic, redundant and pleiotropic biological effects can affect or not the immune response against *Mtb.* The cytokines can be regulated for the control of the immune system and the maintenance of homeostasis[86].

Study has provided important details on the *Mtb* lineage-specific patterns of growth and cytokine induction. The lineage 2 *Mtb* strains induce low levels of TNF-α and IL12p40, lineage 3 strains induce high levels of TNF-α, but low levels of IL12p40 and the lineage 4 strains induce high levels of both cytokines[135]. The Modern lineages (lineages 2, 3 and 4) induce lower levels

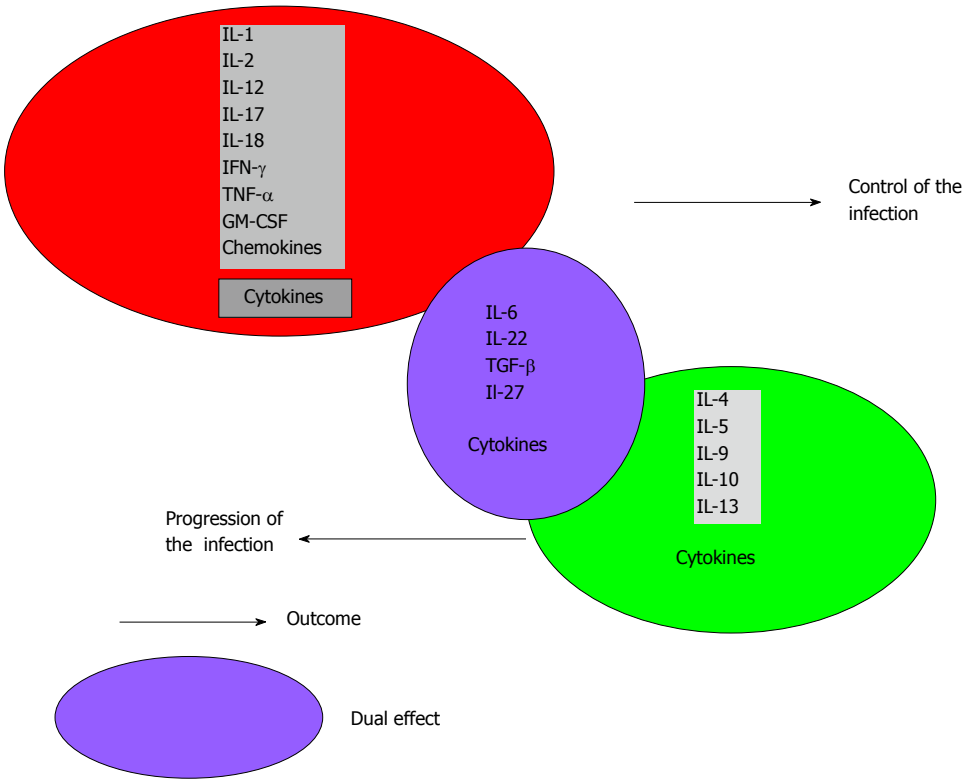

Figure 6 Cytokines in the control and progression of the *Mycobacterium tuberculosis* infection. The concentrations of cytokines, microenvironment and other factors contribute to modify the outcome. TGF-β: Transforming growth factor-beta; GM-CSF: Granulocyte macrophage colony-stimulating factor; IL: Interleukin; IFN-γ: Interferon-γ; TNF-α; Tumor necrosis factor α.

of proinflammatory cytokines when compared with ancient lineages (lineages 1, 5 and 6)[136]. The variability of the immune post challenge response with the strains of those lineages, establishes that studies realized without knowledge of the participant strain, conduces to controversial investigative results.

Strains of *Mtb* influence in the immune response and the evolution of the disease depending of their virulence. Strains of the modern or ancient Beijing (Bj) genotype, as well as the Euro-American lineage, have been used for the induction of ex-vivo cytokine production by PBMCs in healthy individuals. Regarding this, researchers have demonstrated that modern and ancient *Mtb* Beijing genotypes induced different cytokine patterns[137].

Every cytokine, based in its biological actions and interactions with elements of the immune system and other factors, will have a relevant effect in the control or eradication of the *Mtb* infection (Figure 6).

IL-1β

IL-1β directly kills *Mtb* in murine and human macro phages and promotes the recruitment of anti-microbial effector molecules. Also, it augments the TNF-α and Tumoral necrosis factor receptor-1 (TNFR1) cell surface expression and results in activation of caspase-3[138,139]. Vitamin D1, 25-dihydroxyvitamin D (1,25D) directly stimulates *IL1B* gene transcription which is important for macrophage response to *Mtb* infection[140].

Pro-IL-1β maturation is dependent on the NOD-like receptor 3 (NLRP3) inflammasome. IL-1β, in combination with 1,25D, leads to the control of mycobacterial proliferation in the macrophage. 1,25D deficiency is seen in patients with active tuberculosis. This vitamin generally boosts infection-stimulated cytokine/chemokine responses and increases its role in innate immune regulation in humans[141]. Researchers have appreciated a correlation between vitamin D deficiency and TB susceptibility[142,143].

IL-1β is important for host resistance to *Mtb* infection. It has been demonstrated by the significantly reduced survival of IL-1β$^{-/-}$ or IL1R$^{-/-}$ mice after infection[144-147]. Investigations realized in infected infants have shown reduced levels of IL-1 and the affectation of its productive capacity demonstrated immune vulnerability to TB in this population[148-150]. A role for IL-1 in human immunity against TB is supported by several studies showing an association between polymorphisms in the IL-1 or IL-1 receptor genes and host resistance[151-154]. The polymorphisms of *IL-1β* and *IL-10* genes may be valuable markers to predict the risk for the development of TB in household contacts[155]. Studies reveal that mice lacking the signaling adaptor molecule utilized by most membrane-bound TLR (MyD88) are extremely susceptible to TB[156-158]. Significant secretion of IL-1β was detected from macrophages cocultured with NETs from *Mtb*-activated neutrophils[41] (Figure 7).

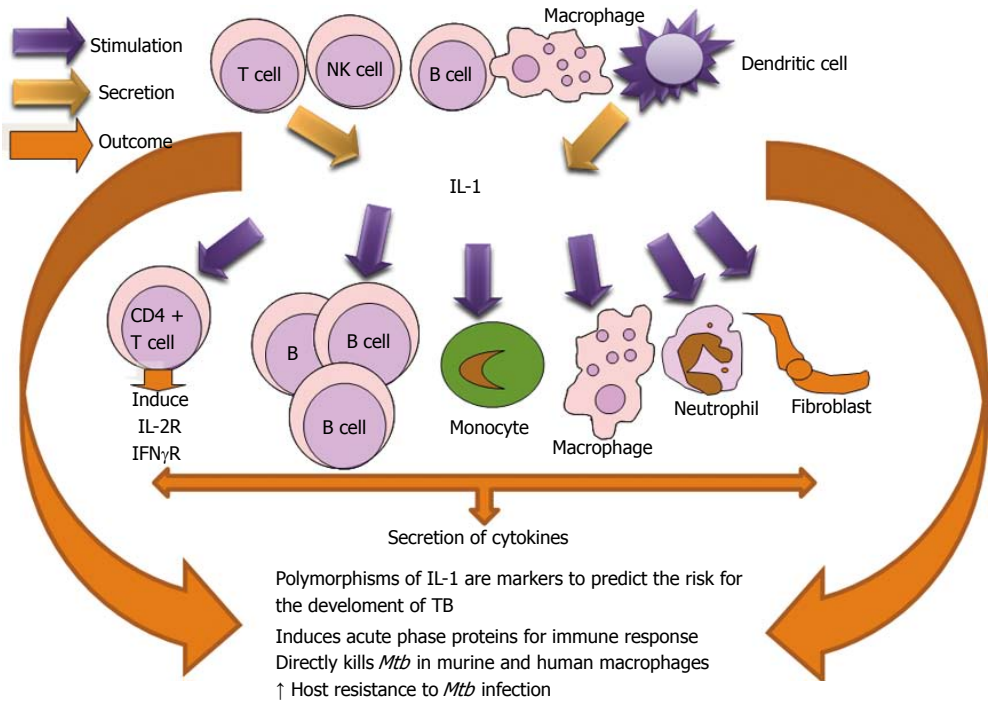

Figure 7 Biological effects of interleukin 1 in the *Mycobacterium tuberculosis* infection. TB: Tuberculosis; NK: Natural killer; IL: Interleukin; CD: Clusters of differentiation; *Mtb*: *Mycobacterium tuberculosis*; IFN: Interferon.

TNFα

TNFα is produced by the Th1, some Th2, and some CTL phenotypes. It induces nitric oxide production and activates microvascular endothelium among other biological actions. It is a cytokine whose deregulated expression may cause immunopathology[159,160]. However, in countries with a high incidence of TB, the biological therapy with anti-TNF-α has been associated with immunosuppression, reactivation of latent TB[161-163] and a risk of new *Mtb* infection[164,165].

The exacerbation of TB occurs with the breakdown of Granuloma which has an important role in the host protection against mycobacterial infections[166-168]. However, the host immunity can decline and provide chance to reactivate the latent form in the granulomas which can be a niche where mycobacteria might persist[169]. *Mtb* induces exacerbated inflammatory responses associated to important tissue lesions and dissemination of the bacilli into the airways[170].

Dysregulated TNF expression has been associated with defective host immunity due to excessive or inefficient inflammation[171]. In HIV patients with pulmonary TB, a clinical trial combining TNF inhibitors with anti-TB drugs showed that TNF inhibitors can be safely administrated during TB treatment and, in addition, higher responses to TB treatment were observed in the group of Enbrel (etanercept, soluble TNFR2-Fc) treated patients[172].

Mtb chemotherapy may be more efficient in the presence of a TNF inhibitor to clear bacilli and reduce lung pathology, which may be considered in acute and chronic *Mtb* infection[173]. However, for other authors the neutralization of TNF α produces disseminated disease in acute and latent *Mtb* infection without alterations in the granuloma structure in a cynomolgus macaque model[174]. TNF expression is necessary for controlling *Mtb* infection *in vivo* and TNF neutralization in monkeys and humans correlates with an increased risk of reactivation of latent tuberculosis[161,174].

Infection of human alveolar macrophages by *Mtb* has been reported to be sufficient to induce apoptosis mediated by TNF-α in an autocrine/paracrine manner and proinflammatory cytokines directly or indirectly modulated apoptotic response depending on the degree of virulence of the strain[175]. It has been observed that serum TNF α and Malondialdehyde (MDA) measure ments may play an important role in the evaluation of the inflammatory phenomena in TB[176]. Also, a positive correlation was found between an increase in serum TNF-α levels and clinical deterioration in patients with a severe form of TB[177] (Figure 8).

IL-2

IL-2 is produced by Th0, Th1 and some CTL. It stimulates growth of B, T and NK cells and is essential for cellular immunity and granuloma formation in *Mtb* infection. The IL-2 liberation is stimulated by TB-specific antigens and was significantly higher in TB patients than in healthy controls and suggested that IL-2 could be a potential biomarker for diagnosing TB[178-180]. The detection of IL-2 and IFN-γ permits to discriminate between active and latent tuberculosis when compared with controls[181]. Another study did not appreciate the utility of the IL-2 as a diagnostic biomarker for TB

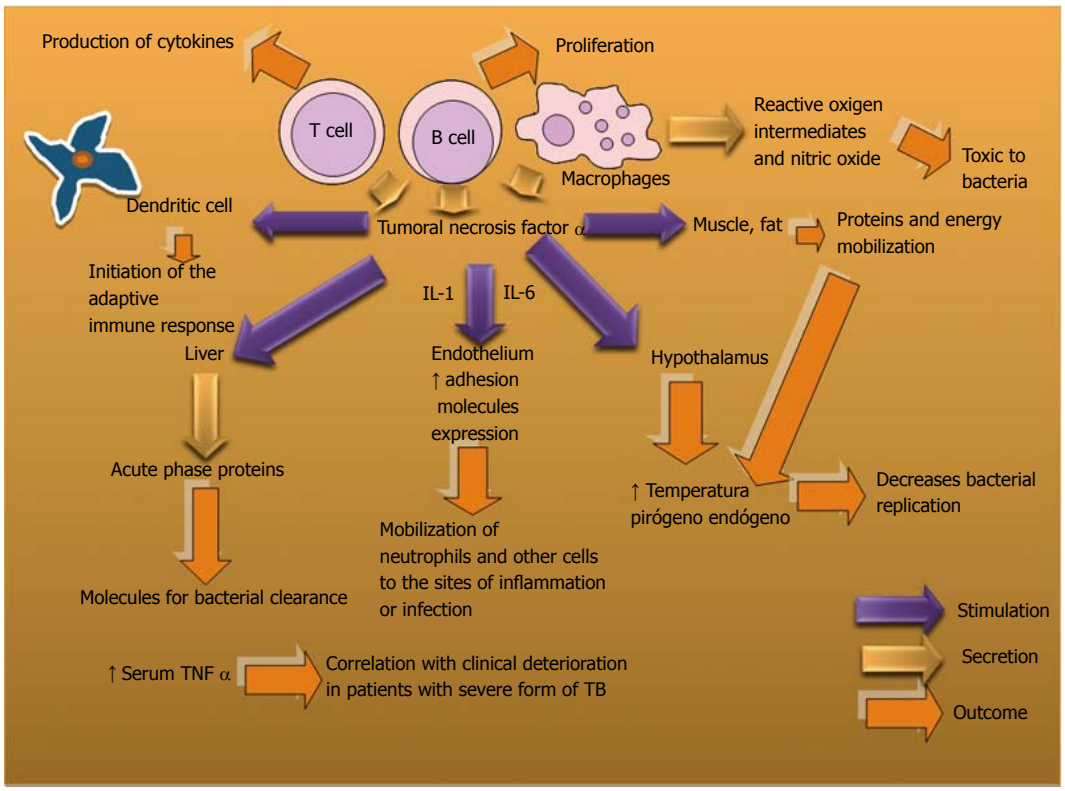

Figure 8 Biological actions of Tumor necrosis factor α to control *Mycobacterium tuberculosis* infection. TB: Tuberculosis; IL: Interleukin.

infection due to its low amount released[182]. Studies have reported that IL-2 and IL-9 expressions are elevated in PBMC (Stimulated by ESAT-6) from TB patients[183,184]. Researches demonstrated that immunotherapy with both IL-2 and GM-CSF may be useful to treat multidrug resistant tuberculosis (MDR-TB). Mice receiving immunotherapy developed fewer lesions in the lungs compared with mice receiving antibacterial therapy alone[185] (Figure 9).

IL-4

IL-4 is produced by lymphocytes Th2 and activated mast cells. This cytokine stimulates the IgG4 and IgE isotype change, acts as an autocrine growth factor for Th2 lymphocytes, also, inhibit the development of Th1 and Th17 lymphocytes and participates in the activation of macrophages[76,186].

Increased production of the Th2 cytokine (IL-4) by bronchoalveolar lavage cells (BAL) is a strong risk factor for TB transmission in South African patients. Increasing IL-4 was associated with BAL PMNs and negatively associated with BAL lymphocytes. IL-4 has been implicated in conversion of LTB infection to active TB[187]. IL-4 has been postulated as key in TB pathogenesis, especially with its ability to down-regulate inducible nitric oxide synthase, Toll-like receptor 2, and macrophage activation[188].

Clinical studies involving patients with latent TB show a clear correlation between the intensity of a Th2 response and the risk of developing active disease and in particular a direct correlation between the level of IL-4 messenger RNA and disease severity[189]. The induction of IL-4 production by DCs generated by BCG-infected monocytes could explain the failure of the BCG vaccine to prevent pulmonary TB[190]. It has been demonstrated that high levels of IL-4 were associated with disease progression in TB-susceptible families when there is lack of IFN-γ expansion. Resistant families have overrepresentation of IFN-γ +874 A allele and an increment of IFN-γ secreting cells[191]. Authors agree in relation to the worsening of the host immune response to *Mtb* due to the effects of IL-4[191,192]. However, the mechanisms of inhibition may be different. Inhibition of autophagy through the autocrine secretion of IL-4 and/or IL-13 by infected macrophages could allow that the bacteria gain a foothold previous to the formation of a protective granuloma[193]. This effect on the autophagy has been demonstrated in murine and human macrophages[194] (Figure 10).

IL-5

IL-5 is produced by Th2 phenotype. It activates to eosinophil and stimulates its growth and differentiation. Also, it stimulates proliferation of lymphocytes and synthesis of IgA antibody[195,196]. This regulating protein may be a factor in the reduction of *Mtb*-specific T cell responses within coinfected (SIV/Mtb) individuals. Researchers found that neutralizing IL-5 in coinfected monocytes partially restored normal T cell TNF production[197]. The presence of eosinophils in the cellular infiltration at the site of mycobacterial infection strongly suggests that increased levels of IL-5 are

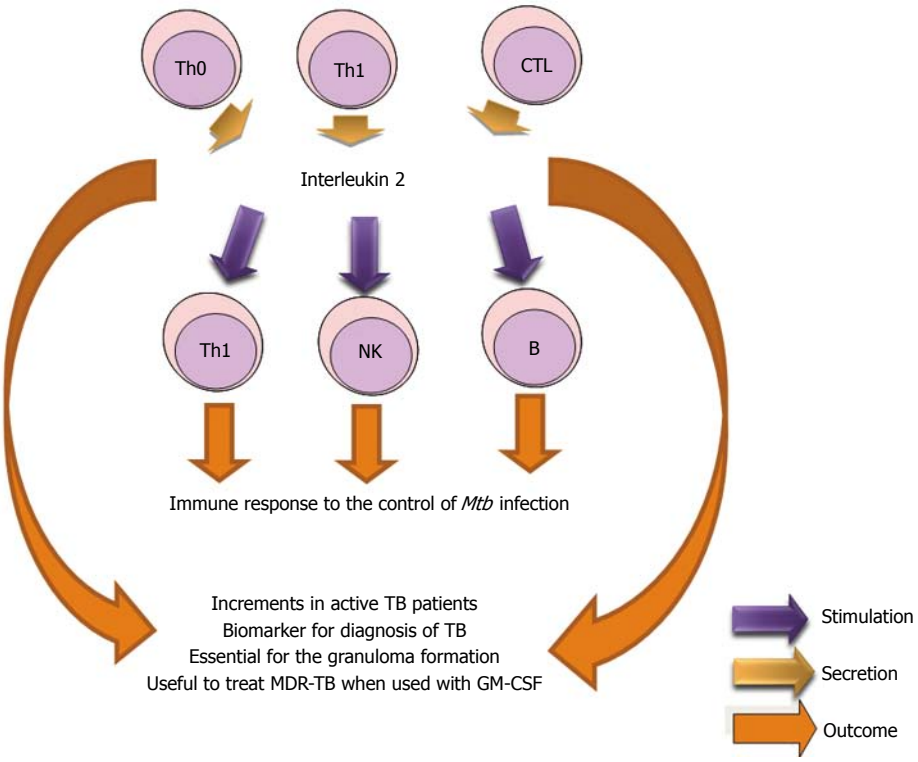

Figure 9 Role of IL-2 in *Mycobacterium tuberculosis* infection. TB: Tuberculosis; MDR-TB: Multidrug resistant tuberculosis; GM-CSF: Granulocyte macrophage colony-stimulating factor; NK: Natural killer; MDR-TB: Multi drug resistant tuberculosis.

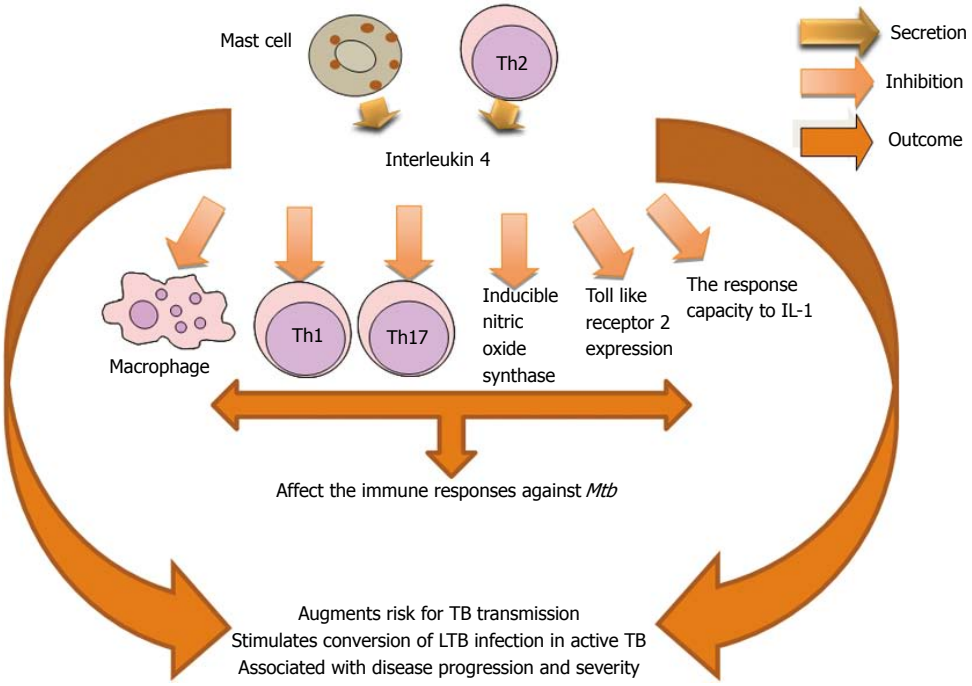

Figure 10 Participation of interleukin-4 in *Mycobacterium tuberculosis* infection. TB: Tuberculosis; LTB: Latent tuberculosis.

produced *in vivo* during *Mycobacterium bovis* bacillus Calmette Guérin (BCG) infection in the absence of IFN-γ signaling[198,199] (Figure 11).

IL-6

IL-6, IL-1 and TNF-α, are important inductors of the acute-phase response. These cytokines are termed endogenous pyrogens because they cause fever and derive from an endogenous source rather than from bacterial components. IL-6, together with the other cytokines aforementioned, has effect on hepatocytes, Bone-marrow, endothelium, hypothalamus, fat, muscles

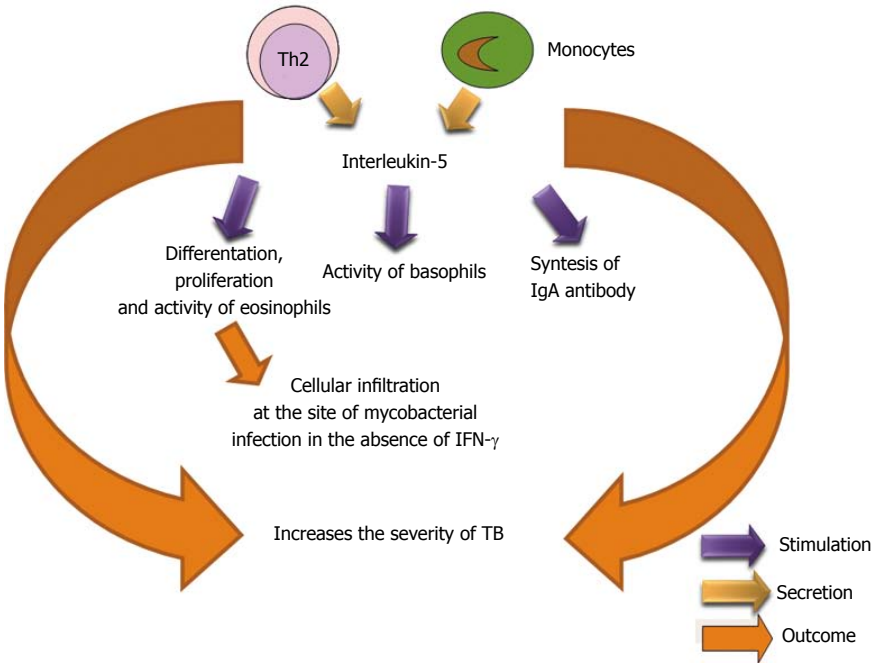

Figure 11 Participation of interleukin-5 in the *Mycobacterium tuberculosis* infection. TB: Tuberculosis; IFN-γ: Interferon-γ.

and DCs[200].

It has been reported that IL-6 plays an important role in protection against murine *Mtb* infection[201,202] due to the influence of the $CD4^+$ T cells response[203]. *Mtb*-infected IL-6-deficient animals show an impaired Th1 response and increased bacterial loads, indicating a requirement for IL-6 in host resistance to *Mtb* infection[201,204]. IL-6 down regulates macrophage microbicidal activity and IL-6 inhibits the production of INF-α and promotes *in vitro* growth of *Mycobacterium avium*[205,206]. IL-6 secreted by *Mtb*-infected macrophages suppresses the responses of uninfected macrophages to IFN-γ[207]. Increased levels of IL-6 in the lungs, along with increased levels of IL-1β and IL-11, is significantly correlated with tuberculosis progression in genetically susceptible mice[208]. Together, these mice studies indicate that IL-6 may play multiple roles and contribute both positively and negatively to host control of *Mtb* infection.

IL-6 has been shown to contribute to the differentiation and activation of cells of the immune response and others not related with this system[209]. It is associated with the pathogenesis of many chronic inflammatory diseases, including tuberculosis[208,210,211]. Genetic variants in *IL-6/IL-6R* have been linked to the susceptibility to the severity of a wide range of diseases, such as: respiratory tract infection, asthma, meningococcal disease, chronic hepatitis C virus infection and rheumatoid arthritis[212-216]. A rare genetic variation in the *IL-6* gene, rs1800796, is significantly associated with tuberculosis disease in the Chinese Han population[217]. Down regulation of IL-6R expression on CD4 T cells in patients with active pulmonary TB is associated with decreased of Th17 phenotype response, suggesting a role for IL-6 in the progression of TB in humans[217-219].

Lung parenchyma can be destroyed during active TB and it provokes immunological alterations for controlling the infection. Patients with radiographically advanced TB showed an increase of the inducible protein-10 (IP-10) and IL-6 production by BAL cells and these are biomarkers of non-cavitary TB. This may reflect an effective Th1 immune response for controlling TB and for attenuating the tuberculous lung destruction. The patients with lung cavities had a higher percentage of polymorphonuclear neutrophils (PMN) in BAL as well as lower IP-10 and IL-6 compared to those without cavities. Also, was demonstrated a negative association between IP-10 and PMN of BAL[220] (Figure 12).

IL-9

It is known that Th9 phenotype cells secrete the regulating proteins IL-9 and IL-10. Th9 cells are involved in the intestinal responses to helminths which were thought to be mediated only by the Th2 phenotype. Studies have demonstrated that the increased expression of IL-9 may contribute to the development of TB and it is associated with an impaired Th1 immune response in patients with tuberculosis[184,221]. Th9 cells with the phenotype of effector memory cells were found in tuberculous pleural effusion as compared with blood. Pleural mesothelial cells were able to function as antigen-presenting cells to stimulate Th9 cell differentiation. Further investigations are needed to reveal the function of this type of cells and their products in pathogen clearance and inflammatory diseases[76,222] (Figure 13).

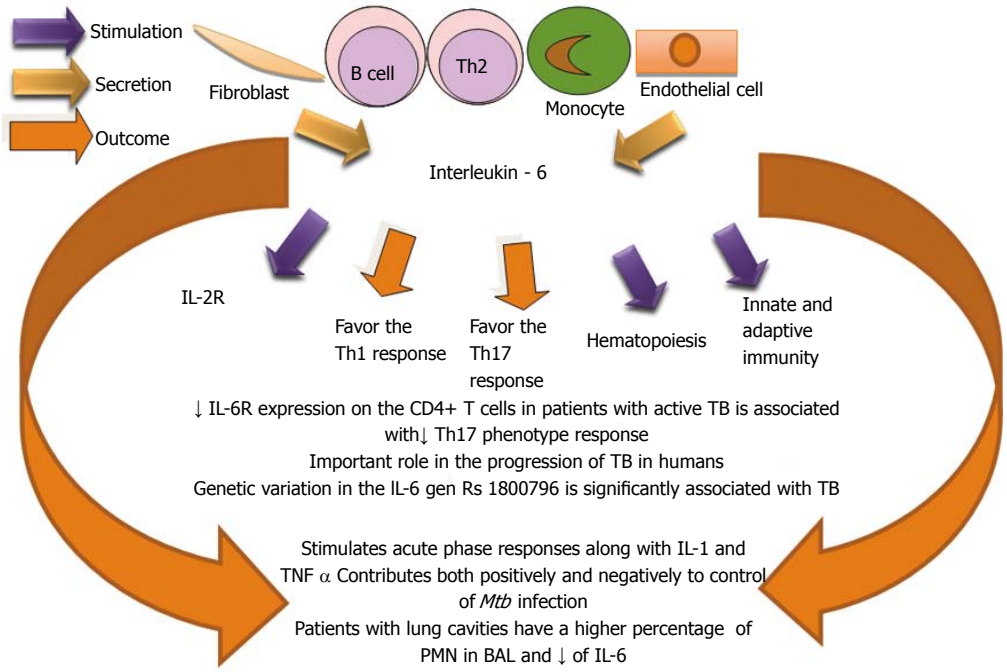

Figure 12 Role of interleukin-6 in the *Mycobacterium tuberculosis* infection. TB: Tuberculosis; PMN: Polymorphonuclear neutrophils; IL: Interleukin.

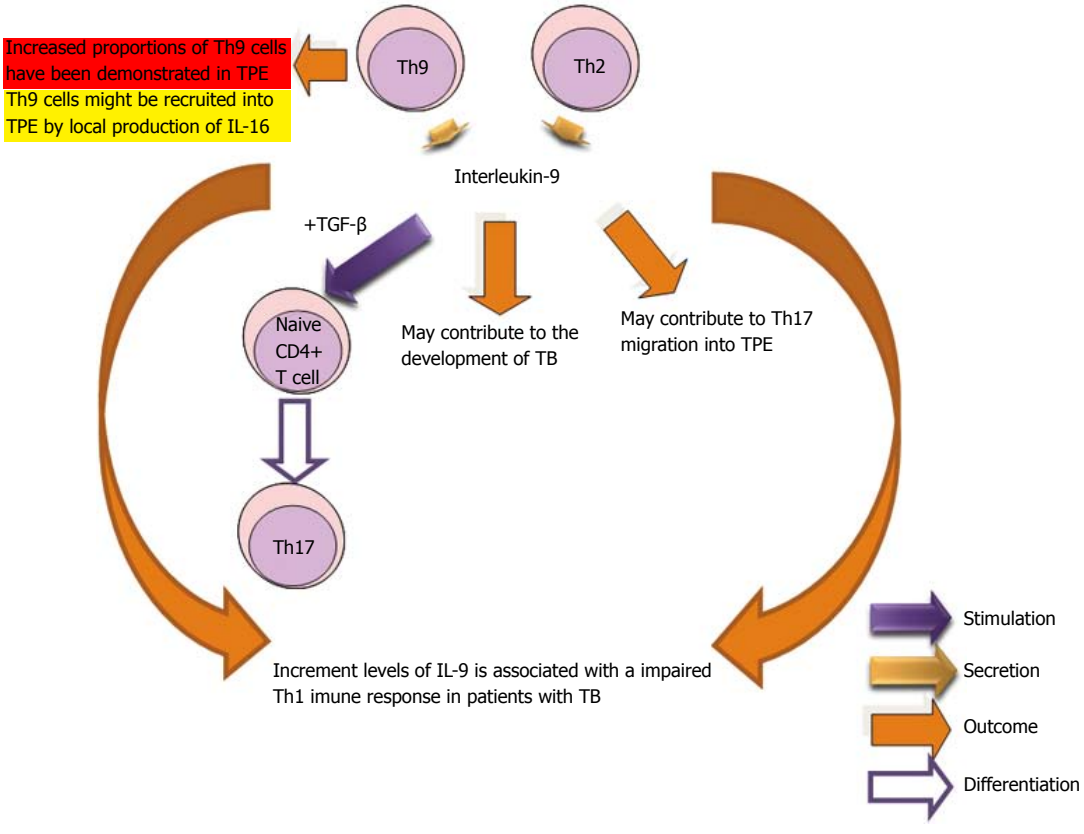

Figure 13 Participation of interleukin-9 in the *Mycobacterium tuberculosis* infection. TB: Tuberculosis; TPE: Tuberculous pleural effusion; TGF-β: Transforming growth factor-beta; CD: Clusters of differentiation; IL: Interleukin.

IL-10

IL-10 is an immunosuppressive cytokine that is produced by Th0, Th1, Th2 and T regs phenotypes among other cellular types. It inhibits Th1, augment MHC class II and gene knock-out of this regulating protein cause inflammatory bowel disease. IL-10 and transforming growth factor-beta (TGF-β) restrict T effector cell response[223]. Increase in $CD4^+CD25^+$ $FoxP3^+$ cells has

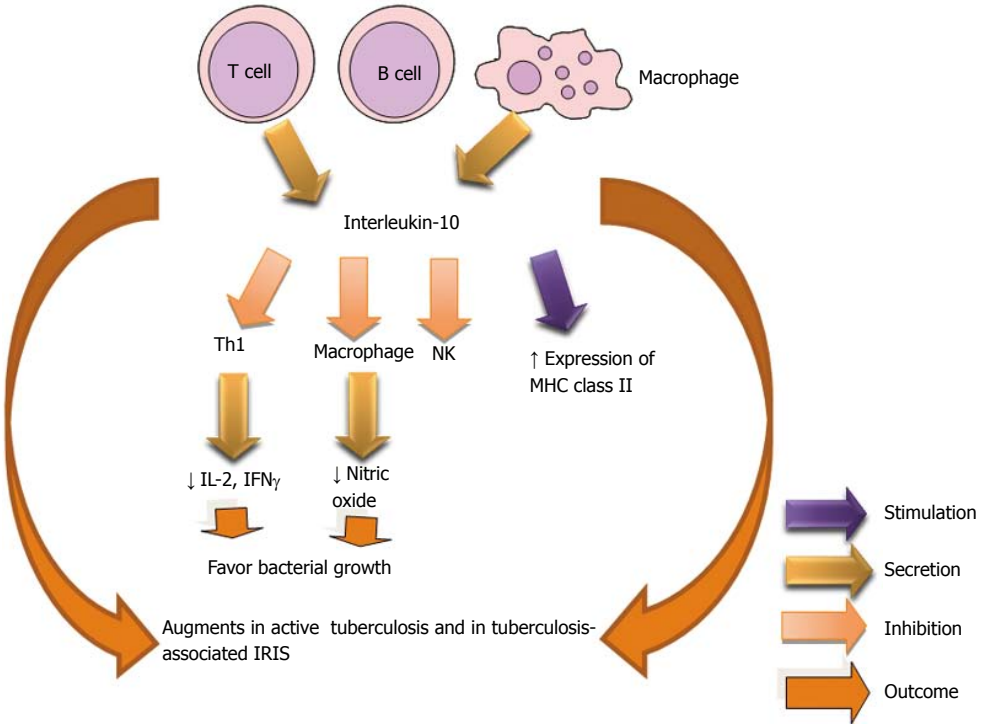

Figure 14 Influence of interleukin-10 in the control of *Mycobacterium tuberculosis* infection. IRIS: Immune reconstitution inflammatory syndrome; IFNγ: Interferon γ; NK: Natural killer; IL: Interleukin.

been shown to decrease Th1 cell responses in patients with TB[224]. IL-10 has been reported to modulate the innate and adaptive immune responses, potentially creating a favorable environment for the persistence of microbes, intracellular pathogens, and chronic infections[225]. The increased ability of macrophages to produce IL-10 when stimulated with Toll-like receptor ligands is also associated with an increased tendency to develop primary progressive tuberculosis[226]. Production of IL-10 has also been reported to be higher in patients who had active TB, compared with tuberculin skin test responders[227].

IL-10 plays an important role in Mtb infection, where the cytokine has shown to reduce the immunity. IL-10$^+$ T cells with immunosuppressive properties are present in anergic TB patients[228]. IL-10 decrease the macrophage activity in the Mycobacterium avium infection and the administration of monoclonal anti-IL-10 diminishes bacterial growth in the spleen[229]. IL-10 helps maintain mycobacterial infections[230]. It has been demonstrated *in vivo* that the production of IL-10 reactivates the chronic pulmonary tuberculosis[231]. The heterogeneity of macrophages may be determinant in disease outcome in intracellular bacterial infection as type I and II macrophages have opposite effects in the cellular immunity[232].

Study revealed an increase in the transcript levels of IL-10 and IL-22 in tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) patients, compared with non-IRIS controls. The serum samples showed statistically significant high concentrations of IL-10 and IL-22 cytokines in tuberculosis-IRIS patients[233]. Two forms of TB-IRIS are recognized: paradoxical and unmasking. The first manifests with new or recurrent TB symptomatology and second with an exaggerated and unusually inflammation. Both forms have occurred during the early anti retroviral therapy[234] (Figure 14).

IL-12 and IFN-γ

IL-12 is crucial for optimal differentiation and main tenance of IFN-γ-secreting antigen-specific Th1 cells[235,236], and in controlling mycobacterial infections in mice and men[237,238]. The increase of IL-12p40 production by BAL cells in sputum of patients with radiographically advanced TB reveals less effective immune control and more complications. It has been demonstrated that IL-12 receptor deficiency is found in healthy individuals with mycobacterial infections[77,187].

Parenteral administration of IL-12p70 to *Mtb*-infected IL-12p40-deficient mice restores CD4$^+$ T-cell production of IFNγ and control of bacterial growth in the lungs and spleen, whereas these effects are lost when administration of IL-12p70 is discontinued[235].

Researchers appoint that IL-12 enhanced the expression of granzyme B, activation inducer molecule (CD69), IL-2 receptor α chain (CD25), Natural Killer Group 2D (NKG2D), IL-12 receptors β1 and β2 on CD45RO$^+$ NK cells from pleural fluid cells (PFCs) from tuberculous patients. Also, they have demonstrated that CD45RO$^+$ NK cells produced significantly more IFN-γ and were more cytotoxic compared with CD45RO$^-$ NK

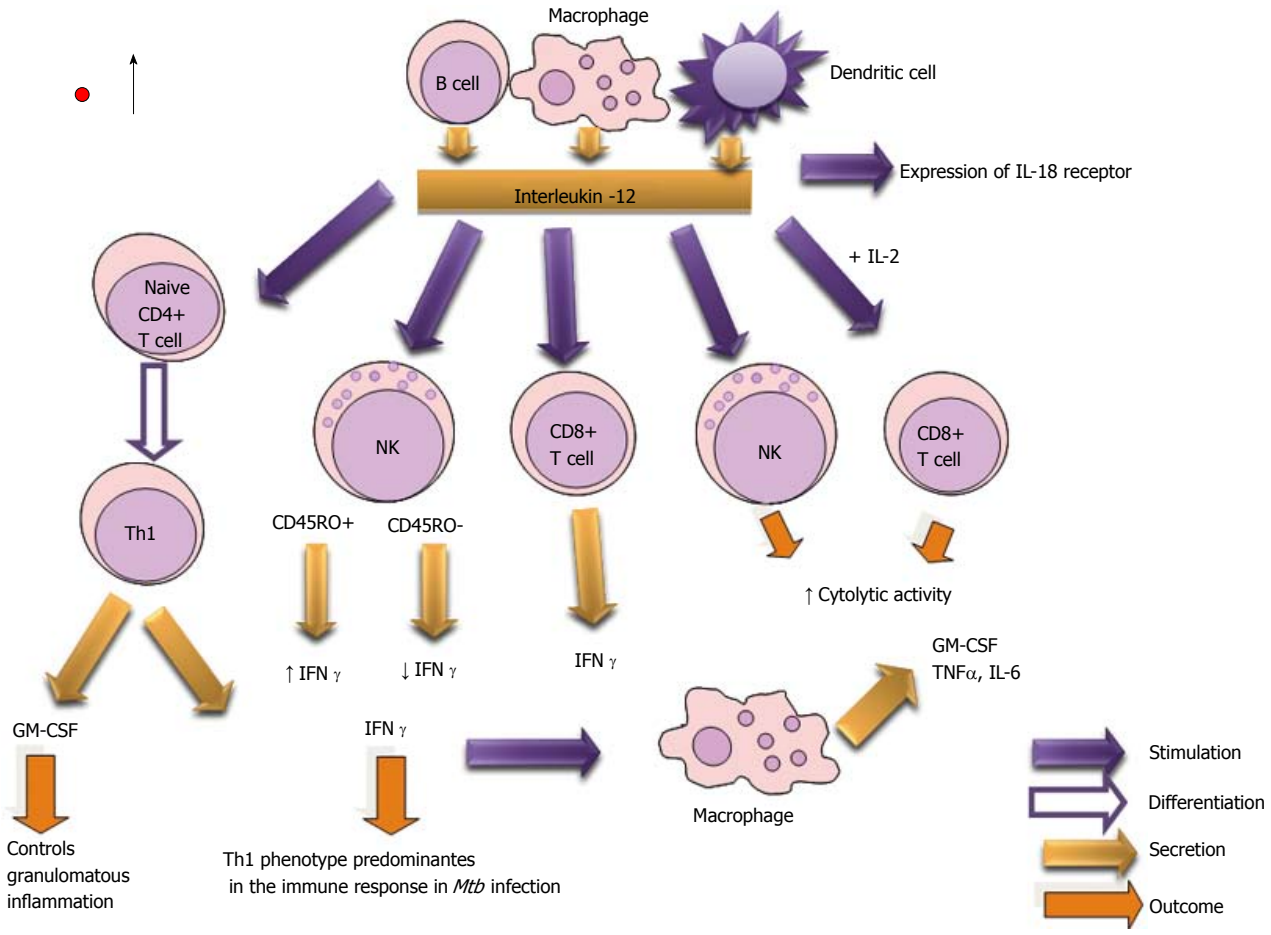

Figure 15 Biological actions of interleukin-12 to control of the *Mycobacterium tuberculosis* infection. GM-CSF: Granulocyte macrophage colony-stimulating factor; NK: Natural killer; CD: Clusters of differentiation; IL: Interleukin; IFN γ:Interferon γ.

cells from PFCs when stimulated with 12 IL-12. The activity of NK cells is associated with early resistance against *M. tuberculosis* infection[118,239] (Figure 15).

Another pro-inflammatory cytokine is IFN-γ which is secreted by Th1, CTL and NK cells. It participates in the synthesis of IgG2a, inhibits the phenotype Th2, activates NK cells and augment MHC class I and II. Also, the gen knock-out produces susceptibility to mycobacteria. IFN-γ has been shown to be an important mediator of macrophage activation involved in the control of a number of intracellular pathogens[240-247].

The active tuberculosis is 5-10 times more frequent in infants than adults. Also, the children have higher rates of severe disseminated disease. It has been shown that infant T cells are less capable of transforming into IFN-γ -producing T cells[244]. IFN-γ stimulated responses are lowered in TB, while the expression of Suppressor of Cytokine Signaling (SOCS) molecules-1 and 3 and $CD4^+CD25^+FoxP3^+$T regulatory cells are increased[247]. The enhanced susceptibility to mycobacterial infection of IFN-γ knockout mice[246,247], and of patients with genetic defects in IL-12/ IFN-γ pathway[248], provides strong evidence that IFN-γ is required in defense against *Mtb*.

BCG is a licensed vaccine in use that mediates immune protection through the production of IFN-γ by CD4 T cells, which activates macrophages to kill *Mtb*. However, some recent studies have reported a lack of correlation between IFN-γ production by CD4 cells and BCG-induced immune protection[249]. IFN-γ is necessary for the control of TB[23,250] and has been the focus of multiple coinfection studies. These studies conclude that HIV reduces IFN-γ production by *Mtb*-specific CD4 T cells in the periphery and airway[251-254].

Study reveals that dehydroepiandrosterone increments the antigen-specific T-cell proliferation and IFN-γ production induced by *Mtb*-stimulated DC. The adrenal axis is important in the modulation of the DCs function in the context of TB[62,255]. Mice deficient in IFN-γ ($IFN\text{-}\gamma^{-/-}$) or the IFN-γ receptor ($IFN\text{-}\gamma R^{-/-}$) are extremely susceptible to infection with tuberculosis-causing organisms[23].

Murine macrophage studies show that IFN-γ induces *Mtb* killing[23,255] but when *IFN*-γ gene has been disrupted is unable to contain or control sublethal dose of *Mtb*[256].

The secretion of IFN-γ and, to a lesser extent, of IL-17 by CD4 (+) T cells plays a major role both in protection and immunopathology[257]. But the effect of IFN-γ in human macrophages remains controversial[258,259]. Regard this, some researchers have shown that IFNγ

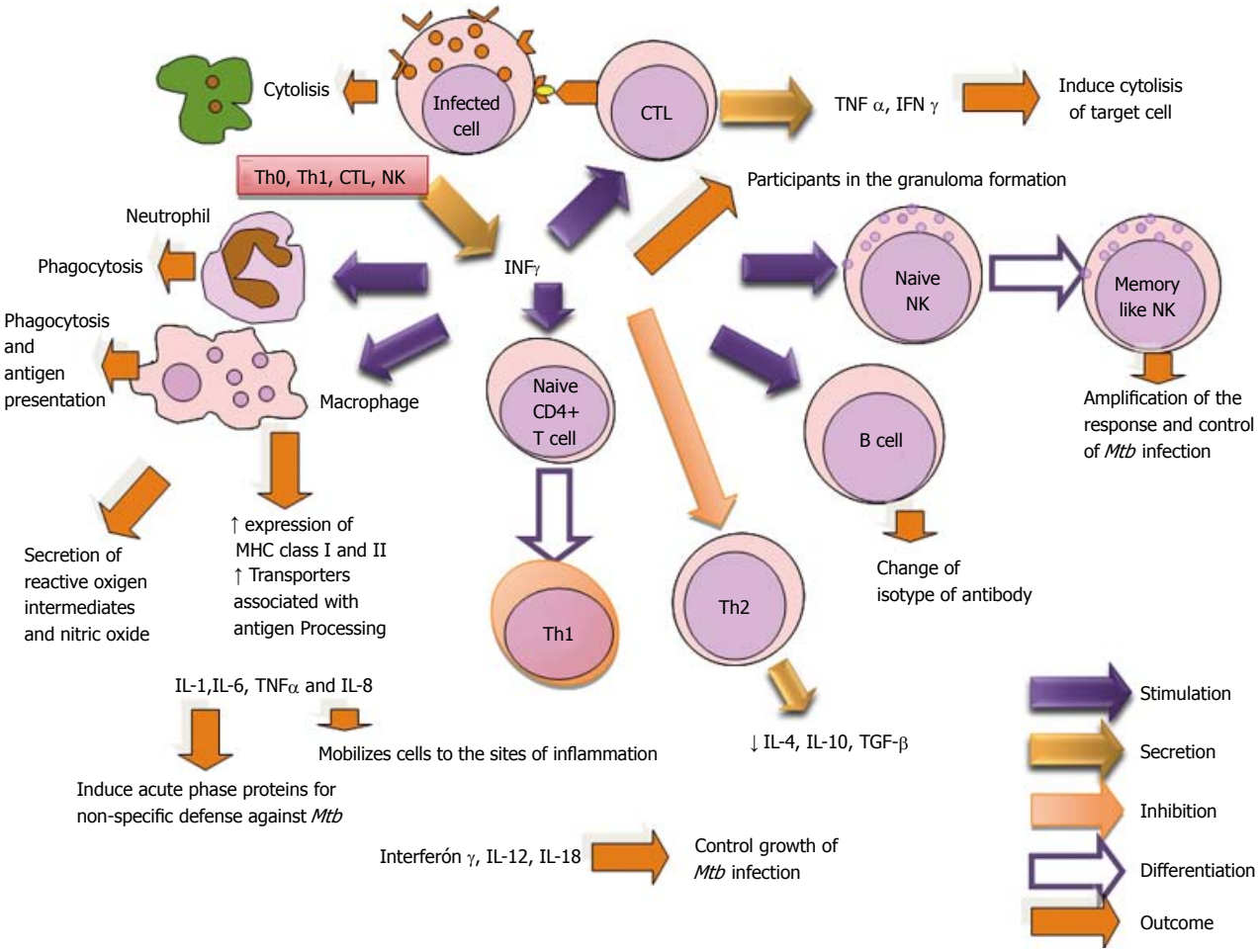

Figure 16 Biological actions of Interferon-γ in *Mycobacterium tuberculosis* infection. TGF-β: Transforming growth factor-beta; NK: Natural killer; CTL: Cytotoxic t lymphocyte; CD: Clusters of differentiation; IL: Interleukin; CTL: Computation tree logic; Th1: T helper type 1.

activates human macrophages to become tumoricidal and leishmanicidal but enhances replication of macrophage-associated mycobacteria[260]. For others the IFN-γ-mediated anti mycobacterial activity requires specific *in vitro* conditions for human macrophages, such as physiological O_2 levels and the presence of the GM-CSF[57]. Extracellular trap formation and mycobacterial aggregation are IFN-γ-inducible events and require the ESX-1 secretion system. In the absence of ESX-1, IFN-γ does not restore any extracellular trap formation, mycobacterial aggregation, or macrophage necrosis[261]. Therefore, the monitoring of the *in vivo* and *in vitro* metabolic activity of both slow-growing and fast-growing mycobacteria, using methods as chronoamperometry and chronopotentiometry is of great importance[262].

Th1 phenotype plays a relevant role in the formation of granulomas. IFNγ is the most characteristic cytokine produced by armed Th1 cells (Figure 16).

IL-13

IL-13 is produced by T lymphocytes and exerts its biological functions on B cells and monocytes, and inhibits pro- inflammatory cytokines production. It upregulated MHC class II expression, also, promotes IgE class switching. This cytokine is a key regulator of the extracellular matrix, and is redundant with IL-4. Concentrations of IL-13 were found to be significantly higher in fast responders to antimycobacterial treatment than in slow responders in the fifth week of treatment. The role of IL-13 in *Mtb* infection is not well defined. IL-13 abrogates autophagy-mediated killing of *Mtb* in human and murine macrophages[194]. However, IL-13 has modulated the resistance to a number of intracellular pathogens including *Leishmania major*, *L. mexicana* and *Listeria monocytogenes.* The elevated level of IL-13 observed in fast responders compared with slow responders may suggest their better resistance to the infection, although the mechanisms for the IL-13 effect are not yet clear[263]. IL-13 can be substituted for IL-4 in several physiological responses. However, the presence of IL-13 inhibits the action of IL-4 on *Mtb*-induced IL-8 secretion but does not affect the inhibition of IL-8 secretion by IL-10[264].

IL-4 and IL-13 are well recognized as activating distinct signaling cascades[83,265-268]. IL-13 inhibits IFN-γ-induced autophagy, but this process is independent of protein kinase B (AKT); instead it is dependent of the signal traducer and activator of transcription 6.

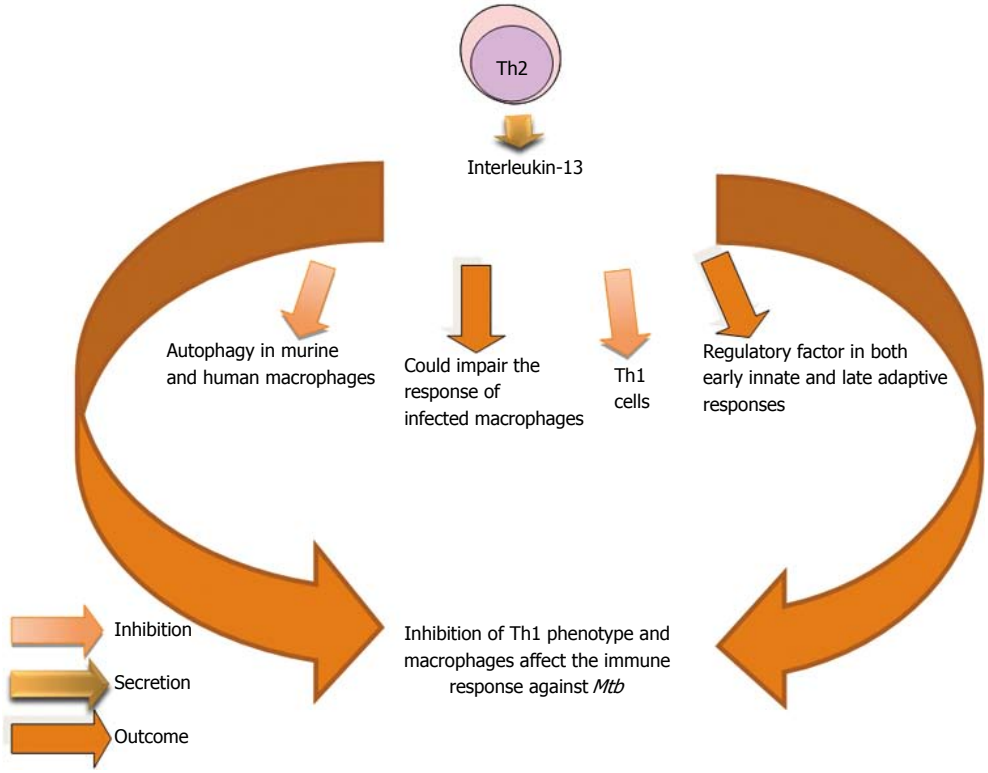

Figure 17 Participation of interleukin-13 in *Mycobacterium tuberculosis* infection. Th1: T helper type 1; Th2: T helper type 2; *Mtb: Mycobacterium tuberculosis*.

Autophagy is a major intracellular pathway for the lysosomal degradation. Therefore, IL-13 could specifically impair the response of infected macrophages[194].

IL-13 released by macrophages infected with virulent strains of *Mtb*[83,85] act in an autocrine manner to inhibit the autophagic process. Treatment of *Mtb*-infected macrophages with either IL-4 or IL-13 promotes the intracellular survival of the bacteria[194] (Figure 17).

IL-17

Generation of human Th17 cells is dependent on IL-23[269,270], IL-1β[269,271,272], TGFβ[270] and IL-6[272]. IL-17A is a cytokine that participates as an immunomodulator in chronic immunological diseases such as: rheumatoid arthritis and inflammatory bowel disease. It can control the pathological mechanisms in the *Mtb* infection through the dysregulating cytokines and chemokines production and promoting granuloma formation. It has been observed that IL-17A significantly enhanced the clearance of intracellular Bacillus Calmette-Guérin (BCG) by macrophages through nitric oxide (NO) -dependent killing mechanism[273].

During the initial stages of infection IL-17 acts on different types of cells and stimulates the secretion of antimicrobial peptides, granulocyte colony-stimulating factor (G-CSF) and cysteine X cysteine (CXC) chemokines. As DCs migrate to the lymph node, both Th1 and Th17 cell are differentiated. Chemokines in the infected lung promote recruitment of protective cells and a mononuclear granuloma is formed, where IL-23 and IL-6 are highly expressed. IL-17-producing cells accumulate in high numbers in the lungs and immunopathological consequences develop[274].

Other investigations appoint that the involvement of Th17 cells remains to be clarified in relation to TB. Researchers demonstrated that *Mtb*-specific Th17 cells are undetectable in peripheral blood and BALs from TB patients[275].

It has been demonstrated that IL-17 plays an important role in the recruitment of neutrophils to the site of inflammation[275-278], including the airways during infection[279,280]. This cytokine is produced by a variety of host cells, including myeloid cells[281], invariant natural killer (iNK) T cells[282], NK cells[283,284], γδ T cells[285-287] and Th17 cells[288]. IL-17 can downregulate IL-10 production and modulate the Th1 response, which has been demonstrated in models immunized with BCG[289]. This vaccination induces Th17 cells that populate the lungs of immunized mice. Th17 cells recruit Th1 cells to the site of infection to restrict mycobacterial growth, upon challenge with *Mtb*[290]. IL-17 can promote tissue damage during *Mtb* infection[274,291] and in the context of other infectious and autoimmune diseases[276,277,292-294]. An increment of IL-17 production is associated with increased neutrophil recruitment and exacerbated lung tissue pathology after repeated BCG vaccinations[295].

B cells can optimize BCG-elicited Th1 immunity by regulating the IL-17/neutrophil response[296]. In human tuberculous pleural effusion (TPE) Th17 cells and regulatory T cells (Tregs) have been found to be increased. Th17 cells were significantly increased in TPE due to local generation and differentiation stimulated

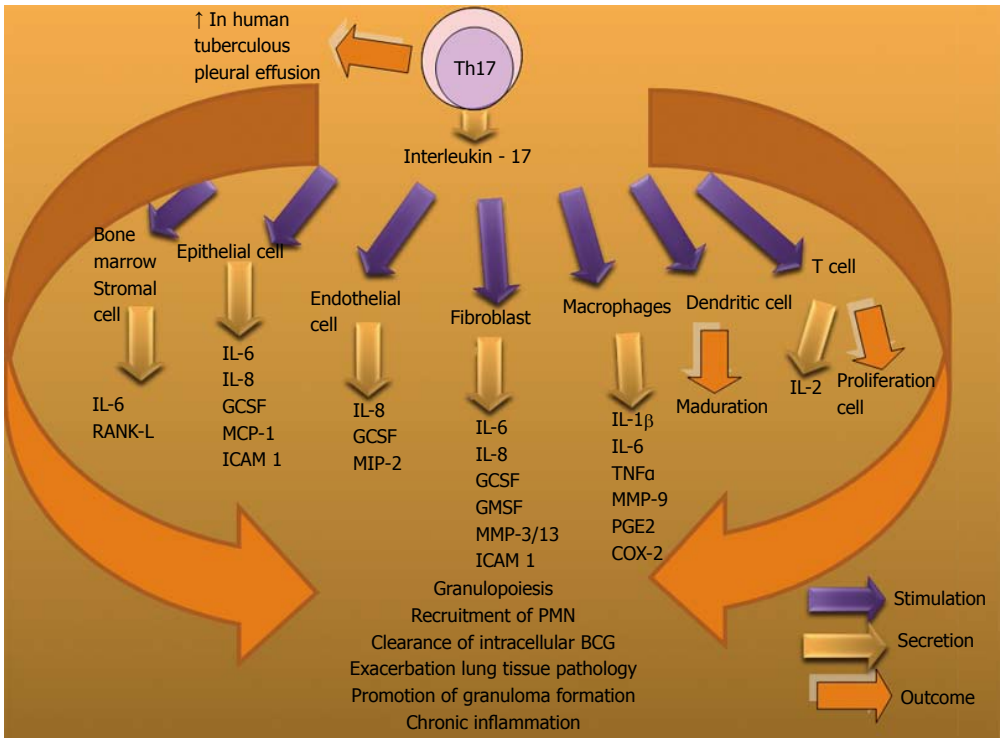

Figure 18 Interleukin-17 in the control of *Mycobacterium tuberculosis* infection. MCP: Monocyte chemoattractant protein; RANK-L: Receptor activator of NF-Kb ligand; MMP-9: Metalloproteinases-9; GCSF: Granulocyte colony stimulating factor; MIP-2: Macrophage inflammatory protein-2; BCG: Bacillus calmette guérin; PGE2: Prostaglandin e-2; COX-2: Cyclooxigenase-2; ICAM 1: Intercellular adhesion molecules-1; IL: Interleukin.

by IL-1β and/or IL-6. $CD39^+$Tregs might participate in the suppression of local immune responses by inhibiting Th17 phenotype[297] (Figure 18).

IL-18

Interleukin- 18 (IL-18) was designed as an IFN-γ-inducing factor, which induces IFN-γ production by splenocytes, hepatic lymphocytes, and type 1 T helper (Th1) cell clones. Its biological actions appear to be similar to those of IL-12[298-300].

Mtb infection in the absence of IL-18 diminishes the Th1 phenotype response. Also, IL-17, chemokines as: CXCL-1 and CXCL-2 cause PMN influx, which exacerbates the immunopathology in IL-18 KO mice. This reveals its immune protective role against *Mtb*[301]. It has been demonstrated that treatment with exogenous IL-18 reduced the bacterial load. This finding does not agree with the studies that have demonstrated that the sizes of the granulomatous lesions in IFN-γ-KO and TNF-α-KO mice infected with *Mtb* were not reduced significantly by recombinant IFN-γ or TNF-α[302].

The inflammatory lesions in IL-18-KO mice were no more severe than those observed in IFN-γ-KO[23,257], TNF-α-KO mice[302] and IL-12-KO[303]. Therefore, IL-18 does not seem to play a role in *Mtb*-induced granuloma formation (Figure 19).

IL-22

IL-22, a member of the IL-10 family, is mainly produced by T and NK cells[304,305]. It is considered to be produced by Th17 cells in an IL-23-dependent manner[306,307] or by a private T cell lineage termed Th22[308,309].

Previously, it had been shown that IL-22 produced by NK cells in humans and $CD4^+$ T cells in macaques could limit *Mtb* growth in macrophages by increasing phagolysosomal fusion. However, IL-22 can play a dual role in tissue homeostasis depending on the cytokine microenvironment where it is induced[310,311].

Study suggests that $NK1.1^+$ cell-derived IL-22 contributes to vaccine-induced protective immunity but not to the primary immune response to *Mtb,* as is the case for IL-17. IL-17 and IL-22 appear to mediate vaccine-induced protective immune responses; however, different mechanisms are involved. IL-17 induces local chemokine production, which leads to optimal priming of T-cells[306], whereas IL-22 inhibits expansion of induced Tregs and enhances antigen-specific T-cell responses, resulting in a reduced bacillary burden after challenge with *Mtb* virulent strains (H37Rv). The mechanisms through which IL-22 inhibits Treg expansion and enhances T-cell responses remain uncertain[310].

IL-22 levels in pericardial fluid correlated positively with MMP-9, an enzyme known to degrade the pulmonary extracellular matrix. Levels of MMP-9 in blood are associated with severity of TB disease[312].

Researchers reported significantly higher IL-22 levels in BAL fluid from patients with pulmonary TB, compared with healthy controls. Also, levels of IL-22 in pleural effusion and pericardial effusions from TB patients were

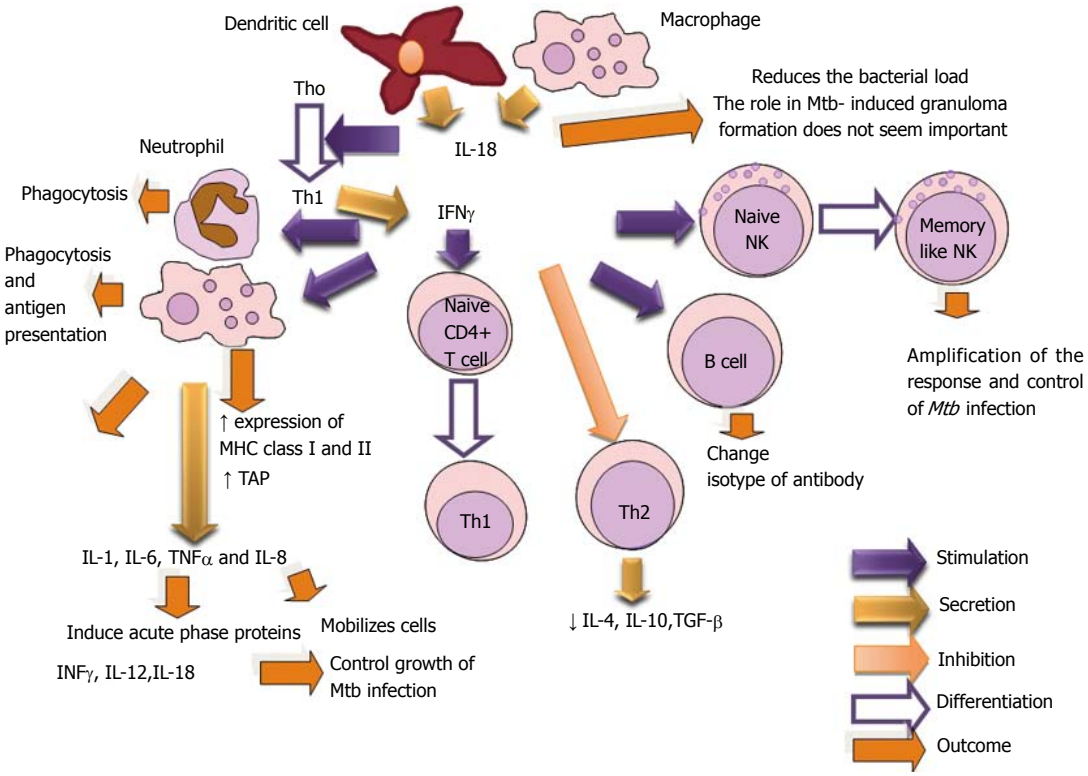

Figure 19 Role of interleukin-18 in *Mycobacterium tuberculosis* infection. TGF-β: Transforming growth factor-beta; NK: Natural killer; TAP: Transporters associated with antigen processing; CD: Clusters of differentiation; IL: Interleukin.

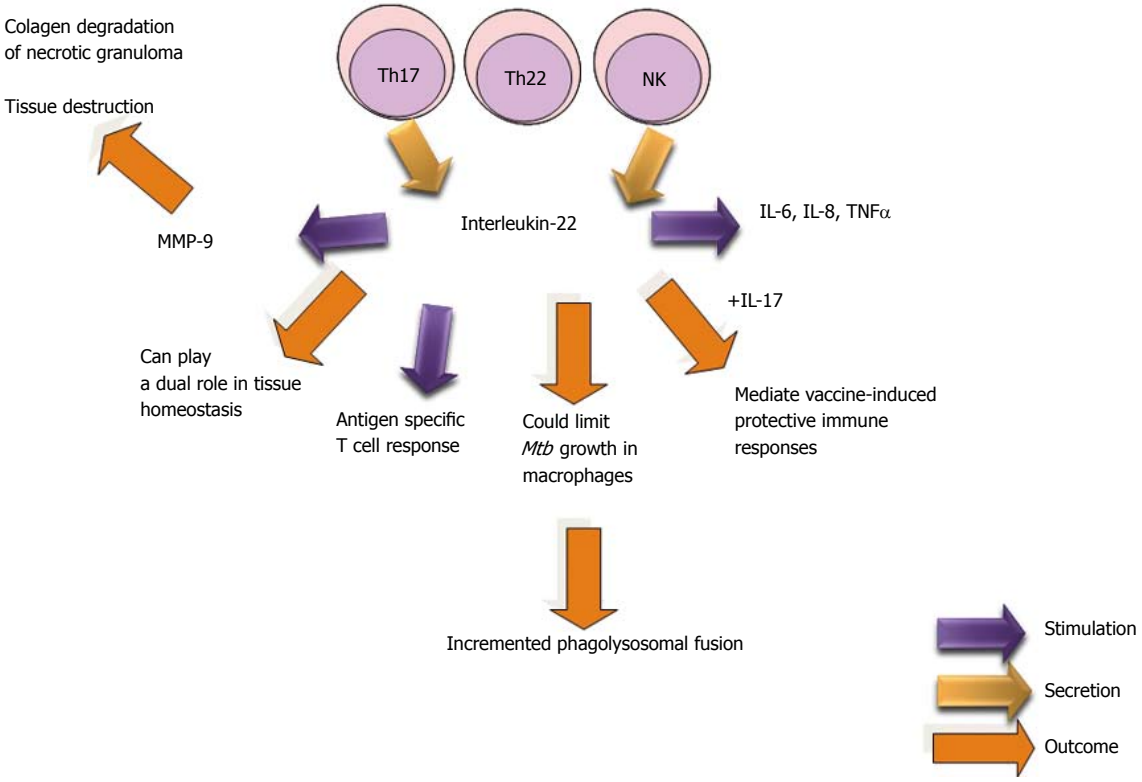

Figure 20 Biological Effects of interleukin-22 in the *Mycobacterium tuberculosis* infection. MMP-9: Metalloproteinases-9; NK: Natural killer; IL: Interleukin.

readily detectable in most[313].

It has been detected IL-22-producing T cells in lung tissue sections and granulomas of *Mtb* infected macaques[314]. However, the treatment of *Mtb* infected

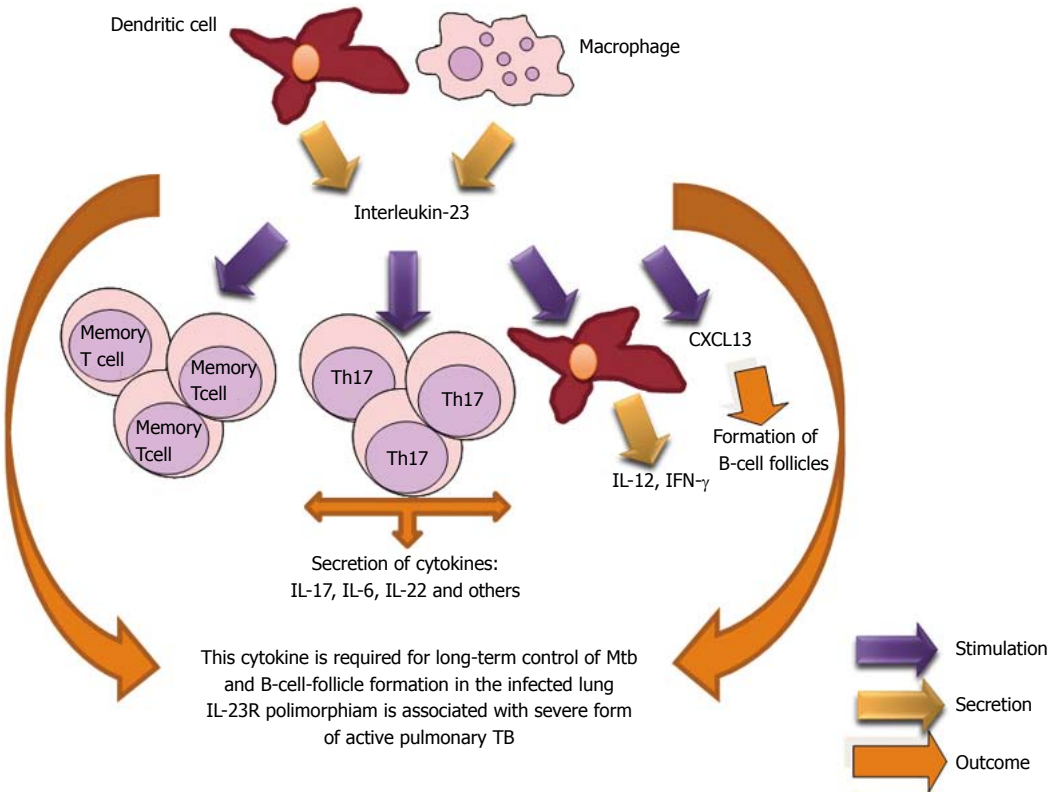

Figure 21 Participation of interleukin-23 in *Mycobacterium tuberculosis* infection. TB: Tuberculosis; IL: Interleukin; IFN-γ: Interferon-γ.

mice with neutralizing anti-IL-22 antibodies did not affect pathology, granuloma formation or bacterial burdens in the lung[315] (Figure 20).

IL-23

IL-23 is a new IL-12 family member. IL-23 mediates its activity through IL-23R. IL-23 is a heterodimeric cytokine composed of a p19 subunit and a p40 subunit. Also, stimulates the proliferation of Th17 cells, a phenotype which produces inflammatory cytokines such as IL-17, TNFα, and IL-6[316,317]. IL-23 is necessary for the expression of IL-17A and IL-22 in the lung. The absence of IL-23 affects the expression of CXCL13 (B cell chemoattractant) within *Mtb*-induced lymphocyte follicles in the lungs and its deficiency is associated with increased T cells around the vessels in the lungs of studied mice[318]. The absence of homeostatic chemokines delays the protective immunity and granuloma formation[319]. Study has demonstrated that the *IL23R* (Arg381Gln) functional polymorphism is associated with an increased risk of development of a severe form of active pulmonary TB. Further studies are necessary[320] (Figure 21).

IL-27

IL-27 is a member of the IL-12 family. IL-27 is an important inhibitory cytokine for the Th17 differentiation and limits inflammation of autoimmune and infectious origin[321-323]. Although the role of this cytokine is still not well understood in TB, two different studies have shown that IL-27R signaling has detrimental effects for the control of *Mtb* in the mouse model[324,325]. IL-27 can serve as a counter-regulatory of cytokines to prevent extensive immunopathology by keeping cellular responses in control. This cytokine can modulate the intensity and duration of many classes of T cell responses[326] (Figure 22).

TGF-β

TGF-β is a key mediator in the immunopathogenesis of TB because it is able to affect quantitative and qualitatively other cytokines, such as IL-1β and TNF-α, and modulate the functions of T lymphocytes and macrophages[327-330]. In pleural tuberculosis, the excessive production of TGF-β is believed to be related to the clinical progression of the disease, particularly in the physiopathology of pleural thickening. TGF-β possesses proinflammatory activity in low concentrations (pleural tuberculosis and healthy contacts of tuberculosis carriers) and anti-inflammatory activity in high concentrations (pulmonary tuberculosis)[329]. It has observed increased levels of TGF-β in the pleural fluid and blood of tuberculosis patients. Although higher TGF-β levels were observed in the pleuropulmonary form, there was no statistical significance when compared to the levels in patients with pleural disease[331]. Pediatric TB is associated with elevated plasma levels of TGF-β, IL-21, and IL-23, which reveal an important role in the disease pathogenesis[332] (Figure 23).

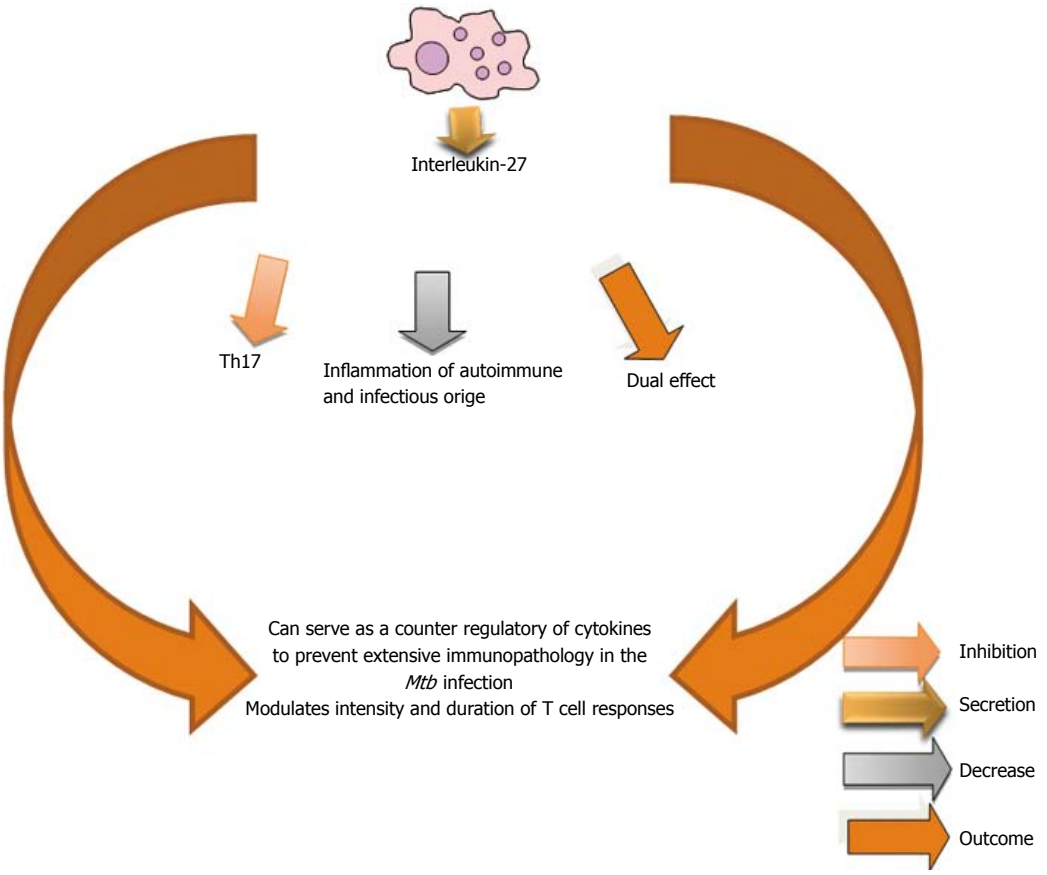

Figure 22 Role of interleukin-27 in *Mycobacterium tuberculosis* infection. Th17: T helper type 17; *Mtb: Mycobacterium tuberculosis*.

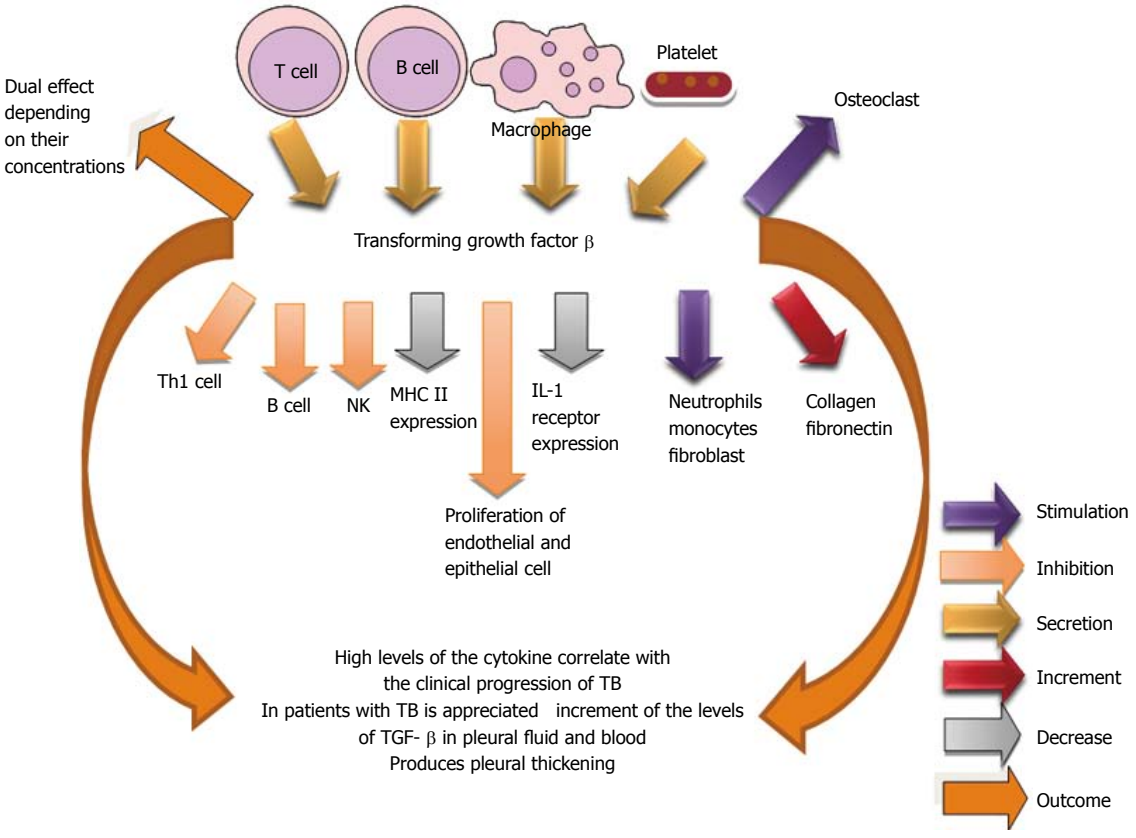

Figure 23 Transforming growth factor-beta in the control of *Mycobacterium tuberculosis* infection. TB: Tuberculosis; Th1: T helper type 1; TGF-β: Transforming growth factor-beta; NK: Natural killer; IL: Interleukin.

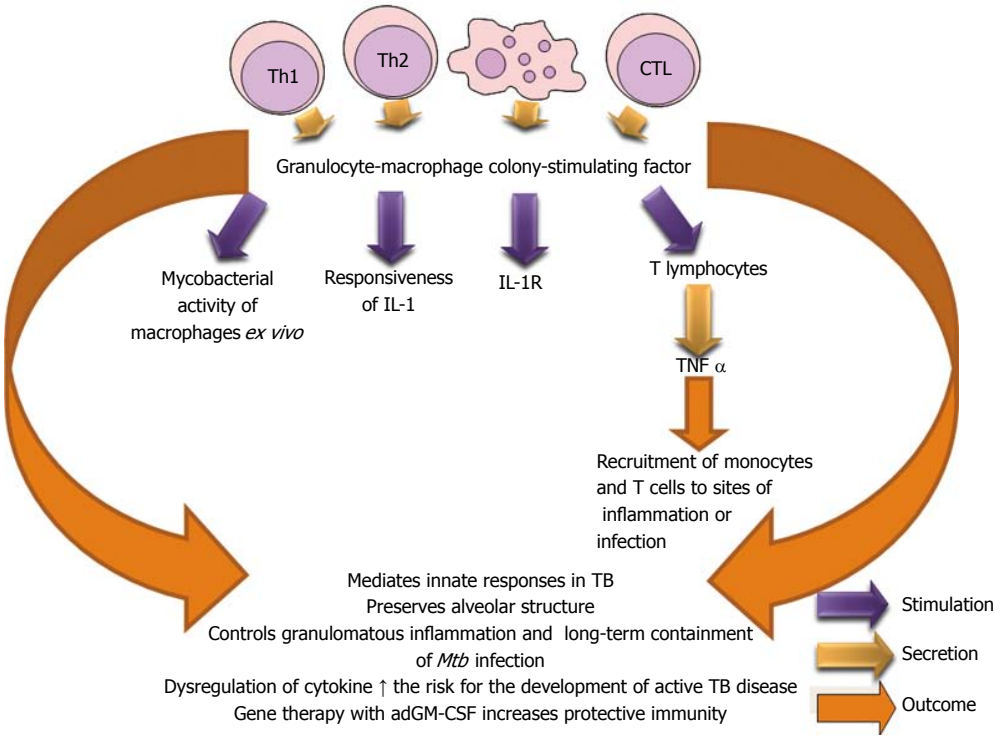

Figure 24 Influence of granulocyte macrophage colony-stimulating factor in the control of *Mycobacterium tuberculosis* infection. GM-CSF: Granulocyte macrophage colony-stimulating factor; IL: Interleukin; *Mtb*: *Mycobacterium tuberculosis*; TB: Tuberculosis; TNF: Tumor necrosis factor.

GM-CSF

GM-CSF is produced by Th1, Th2 and CTL. This cytokine augments the production of granulocytes, macrophages and dendritic cells. GM-CSF and IL-3 stimulate the production of new macrophages when those cytokines act on primary hematopoietic cells of the bone marrow. GM-CSF has a fundamental role in a balanced innate host defense against tuberculosis by its role in preserving the integrity of alveolar epithelial cells and in regulating macrophages and dendritic cells to facilitate containment of virulent mycobacteria in pulmonary granulomas. Prolonged dys-regulation of GM-CSF expression favors the development of pulmonary tuberculosis in immuno-competent individuals[333]. Impaired GM-CSF signaling determines a defective innate activity in alveolar macrophages and allows high susceptibility to lung infections[334].

Invariant natural killer T (iNKT) cells produced GM-CSF in vitro and in vivo in a cluster of differentiation molecule 1 d (CD1d)-dependent manner during *Mtb* infection, and GM-CSF were both necessary and sufficient to control *Mtb* growth. GM-CSF has a potential role in T cell immunity against *Mtb*[335]. GM-CSF and/or TNF-α contributed with the most successful cellular differentiation and appoint that the culture conditions can limit or favor the replication of the bacteria in macrophages[57].

GM-CSF is an important cytokine in the immune protection against Mtb and gene therapy with recombinant adenoviruses encoding granulocyte-macrophage colony-stimulating factor increased protective immunity when administered in a model of progressive disease, and when used to prevent reactivation of latent infection or transmission[336] (Figure 24).

Chemokines

Chemokines belong to a large family of proteins called chemotactic cytokines and have an average molecular mass of 8-14 kDa. They can mediate the constitutive recruitment of leukocytes from the blood into tissues[337,338].

CCL2 (monocyte chemoattractant protein, MCP-1) promotes polarization to Th2 phenotype, resulting in a defective control of Mtb infection. Serum levels have been associated with TB disease activity and treatment response. CCL-3 [macrophage inflammatory protein 1α (MIP-1α)] mobilizes more Th1 than Th2 cells. CCL5 (Regulated upon Activation, Normal T cells Expressed and Secreted, RANTES) is important in the recruitment of Th1 cells to form lymphocyte-enriched granulomas and it has a relevant role in early response of IFNγ producing Tcells. CCL7 (monocyte chemoattractant protein-3, MCP-3) mobilizes phagocytic cells, NK cells and T Lymphocytes. This chemokine has been found elevated in bronchoalveolar lavage fluid and biopsy specimens of subjects with pulmonary tuberculosis. CCL12 (monocyte chemoattractant protein-5, MCP-5) is chemotactic for eosinophils, monocytes, and T and B lymphocytes. CXCL2 (GRO-β) mobilizes neutrophils and fibroblasts. CXCL8 (IL-8) increases the capacity of

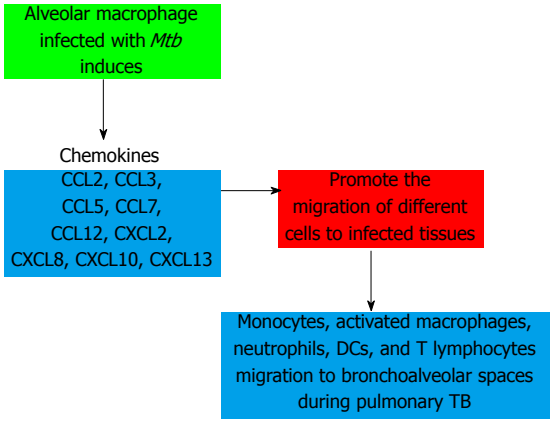

Figure 25 Participation of chemokines in pulmonary tuberculosis. TB: Tuberculosis; DCs: Dendritic cells.

the neutrophil to kill *Mtb* among other functions and CXCL10 (IFN-γ induced protein, IP-10) is a good marker for monitoring of the treatment in adults with active TB[337, 338].

IL-8 (CXCL8) is a strong neutrophil, monocytes and T-cells chemoattractant[339,340]. TB patients presented increased of CXCL8 levels in plasma and bronchoalveolar lavage fluids[341,342] which activates phagocytes as neutrophilis[343]. These cells are found in abundantly in the sputum of TB patients and are persistently recruited to sites of chronic mycobacterial infection[344,345]. Researchers have demonstrated that Mycobacterial infection of alveolar epithelial cells induce the secretion of CXCL8 and IL-6, but not secretion of the monocyte chemotactic CCL2 or pro-inflammatory TNF-α[346].

Study reveals that up-regulation of CCL18 and IL-10 in macrophages by *Mtb* may be involved in the recruitment of naïve Tcells in association with local suppressive immunity against intracellular pathogen[347]. The relationship between mycobacterial antigen-induced IFN-γ and CXCL9 may play a role in determining disease severity in TB[348]. CCL20 attracts immature dendritic cells and down-regulates the characteristic production of reactive oxygen species induced by *Mtb* in monocytes which may affect the activity of the cells. This chemokine inhibits apoptosis mediated by the mycobacteria[349]. CCL22 might be capable of inducing the migration of Tregs to the pleural space of the patients with TPE[350].

It has proposed a model in relation to the formation of granuloma and the participation of chemokines for host defense during *Mtb* infection. Alveolar macrophages uptake *Mtb* and secrete chemokines. Other cells such as epithelial cells and fibroblasts also produce chemoattractant proteins. This chemokine cascade causes an initial recruitment of neutrophils and monocytes. Meanwhile, lung DCs infected by *Mtb* increase the expression of CCR7 and migrate in response to chemokines expressed within lymphoid organs to polarize T cells into phenotypes productors of cytokines. CXCL13 and CCL19 may then mediate correct spatial localization of immune cells to form granulomas and mediate the control of *Mtb*[351] (Figure 25). The complexity of the network of cytokines and chemokines is observed by a recent study which shows that patients with coinfection HIV/*Mtb* have similar pattern of regulating proteins. Anti TB treatment significantly improves the level of pro-inflammatory cytokines (Th1 phenotype) and chemokines but does not restore the immune response in HIV-positive patients[352].

CONCLUSION

The existence of lineages, sublineages, strains and substrains reveal the complexity of *Mtb* and hence differences in the behavior of the immune system and the evolution of the disease. There is evidence suggesting some strains of *Mtb* may result in higher rates of disease progression, treatment failure, and relapse. The presence of persisting immune activation and high frequencies of Treg lymphocytes may reflect immune dysregulation that predisposes individuals to clinical tuberculosis, specifically to extrapulmonary tuberculosis. There is no doubt that immunity to *Mtb* depends on Th1-cell activity (IFN-γ and IL-12 and the production of TNF-α), but Th1 immunity alone is not sufficient to protect the host from *Mtb* infection, development of the disease, or dissemination. CD8+ T and γδ T cells exhibit cytolytic effector functions in the *Mtb* infection which amplifies the response. Studies of B cell immunodeficiency in both humans and mice have questioned whether these lymphocytes impart a protective effect against *Mtb*.

Recently, has been demonstrated that NK cells have the capacity for memory-like responses which permit greater control of the bacterial infection. IFN-γ, TNF-α, IL-12 and IL-17 are important participants in Mycobacterium-induced granuloma formation. Cytokines produced by Th17 phenotype enhance the clearance of intracellular Bacillus Calmette-Guérin (BCG) by macrophages.

IL-27 and IL-10 can serve as counter-regulatory of the cytokines to prevent extensive immunopathology by keeping anti-bacterial cellular response in control. The excessive production of TGF-β is believed to be related to the clinical progression of the disease, particularly, in the physiopathology of pleural thickening. Some chemokines may mediate correct spatial localization of immune cells to form granulomas and mediate the control of *Mtb* and others are also involved in the migration of different cells to infected tissues. As appreciated, the immune system is an extensive network and its final outcome is based in biological actions of cytokines and the participation of the factors aforementioned.

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