Review of Literature
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Historical Perspectives:

Tuberculosis has a lineage that can be traced to the earliest chronicle of mankind. *M. tuberculosis* (Mtb) the causative organism of TB was shown to exist as early as 5000 BC when archaeologists found evidence in human bones of the presence of TB [18,19]. There is archaeological evidence of human infection of Mtb of spine (Potts disease 5000 – 1000 BC). Earliest tangible records of pulmonary TB (PTB) were between 668 – 626 BC. The classic signs of TB – cough, sputum, hemoptysis, wasting of body were well recognized and documented. The earliest written evidence was from the library of the Assyrian king Assurbanipal (668-626 BC) where he had stated in his Opera Medica of 1679 that Sylvius was the first to identify actual tubercules as a consistent and characteristic change in lungs in PTB. In 1882, Robert Koch was first to identify the bacilli by a staining technique that enabled him to see Mtb.

Epidemiology of tuberculosis: Global situation

Tuberculosis (TB) remains a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). The latest estimates included in this report are that there were almost 9 million new cases in 2011 and 1.4 million TB deaths (990 000 among HIV negative people and 430 000 HIV-associated TB deaths). This is despite the availability of treatment that will cure most cases of TB. Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s (WHO, 2012). The World Health Organization (WHO) declared TB a global public health emergency in 1993. Starting in the mid-1990s, efforts to improve TB care and control intensified at national and
international levels. Geographically, the burden of TB is highest in Asia and Africa. India and China together account for almost 40% of the world’s TB cases. About 60% of cases are in the South-East Asia and Western Pacific regions. The African Region has 24% of the world’s cases and the highest rates of cases and deaths per capita. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB. India, China, the Russian Federation and South Africa have almost 60% of the world’s cases of MDR-TB. The highest proportions of TB patients with MDR-TB are in Eastern Europe and central Asia (WHO, 2012).

**TB Burden in India**

India is the second-most populous country in the world; India has more new TB cases annually than any other country. In 2009, out of the estimated global annual incidence of 9.4 million TB cases, 2 million were estimated to have occurred in India, thus contributing to a fifth of the global burden of TB. It is estimated that about 40% of Indian population is infected with TB bacillus. (TB India, Revised RNTCP report, 2012). In India, more than 1,000 people die from TB every day more than 450,000 per year, 1 every minute. Although TB is primarily a disease of men, it kills more women in India than any other infectious disease


**Impact of Other Determinants of TB Burden:**

Broadly described, these risk factors may be biomedical (such as HIV infection, diabetes, tobacco, malnutrition, silicosis, malignancy), environmental (indoor air pollution, ventilation) or socioeconomic (crowding, urbanization, migration, poverty). The impact of these other determinants on TB epidemiology in India has yet to be fully understood. The most recent estimates of the global burden of diabetes mellitus (DM) come from the 2011 Diabetes Atlas of the International Diabetes Federation. Diabetes has been shown to be an independent risk factor for tuberculosis in community based study from South India and multiple studies globally.
Modeling has suggested that diabetes accounts for 14.8% of all tuberculosis and 20.8% of smear-positive TB. In 2011, there were an estimated 366 million cases of DM globally, and by 2030 it is expected that this number will have risen to 552 million. 80% of people with DM live in low- and middle-income countries and 50% of all people with DM (183 million) are undiagnosed. It is estimated that DM caused 4.6 million deaths in 2011. As a consequence of urbanization as well as social and economic development, there has been a rapidly growing epidemic of DM in India. Available data suggest that an estimated 11% of urban people and 3% of rural people above the age of 15 years have DM. Among them about half in rural areas and one-third in urban areas are unaware that they have DM. Most recent estimates from the International Diabetes Federation put the number of persons with diabetes mellitus at 61.3 million (10% of the adult population), with a further 77 million having impaired glucose tolerance. While the HIV epidemic in India appears to have peaked, the total number of persons living with HIV/AIDS remains high, and with time the level of immunodeficiency and TB vulnerability may increase. Malnutrition remains highly prevalent in India, and will remain a significant factor for years to come. India is urbanizing at a fantastic pace, bringing larger numbers of persons into urban areas with documented higher rates of TB transmission (TB India, Revised RNTCP report, 2012).

**Pathogenesis**

The development of TB disease from infection may be viewed as a series of battles between the host defenses and the bacilli. Infection is initiated by inhalation of droplet nuclei, which are particles of 1–5 µm in diameter containing *M. tuberculosis*, expectorated by patients with active pulmonary TB, typically when the patient coughs. The droplet nuclei, due to their small size, can remain suspended in the air for several minutes to hours. The risk of infection is dependent on several factors such as the infectiousness of the source case, the closeness of contact, the bacillary load inhaled, and the immune status of the potential host [20,21]. After it is
inhaled as respiratory droplets and deposited in the distal alveoli, *M. tuberculosis* is presumed to first encounter and be ingested by alveolar macrophages. Various phagocytic cells recruited to the infected lung, including neutrophils, monocyte-derived macrophages, and dendritic cells (DCs) also ingest bacteria and probably play an important role in the outcome of the infection [22]. *M. tuberculosis* can gain entry into macrophages, their host cell, by utilizing a wide array of receptors. It is possible that all the invading bacilli are killed immediately within the macrophages, thereby preventing infection.[23,24,25]. In the vast majority of the infected individuals, an effective cell-mediated immune response develops weeks after infection that stops further multiplication of the tubercle bacilli. The activated T lymphocytes, macrophages, and other immune cells form granulomas that wall off the growing necrotic tissue limiting further replication and spread of the tubercle bacilli. Most of the *M. tuberculosis* are killed in the caseating granulomas, and disease progression is arrested. However, the pathogen is not completely eradicated in some individuals as *M. tuberculosis* has evolved effective strategies to evade the immune response resulting in survival and persistence of some bacilli in a non replicating state in the host latent TB infection [20,26,27]. A person with latent TB may reactivate even after many years under a variety of conditions such as HIV, malnutrition, age or steroid use. However, more commonly the infected person never develops disease [28,29]. It is not fully understood how or why reactivation occurs or whether the bacilli are dormant or proliferating during this period. Approximately 5-10% of primary infections progress to active pulmonary TB in which a lesion will generally be visible upon chest radiograph. Only up to 10% of humans infected with *M. tuberculosis* will progress to active tuberculosis disease during their lifetime [30]. *M. tuberculosis* has evolved elaborate survival mechanisms in humans, allowing the bacterium to remain in a clinically inactive state, although it constantly engages with the human immune system. In this state, the immune response prevents active replication but fails to
eradicate the bacteria. Any subsequent weakening of the host immune system may result in clinical disease. The mechanisms for these differential outcomes to *M. tuberculosis* exposure remain unclear [31]. Live *M. tuberculosis* may also persist after an initially successful treatment of active tuberculosis, and dynamic interchanges between host and pathogen determine whether relapse to active disease will occur. These interchanges may be particularly relevant in immune-compromised individuals [32]. The traditional views of *M. tuberculosis* infection as either a latent or active disease have been replaced by a model where a continuum of host–pathogen interactions exists, resulting in a spectrum of immune responses [33].

**Host Immune Response to *Mycobacterium tuberculosis***

**Innate Immune Responses:**

Most human infections with Mtb occur through inhaled carrier droplets into the lower airways where the microbe encounters the alveolar macrophage (AMac) and sub mucosal dendritic cell (DC). The outcome of the ensuing battle will determine whether the infection will remain locally limited within the engulfing cells of the innate immune system, or will continue to spread, causing the individual to become a clinically active TB patient [34,35,36]. During the first contact, the alveolar macrophages (AMac) recognize the microbe through pattern recognition receptors (PRRs), which sense microbial biochemical components, such as outer coat mannosylated lipoarabinomannan (ManLam), trehalose dimycolate and N-glycolymuramyl dipeptide. These molecules act as pathogen-associated molecular patterns (PAMPs), which trigger an intracellular signaling cascade in the AMac, which leads to a phagocytic activity, which, if successful, will result in the complete engulfing of the microbe into cytosolic vesicles-the phagolysosomes and secretion of pro-inflammatory cytokines, such as tumor-necrosis factor alpha (TNFα). ManLam also binds directly to mannose receptors on macrophages and DCs (Zeev Theodor Handzel, 2013).
Toll-like receptors (TLRs) are phylogenetically conserved mediators of innate immunity which are essential for microbial recognition on macrophages and dendritic cells [37,38,39]. The best studied Toll-like receptors of which 10 have been identified in humans, TLR2 and TLR4 recognize bacterial products [40,41], TLR-2 having a major role in recognizing Mtb in the lung. The interactions between *M. tuberculosis* and TLRs are complex and it appears that distinct mycobacterial components may interact with different members of the TLR family. *M. tuberculosis* can immunologically activate cells via either TLR2 or TLR4 in a CD14-independent, ligand-specific manner [42].

Neutrophils also play a defensive role, not only as first-line non-specific phagocytes, at the site of multiplication of bacilli, but are also the first cells to arrive followed by NK cells, γ/δ cells and α/β T cells. There is evidence to show that granulocyte-macrophage-colony stimulating factor (GM-CSF) enhances phagocytosis of bacteria by neutrophils. Neutrophils loaded by phagocytized bacteria become apoptotic, thereby eliciting macrophage activation [43].

NK cells are also the effector cells of innate immunity. The effector functions of NK cells are finely regulated by a series of inhibitory or activating receptors [44]. The inhibitory receptors, specific for major histocompatibility complex (MHC) class I molecules, allow NK cells to discriminate between normal cells Accordingly, lack of interaction of these receptors with MHC class I molecules may result in the killing of the target cells [45]. This occurs when target cells have lost or express insufficient amounts of MHC class I molecules. The inhibitory form of NK receptors provides the protective immunity through recognizing class I MHC molecules with self-peptides on healthy host cells, and cells that have lost the expression of MHC class I. Natural killer (NK) cells recognize endogenous host molecules with altered expression due to
cellular stress through a combination of stimulatory and inhibitory receptors. Human NK cells recognize *M. tuberculosis*-infected macrophages via the activating receptor NKp46 and can lyse *M. tuberculosis*-infected cells in vitro [46]. Human NK cells express the protein granulysin, which has direct anti-mycobacterial activity; these cells may directly lyse the pathogens or can lyse infected monocytes. During early infection, NK cells are capable of activating phagocytic cells at the site of infection. NK cells, which are large granular circulating lymphocytes, are attracted to the sites of bacterial infections, where they specialize in recognizing and destroying infected host cells. During this process they secrete interferon gamma (IFN-γ), which activates macrophages, inducing them to secrete the cytokines IL-12, IL-15 and IL-18, which activate CD8⁺ T-cells, thus forming the link to the adaptive immune system [36,47].

**Adaptive Immune Responses to Mycobacterium tuberculosis**

Adaptive immune responses are mediated by B and T lymphocytes. Adaptive immune responses mediated by T cells play a vital role in the elimination of *M. tuberculosis* [48,49]. Cytotoxicity and cytokine production are the two major effector mechanisms utilized by T cells against intracellular pathogens.

**Cellular Immune Responses**

Tuberculosis is primarily a disease of the lung, and dissemination of the disease depends on productive infection of this critical organ. Upon aerosol infection with *M. tuberculosis*, the acquired cellular immune response is slow to be induced and to be expressed within the lung. This slowness allows infection to become well established; thus, the acquired response is expressed in an inflammatory site that has been initiated and modulated by the bacterium. The most important aspect of the acquired cellular response is the rapidity with which it is expressed. If the response is too slow, bacteria grow and reach a point where although a potentially
protective response is being expressed, the environment is such that it is not effective [50]. In this same vein, it is clear that dose plays a role in the ability of the host to control bacteria. Specifically, if one is infected by too high a dose, then the local bacterial burden may reach a level that interferes with the efficient expression of protective immunity. These ideas were brought together eloquently by Rich (Rich A, 1944) using the lung histopathology from patients in the pre drug era to describe the natural history of the disease. He suggested that the acquired cellular response could control bacterial growth but that it failed to do so in the face of high numbers of bacteria.

**Role of T cells in protective Immune responses to Tuberculosis**

**CD4 T cells**

CD4⁺ T cells are major T cell subset that play a central role in immune system function when naive CD4⁺ T cells differentiate into effector and/or memory cells after encountering their cognate antigen via antigen-presenting cells (APCs). The phenotypes of effector CD4⁺ T cells differ depending on the stimulating conditions and can be categorized into various lineages. In the lungs, DCs bridge innate and adaptive immunity, and depending on context, they also induce various CD4⁺ T cell responses to infectious agents [51]. A crucial role for CD4⁺ T cells in immunity against Mtbf is indisputable and confirmed by published evidence including the effects of HIV-1–induced CD4⁺ T-cell depletion on susceptibility to Mtbf infection and TB development [52]. Protective immunity and delay of control of bacterial growth during *M. tuberculosis* infection depend on CD4⁺ T cells because CD4⁺ T cell–deficient (or MHC class II–deficient) mice are unable to control bacterial growth and thus succumb to disease, and CD4⁺ T cell lymphopenic HIV patients are highly susceptible to TB [53,54]. The CD4⁺ T helper cells can be differentiated into Th1, Th2, Th17 and Treg cells. The Th1 cells produce cytokines, notably IFN-γ, TNF-α, IL-2, lymphotoxin and granulocyte-macrophage colony-stimulating factor (GM-
CSF), which prompts stimulation of Th1 cells, CTL, and maturation and activation of macrophages as well as granulocytes. The Th2 cells produce B cell-stimulation factors such as IL-4, IL-5, IL-10 and IL-13, which promote antibody production but suppress the Th1 type immune response. The Th17 cells, a distinct subset of helper T cells, produce unique cytokines of IL-17A, IL-17F, IL-21 and IL-22, which stimulate defensin production and recruit neutrophils and monocytes to the site of inflammation, and are involved in the early phase of host defense [55].

**Th1 Cells**

Th1 cells are characterized by the production of their cytokines, notably IFN-γ, TNF-α, IL-2, lymphotoxin and granulocyte-macrophage colony-stimulating factor (GM-CSF), which prompts stimulation of Th1 cells, CTL, and maturation and activation of macrophages as well as granulocytes. The differentiation of Th1 cells requires the cytokine IL-12, the master transcription factor TBX [56] and the signaling transducer and activator of transcription STAT4.

**IFN-γ**: IFN-γ, a key cytokine in control of *M.tuberculosis* infection is produced by both CD4+ and CD8+ T cells, as well as by NK cells. IFN-γ might augment antigen presentation, leading to recruitment of CD4+ T-lymphocytes and/or cytotoxic T-lymphocytes, which might participate in mycobacterial killing. Although IFN-γ production alone is insufficient to control *M. tuberculosis* infection, it is required for the protective response to this pathogen. In macrophages, IFN-γ induces respiratory burst contributing to the production of RNIs and ROIs [57]. Mycobacterial antigen-specific IFN-γ production in vitro can be used as a surrogate marker of infection with *M. tuberculosis* [58]. IFN-γ has long been implicated as a regulator of T cell responses in mycobacterial disease [57]. In the mouse, IFN-γ acts on T cells to promote apoptosis by...
modulating both T cell susceptibility to apoptosis and altering the level of apoptotic signals during mycobacterial disease [59]. In humans lacking a functional IFN-γ receptor 1 binding chain, CD4 (but not CD8) T cells express low levels of FasL, are less susceptible to activation induced cell death and have reduced ability to kill mycobacteria infected compared to controls [60]. IFN-γ is also responsible for the loss of established CD8+ T cell memory following mycobacterial infection [61]. Humans defective in genes for IFN-γ or the IFN-γ receptor are prone to serious mycobacterial infections, including M. tuberculosis [62]. Although IFN-γ production may vary among subjects, some studies suggest that IFN-γ levels are depressed in patients with active TB [63]. Another study demonstrated that M. tuberculosis could prevent macrophages from responding adequately to IFN-γ [64], this suggests that the amount of IFN-γ produced by T cells may be less predictive of outcome than the ability of the cells to respond to this cytokine.

The main function of IFN-γ is macrophage activation, rendering them able to exert their microbicidal functions. It operates by also enhancing the antigen presentation through the induction of the expression of molecules from the major histocompatibility complex (MHC) class I and II and promoting the differentiation of CD4+ T lymphocytes to the Th1 subpopulation [65,66]. IFN-γ induces the transcription of more than 200 genes in macrophages, including those for the production of antimicrobial molecules such as oxygen free radicals and nitric oxide, which represent one of the best effector mechanisms for elimination of M. tuberculosis [50]. Individuals with a deficiency in the IFN-γ receptor gene have shown to be extremely susceptible to mycobacterial infections [67]. The complete deficiency of IFN-γ receptor in humans is associated with increased severity in the course of infection, poor formation of granulomas, multi-bacillary lesions, and progressive infection [8]. Studies with individuals that presented
genetic mutations in the IFN-\(\gamma\) receptor have also proven that they presented high susceptibility to atypical mycobacterial infections [62].

**Tumor Necrosis Factor (TNF-\(\alpha\))**: TNF-\(\alpha\) is a pro-inflammatory cytokine, which exerts multiple biological effects in the process of mycobacterial infection control. TNF-\(\alpha\) seems to have a primordial role, acting upon a wide variety of cells. The main producing cells are activated macrophages, T lymphocytes, and dendritic cells [68, 69,70]. This cytokine acts in synergy with IFN-\(\gamma\), stimulating the production of reactive nitrogen intermediates (RNIs), thus mediating the tuberculostatic function of macrophages [71,72]. TNF-\(\alpha\) also stimulates the migration of immune cells to the infection site, contributing to the granuloma formation, capable of controlling the disease progression [73]. This cytokine is involved in both immune and immuno-modulatory responses and acts in synergy with IFN-\(\gamma\) to enhance the expression of iNOS and the antimycobacterial activity of macrophages [74,75] TNF-\(\alpha\) also initiates cell migration and formation of microbicidal granulomas while disruption of TNF-\(\alpha\) responses leads to overgrowth of the mycobacterial pathogens [50,74]. The TNF-\(\alpha\) produced by the infected macrophages induces the expression of chemokines, such as IL-8, MCP-1, and RANTES which provide signals for migration of immune cells to the sites of *M. tuberculosis* infection [76]. Both T cell- and macrophage-derived TNF-\(\alpha\) are required for sufficient and long-term protection against *M. tuberculosis* infection. The reactivation of TB seen upon administration of monoclonal antibodies against TNF [73,77,78] was consistent with the theory that granulomas benefited the host by containing and controlling *M. tuberculosis* [48]. However, work using the mouse model of *M. tuberculosis* infection showed that granuloma formation could occur even in the absence of TNF signaling, although these granulomas were delayed and were more necrotic, with higher bacillary numbers [79]. Moreover, more recent reports of patients developing TB after anti-TNF treatment found that biopsies of these patients displayed classical granuloma structures [80].
**Interleukin-2 (IL-2):** Interleukin (IL)-2, a cytokine produced by activated T lymphocytes, has a central role in the activation and expansion of T cells. It has a pivotal role in generating an immune response by inducing an expansion of the pool of lymphocytes specific for an antigen. IL-2 promotes T cell replication and is essential for cellular immunity and granuloma formation. Central memory T cells predominantly produce IL-2. Therefore, IL-2 secretion by the protective CD4+ Th1 cells is an important parameter to be measured and several studies have demonstrated that IL-2 can influence the course of mycobacterial infections, either alone or in combination with other cytokines [81]. In murine models of *Mycobacterium avium* and *Mycobacterium bovis* BCG infection, IL-2 has been shown to limit mycobacterial replication, possibly by macrophage activation via interferon-mediated pathways or directly by the development of cytotoxic T lymphocytes recognizing mycobacterial antigens [82,83].

**Interleukin-12 (IL-12):** IL-12 is a key player in host defense against *M. tuberculosis*. IL-12 is produced mainly by phagocytic cells, and phagocytosis of *M. tuberculosis* seems necessary for its production [69,84] IL-12 has a crucial role in the induction of IFN-γ production [85]. Apparently, IL-12 is a regulatory cytokine which connects the innate and adaptive host response to mycobacteria [85,86,87] and which exerts its protective effects mainly through the induction of IFN-γ [88]. Mtb efficiently promotes the production of IL-12p40 subunit. IL-12 is a cytokine that promotes the development of Th1 responses and is rapidly produced by DCs through the interaction of Mtb with TLRs. Interestingly, some studies have suggested that induction of IL-12 production is dependent on TLR9 in DCs and that it is dependent on TLR2 in macrophages [89]. The importance of IL-12 is also evident from increased susceptibility of mice and humans deficient in IL-12 responses to mycobacterial infections [90]. Individuals with defects in the
production of IL-12 or its receptor are highly susceptible to active TB disease [91]. The T-cell-derived cytokines, IFN-γ and TNF-α, are produced abundantly by activated CD4+ T cells under the influence of IL-12.

**Th2 Cells**

Th2 cell differentiation requires the cytokine IL-4 and is controlled by master transcription factors, GATA3 and STAT6. Th2 immune responses are characterized by the production of IL-4, which can serve as an autocrine factor for Th2 differentiation and can stimulate activated B cells and promote differentiation of B cells into plasma cells. Th2 cells also produce IL-5, a key mediator of eosinophilopoiesis and eosinophil activation. IL-13, a product of Th2 cells, has some overlapping functions with IL-4. Th2 cells fail to produce IFN-γ and produce the signature cytokines IL-4, IL-5, and IL-13. A variety of different cell types can make IL-4 [T cells, eosinophils, basophils, mast cells, natural killer (NK) cells and some antigen-presenting cells (APCs)]. IL-4 can be involved in driving Th1 responses [92] and CTLs. IL-4 present at later stages down regulates Th1 responses [92] and this must be happening in TB, where at least some of the Th2 cytokines are coming from T cells [93,94]. IL-4 in TB has a necessary regulatory or anti-inflammatory role. Under some circumstances, regulatory T cells express IL-4 in addition to classical regulatory cytokines, such as IL-10 and transforming growth factor - beta (TGFβ) [95]. However, the evidence is against this role for IL-4. In progressive disease, IL-4 causes increased, rather than diminished, immunopathology [96]. The presence of specific IgE antibody and of T cells that release IL-4 in vitro when driven by TB antigen [97] indicates a genuine antigen-specific Th2 lymphocyte response.
**Th 17 cells**

Th17 CD4 T cells have been characterized to produce the cytokines IL-17A (IL-17) and IL-17F, as well as IL-21 and IL-22. The differentiation of Th1 or Th17 cells occurs following exposure to APC-derived polarizing cytokines such as IL-12 [98] generation of human Th17 cells is dependent on IL-23, [99,100] IL-1β, [101,102] TGFβ [101] and IL-6 [102], These polarizing cytokines further induce the expression of the transcription factors T-bet or RORγt and RORα for Th1 and Th17 differentiation respectively [103,104].

**Interleukin-17 (IL-17)**

The potential for IL-17 to mediate immune pathology as seen in autoimmune diseases and infection models, suggests that IL-17 may have detrimental effect in chronic bacterial infections such as TB. IL-17 is recognized as an inflammatory cytokine capable of inducing chemokine gradients and initiating inflammation, particularly in the lung [105,106,107]. As IL-23 is responsible for the persistence and function of Th17 cells [107] it is also likely a key player in inflammation. T cells associated with innate response can also make IL-17. In particular, the γδ T cell population is a primary source of Mtb-induced IL-17 in the mycobacterial infection model [108,109]. Regulation of immunopathology during chronic Mtb infection is essential for host survival. As immunopathology is a central feature of Mtb lung infection, it is not surprising that IL-17 and Th17 cells have a role to play. Importantly, this role also seems to be mediated, at least in part, by neutrophils. IL-17, specially, was estimated to mediate immune pathology in animal models of autoimmune diseases and infections, suggesting that IL-17 may make detrimental effect in TB pathology [110]. IL-17 was recognized as an inducer of inflammation by induction of chemokines and accumulation of both polymorphic and mononuclear cells which could kill Mtb *in vivo* under appropriate environment or situation [111]. The role of IL-17 in the development of antimicrobial responses, chemokine production, and recruitment of
inflammatory cells for control of pathogens has been described in several studies [105,106,107]. Th17 cells also participate in the inflammatory response at an early mycobacterial infection; however, the production of IL-17 in the lungs is mainly immunosuppressive of IFN-γ. The protective potential role of Th17 cells during the early phase of infection with *M. tuberculosis* is unknown. Pulmonary infected IL-17 deficient mice with BCG showed a reduction in the delayed hypersensitivity responses, with a deficiency in granuloma formation in the lungs, suggesting that IL-17 is required for an efficient development of Th1 responses [112].

**Interleukin-23 (IL-23)**

It has been demonstrated that the IL-23/IL-17 pathway may have a crucial role in the immunity against several pathogens, particularly in mycobacterial infection [113,114]. These cytokines have been involved in the development of protective and regulatory immune responses in mice and humans infected with Mtb. IL-23, is not involved in primary resistance to *M. tuberculosis* even though IL-23 is required for the generation of an IL-17-producing, mycobacteria-specific CD4+ T cell response [115,116] Despite the lack of involvement of IL-23 in primary resistance to *M. tuberculosis*, the fact that IL-23 acts on T cells with an activated or memory phenotype [117,118] suggests that this cytokine may be involved in recall responses. IL-23 is responsible for the persistence and function of Th17 cells [119]; it is also likely a key player in inflammation. It is surprising therefore that in the absence of IL-23 the inflammatory consequences of Mtb infection are modest. The secretion of IL-23 is essential for the secretion of IL-17, and people with deficiency in the IL-12Rβ1 gene have low capacity to produce IL-23, and they have a lower production of IFN-γ. IL-12 is a cytokine that reduces the expression of IL-17, and this appears to show a self-regulation on inflammation. The balance between the secretions of IL-23/IL-17 and IL-12/IFN-γ appears to be essential for the regulation of inflammation in response to *M. tuberculosis* and other mycobacteria.
**Interleukin-22 (IL-22)**

IL-22 is a member of the IL-10 family, mainly produced by T cells and natural killer (NK) cells and represents an effector cytokine of the TH17 lineage [120,121,122] that mediates immunopathology in inflammatory diseases, such as psoriasis or arthritis [123,124]. It is considered to be produced by IL-17A secreting TH17 cells in an IL-23-dependent manner [115,121] or by a private T cell lineage termed TH22. IL-22 production by activated memory CD4+ T cells is much higher than that from activated naive T cells. There is also greater induction of IL-22 under Th1 cell differentiation conditions than there is under Th2 cell differentiation conditions. The emergence of the Th17 cell subset prompted several groups to examine the production of IL-22 by these cells [121,124,125]. Although Th1 cells make more IL-22 as compared to Th2 cells or undifferentiated T cells, Th17 cells are clearly the dominant IL-22 producers by far, as demonstrated at both the mRNA and protein levels. These data unequivocally establish that IL-22 is another effector cytokine produced by Th17 cells.

**Regulatory Cytokines**

**Interleukin-10 (IL-10)**

IL-10 is produced by macrophages and T lymphocytes during *M. tuberculosis* infection. IL-10 is an immunosuppressive cytokine essential for dampening the immune response and limiting host immune pathology to numerous intracellular pathogens and gut flora, but, if overproduced, IL-10 can contribute to chronic infection [126]. A major mechanism whereby IL-10 achieves its effects is by inhibiting the antigen-presenting cell function of macrophages and DCs and the production of cytokines such as IL-12, thus inhibiting the development of Th1 responses [127,128]. In addition, IL-10 can inhibit the killing of intracellular pathogens by macrophages, induction of nitric oxide, and production of TNF [128,129]. On the basis of these functions, we can predict a role for IL-10 in the regulation of the immune response to *M. tuberculosis* and disease outcome.
IL-10 plausibly functions at many levels to limit the response to *M. tuberculosis* infection first by inhibiting macrophage and DC function, and then by inhibiting the cytokines/chemokines required for the migration of infected myeloid cells to the lymph node and for the migration of Th1 cells from the lymph node to the lung [131]. The induction of IL-10 may differ between Mtb isolates, and the cellular source of IL-10 during infection appears to be dynamic, probably depending on the stage of infection, the anatomical location of the disease and the specific pathogen [130].

**Transforming growth factor-beta (TGFβ)**

TGFβ also seems to counteract protective immunity in tuberculosis. Mycobacterial products induce production of TGFβ by monocytes and dendritic cells [133]. Like IL-10, TGFβ is produced in excess during tuberculosis and is expressed at the site of disease [133,134]. TGFβ suppresses cell-mediated immunity: in T cells, TGFβ inhibits proliferation and IFN-γ production; in macrophages it antagonizes antigen presentation, pro-inflammatory cytokine production, and cellular activation [133]. TGF-β has important anti-inflammatory effects, including deactivation of macrophage production of ROI and RNI [135], inhibition of T cell proliferation [136], interference with NK and CTL function and down regulation of IFN-γ, TNF-α and IL-1 release [137]. In addition may be it is involved in tissue damage and fibrosis during tuberculosis, as it promotes the production and deposition of macrophage collagenases [133] and collagen matrix. Naturally occurring inhibitors of TGFβ eliminate the suppressive effects of TGFβ on mononuclear cells from tuberculosis patients and in macrophages infected with *M. tuberculosis* [138]. Within the anti-inflammatory response, TGFβ and IL-10 seem to synergize: TGFβ selectively induces IL-10 production, and both cytokines show synergism in the suppression of
IFN-β production [139]. TGFβ may also interact with IL-4. Paradoxically, in the presence of both cytokines, T cells may be directed towards a protective Th1-type profile [140].

**IL-1 Cytokines Family and Type I IFNs**

The major IL-1 family cytokines IL-1α, IL-1β, IL-18, and IL-33 have potent but diverse immunological activities in inflammation and immune response regulation. Most TLRs and receptors for the IL-1 family members share a common adaptor molecule, MyD88. When MyD88 was shown by several groups to be critical for mouse resistance to both Mtb and *Mycobacterium avium*, this was interpreted as important evidence for the role of TLRs in innate recognition of these pathogens [141,142,143,144]. More recently, it has become clear that IL-1 is also of critical importance for host control of Mtb infection given that mice deficient in IL-1R or its adaptor MyD88 succumb rapidly to low-dose aerosol infection with Mtb [145,146]. A major feature of IL-1 is its complex control at the transcriptional, post transcriptional, and signal transduction levels, which is highlighted by the wide variety of immunopathologies and auto inflammatory diseases that occur in the absence of normal IL-1 regulation [147,148]. In humans, a role for IL-1 signaling in host resistance to Mtb is supported by a number of genetic studies demonstrating an association of polymorphisms in the IL-1 or IL-1R genes with altered disease progression and susceptibility [149,150,151]. IL-1 blockade has become an accepted therapy for many auto-inflammatory diseases and rheumatoid arthritis, and if indeed IL-1 signaling is important for control of Mtb in humans, there is a potential risk for disease exacerbation or reactivation of latent infection in Mtb-exposed individuals undergoing such treatment. IL-1 has a critical role in the control of human Mtb infection analogous to that previously revealed by cytokine blockade for TNF [152].
The types I IFN family of cytokines are perhaps best known for the induction of antiviral immunity, although they have pleiotropic effects on the broader immune response [153]. There has been relatively limited information on the role of type I IFN during human TB. However, Anne O’Garra et al. reported that patients with active TB have a prominent type I IFN–inducible gene signature in their blood that correlated with the extent of radiographic disease and diminished upon successful treatment [154], which has added to the literature from experimental *M. tuberculosis* infection that suggests a detrimental role for type I IFN during TB. Type I IFN–mediated changes in cellular populations also appear to be important, with the generation and trafficking to the lung of *M. tuberculosis*–permissive innate cells that contribute to exacerbated disease [155,156]. It is possible that other environmental insults such as acute viral infections or adjuvants that result in increased levels of type I IFN may also exacerbate *M. tuberculosis* infection via a type I IFN dependent mechanism, expanding the myriad of potential environmental factors, in addition to genetic changes in both host and pathogen, that can result in the development of active TB.

**Regulatory T cells**

As functional T lymphocytes, Tregs mature in the thymus and account for 5%–10% of the total CD4+ T lymphocytes in the peripheral blood. Regulatory T cells (Tregs), whose development depends on the cytokine transforming growth factor β and the transcription factor FoxP3 are also emerging as important contributors to TB immunity. Tregs also clearly prevent excessive inflammation, so understanding their expansion, trafficking, and regulation is likely to illuminate important aspects of the balance between protection and pathology in TB. Tregs are found at high frequencies in humans with active TB disease [51] and are more frequent in tissue sites in miliary TB than in pleural TB [157,158], although it is not known whether this greater frequency is the cause or the consequence of widespread infection in miliary TB. Two main types of
Figure 8.2 (A) Plasma concentrations of HO-1 were also tested for correlations with glycaemia (plasma glucose levels), percent of circulating glycosylated hemoglobin (HbA1c) and LDL cholesterol using Spearman rank tests. (B) *M. tuberculosis* quantitative bacillary sputum grade determined by AFB staining was compared between diabetic and nondiabetic individuals with active tuberculosis using the Mann-Whitney test. (C) The study participants were stratified according to the quantitative bacillary sputum grade and levels of HO-1 were compared between diabetic and non-diabetic individuals with tuberculosis with similar sputum grades using Mann-Whitney tests. Correlations between plasma levels of HO-1 and IFN-γ (D), TNF-α (E) or IL-17A (F) were assessed using Spearman tests. In (D-F), graphs on the right show frequency of individuals displaying simultaneously values of HO-1 and IFN-γ, TNF-α and IL-17A plasma concentrations higher their respective medians in the study population. Data were analyzed using Fisher’s exact test. In (B), data represent mean and standard deviation. In (C), bars represent medians values. *P<0.05; **P<0.01; hi, higher than median values.
regulatory T (Treg) cells have been identified: Extra thymically derived adaptive (or induced) CD4⁺Foxp3⁺ regulatory T (iTreg) cells can be phenotypically and functionally distinguished from thymus-derived natural Foxp3⁺ regulatory T (nTreg) cells. Both play significant roles in tuning down effector immune responses, however. Tregs suppress antigen-specific human memory γδ T cell responses to *M. tuberculosis* [159]. Tregs expand in response to *M. tuberculosis* in healthy tuberculin reactors and that expanded Tregs inhibit IFN-γ production by T cells [160], suggesting that Tregs may limit tissue inflammation and destruction. However, the cellular mechanisms that mediate expansion of *M. tuberculosis*–induced Tregs are unknown. Various studies indicate that unregulated expansion of Tregs can suppress the host immune responses and can cause reactivation of tuberculosis in some individuals. It is therefore important to study the role of Tregs in human *M. tuberculosis* infection.

**Role of Multifunctional T cells in Mtb**

Multifunctional T cells expressing Th1 cytokines have been described as immune correlates for protection against intracellular pathogens. In contrast to these responses, however, multifunctional CD4⁺ T cell responses in humans with TB have been correlated with active disease or higher bacterial burden rather than protection. Multifunctional T cells, defined by their ability to coexpress ≥2 cytokines, have also been associated with resistance to infection in animal models [161]. Thus, while some studies have implicated multifunctional Th1 cells in protective immunity against pulmonary disease [162,163]. Other studies have shown that multifunctional Th1 cells might merely reflect the presence of active disease [164,165]. Multifunctional CD4⁺ T cells secreting IFNγ, TNFα and IL-2 have been proposed as a major component of such responses, and subsequently were also shown to correlate with protection in *Leishmania major* infection in mice. Combined analyses of different cytokines co-expressed by multifunctional T cells can improve discrimination between TB patients and LTBI and prediction
of vaccine induced protection in the animal model of TB therefore, quality rather than quantity of
*M. tuberculosis*-specific T cell responses appears to indicate protection and the capacity of
generating long-term memory.

**CD8 T cells**

CD8+ T cells are cytotoxic T cells and are also major producers of IFN-γ, TNF-α, and IL-2. The
release of cytotoxic molecules, granzyme and perforin and antiviral cytokines (e.g., TNF-α and
IFN-γ) can also contribute to lung pathology [166]. The protective role that CD8+ T cells play in
immunity to *M. tuberculosis* has also been well appreciated. Antigen-specific CD8+ T cells
recognize and lyse *M. tuberculosis*-infected cells and produce cytokines such as TNF-α and
IFN-γ, both of which are critical for macrophage activation. CD8+ T cells and TNF are believed
to participate in the immune response to Mtb infection in humans [76,79,167,168,169]. It has
been demonstrated repeatedly that mycobacteria-specific CD8+ T cells are induced in response to
Mtb infection and that these cells can recognize Mtb infected macrophages [170,171]. Cytotoxic
activity of CD8+ T cells includes at least two separate mechanisms: apoptosis via the Fas- FasL
pathway and killing via perforin and granulysin [172]. In humans, CD8+ T cells can kill
intracellular mycobacteria via the release of the antimicrobial peptide granulysin [10]; however,
this molecule is not present in the mouse.

**Matrix metalloproteinases in tuberculosis**

The biochemistry of the lung extra cellular matrix predicts that matrix metalloproteinases
(MMPs) will be among the proteases that contribute to lung matrix destruction in TB [172].
Since that first report, 24 mammalian MMPs have been identified, with partially overlapping
substrate specificities and functions. MMPs are zinc-dependent proteases and consist of two
conserved domains, a pro-domain and a catalytic domain [173]. Cooperatively, MMPs can effectively degrade all components of the extra cellular matrix, including collagens, laminin, fibronectin, vitronectin, and proteoglycans. MMP activity is tightly controlled, not only by gene expression, but also by its localization in the cell, its requirement for proenzyme activation, and the concurrent expression of tissue inhibitors [173]. MMPs also activate intestinal pro-\(\alpha\)-defensins and function as antimicrobials. Several MMPs, through proteolytic cleavage, can modulate the activity of cytokines and chemokines, including IFN-\(\gamma\), IL-1\(\beta\), TNF-\(\alpha\), CXCL8, and CCL7 [174].

The role of MMPs in TB is that \(M.\) \textit{tuberculosis} induces tissue remodeling via induction of MMP-9 to establish itself in the host. Once \(M.\) \textit{tuberculosis} is established within the granuloma, maintaining intact granulomas is beneficial to the host, since it keeps the pathogen under check. During reactivation of a latent infection, excessive MMP-1 secretion leads to matrix degradation and cavitation. Much remains to be learned regarding the spatial and temporal regulation of specific MMPs during lung remodeling in TB. MMP-1 is a key collagenase upregulated in patients with TB and associated with increased lung pathology in transgenic mice [176,177]. MMP-9 has been implicated in the pathogenesis of several inflammatory diseases and is highly expressed in TB [175]. In humans, MMP-9 activity has been correlated with worse outcomes in TB, suggesting a role in susceptibility to \(M.\) \textit{tuberculosis} infection. In zebrafish, MMP-9 regulates monocyte recruitment to the granuloma [178], indicating that MMPs both modulate the immune response to \(M.\) \textit{tuberculosis} and drive pathology [172].
**Heme Oxygenase -1**

HO-1 is a ubiquitously expressed stress-responsive enzyme that catabolizes iron (Fe) protoporphyrin IX (i.e. heme) into equimolar amounts of labile Fe, biliverdin and carbon monoxide (CO) [179]. In contrast to the Fe contained within the protoporphyrin IX ring of heme, which can catalyze the production of free radicals via the Fenton chemistry, several Fe metabolic pathways can neutralize the labile Fe produced through heme catabolism by HO-1. Among those, the induction of ferritin heavy chain (FtH) expression by labile Fe mediates to a large extent the protective effects of HO-1 [180]. The biliverdin produced through heme catabolism by HO-1 can be converted, by biliverdin reductase, into the cytoprotective antioxidant bilirubin [176]. Moreover, CO is also cytoprotective [182] as well as anti-inflammatory [183] presumably, these end-products of heme catabolism can each alone or in combination contribute to the protective effects of HO-1.

Heme oxygenase-1 is one of several molecules emerging as a central player in diseases of the lung and intensive care unit. Although the apparent enzyme is to dispose of heme, its activity results in cytoprotection against oxidative injury and cellular stresses. As the lung interfaces directly with an oxidizing environment, it is expected that heme oxygenase-1 would be involved in many aspects of lung health and disease. The protective effects of heme oxygenase-1 and products of its enzymatic activity, including carbon monoxide, biliverdin and bilirubin, and ferritin, have opened the door to potential therapeutic and disease-monitoring possibilities that one day may be applicable to pulmonary medicine [177]. The heme-catabolizing enzyme heme oxygenase-1 (HO-1; encoded by the Hmox1 gene) inhibits the pathogenesis of several immune-mediated inflammatory diseases. This unusually broad salutary effect is thought to rely on the immunoregulatory actions of HO-1, exerted on innate and adaptive immune cells. According to this notion, HO-1 ‘dampens’ innate and adaptive immune responses, limiting immune-mediated
tissue injury and thus suppressing the pathogenesis of immune-mediated inflammatory diseases [178].

**Extra-pulmonary Tuberculosis An overview**

Extra-pulmonary tuberculosis (EPTB) is an infection spreads outside the respiratory organs causing other forms of tuberculosis. Extra-pulmonary TB occurs most commonly in immuno suppressed persons and young children. Extra-pulmonary involvement can be seen in more than 50 percent of patients with concurrent AIDS and tuberculosis [186,187,188]. The risk of extra-pulmonary tuberculosis and mycobacteremia increases with advancing immuno-suppression. [179]. The most common sites of extra-pulmonary tuberculosis consist of lymphatic, genitourinary, bone and joint, and central nervous system involvement, followed by peritoneal and other abdominal organ involvement[180]. Following the initial bacillemia during the primary infection, multiple sites are seeded with mycobacteria. The local immune responses controlled by macrophages and T lymphocyte contains the bacilli within these sites but is not effective enough to render these sites sterile. These sits are generally those with a rich blood supply, facilitating both the delivery of the mycobacteria and their growth in an oxygen rich environment, leading to extra-pulmonary tuberculosis.

**Tuberculous Lymphadenitis**

Lymphadenitis is the most commonly occurring form of extra-pulmonary tuberculosis. Cervical adenopathy is most common, but inguinal, axillary, mesenteric, mediastinal, and intramammary involvement all have been described [191,192,193]. Lymphadenitis is considered to be the local manifestation of a systemic disease. Patients usually present with slowly enlarging lymph nodes and may otherwise be asymptomatic.
Epidemiology

There are nearly 9 million new cases and 2 million deaths from tuberculosis worldwide every year. (WHO Report, 2005) The incidence of mycobacterial lymphadenitis has increased in parallel with the increase in the incidence of mycobacterial infection worldwide. TB lymphadenitis is seen in nearly 35 per cent of extra-pulmonary TB, which constituted about 15 to 20 per cent of all cases of TB in HIV-positive patients, extra-pulmonary TB accounts for up to 53 to 62 percent cases of TB [1,158,194]. In India, extra-pulmonary TB comprises 20% of all TB cases. Its prevalence in the country varies between 8.3% to 13.1% in different districts according to cohort analysis by the Central TB Division, Ministry of Health and Family Welfare in 2002 [181]. Cervical lymph nodes are the most common site of involvement and reported in 60% to 90% patients with or without involvement of other lymphoid tissue[182]. Cervical lymphadenitis, which is also referred to as scrofula, may be manifestation of a systemic tuberculous disease or a unique clinical entity localized to neck. Mycobacterium tuberculosis is the most common causative agent in India (ICMR special report [197,198]. The incidence of mycobacterial lymphadenitis primarily depends on the endemicity of the Mycobacterium tuberculosis. Lymphadenopathy due to non-tuberculous mycobacterial (NTM) is uncommonly reported from India [158]. In non-tuberculous adenitis, Mycobacterium avium-intracellular complex is the most common causative agent

Pathogenesis

Tuberculous lymphadenitis is a local manifestation of the systemic disease [183] and it may occur during primary tuberculous infection or as a result of reactivation of dormant foci or direct extension from a contiguous focus. Primary infection occurs on initial exposure to tubercle bacilli. Inhaled droplet nuclei are small enough to pass muco-ciliary defenses of bronchi and lodge in terminal alveoli of lungs. The bacilli multiply in the lung, which is called Ghon focus.
The lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. The infection may spread from primary focus to regional lymph nodes. From the regional nodes, organism may continue to spread via the lymphatic system to other nodes or may pass through the nodes to reach blood stream, from where it can spread to virtually all organ of the body[184]. Hilar, mediastinal and paratracheal lymph nodes are the first site of spread of infection from the lung parenchyma. Supraclavicular lymph node involvement may reflect the lymphatic drainage routes for the lung parenchyma [185]. Cervical tuberculous lymphadenitis may represent a spread from the primary focus of infection in the tonsils, adenoids sinonasal or osteomyelitis of the ethmoid bone [193,197]. In initial stage of superficial lymph node involvement progressive multiplication of the M. tuberculosis occurs, the onset of delayed hypersensitivity is accompanied by marked hyperemia, swelling, necrosis and caseation of the centre of the nodes. This can be followed by inflammation, progressive swelling and matting with other nodes within a group. Adhesion to the adjacent skin may result in induration and purplish discolouration. The centre of the enlarging gland becomes soft and caseous material may rupture into surrounding tissue or through skin with sinus formation [184].

Clinical presentation

The unusual features of TB lymphadenitis are its gender and age distribution, as it is more common in females and in the younger age groups, in contrast to pulmonary tuberculosis which is more common in males and in the older age group (Shubha AB et al., 2010). It has a peak age of onset of 20 to 40 years [202]. Patients usually present with slowly enlarging lymph nodes which may otherwise be asymptomatic. Some patients may manifest systemic symptoms such as fever, weight loss, fatigue, and occasional night sweats. These symptoms are more commonly seen in HIV positive patients. M. tuberculosi commonly involves the jugular, posterior triangle,
or supraclavicular lymph nodes (Kumar A, 2009). NTM lymphadenitis commonly involves upper cervical lymph nodes, salivary glands, and surrounding nodes. Lymph node enlargement may appear rapidly and may be associated with fistula formation. Systemic symptoms are not a prominent feature.

**Diagnosis**

A high index of suspicion is needed for the diagnosis of mycobacterial cervical lymphadenitis. A thorough history and physical examination, tuberculin test, staining for acid-fast bacilli, radiologic examination, and fine-needle aspiration cytology (FNAC) will help to arrive at an early diagnosis of mycobacterial lymphadenitis which will allow early institution of treatment before a final diagnosis can be made by biopsy and culture. (Ibekwe AO et al., 1997 and Albright JT et al., 2003).

**Tuberculosis and Type 2 diabetes mellitus**

India accounts for one-fifth of the global burden of tuberculosis (TB) (WHO Report, 2012) and ranks second in the top 10 countries, next to China with a higher burden of diabetes too [189]. Case detection rates for all forms of TB are 59%, but in those patients detected treatment success rates are high at 88%. Diabetes is a chronic metabolic disorder known for its progressive nature and associated with wide range of complications. Apart from this, impairment in immune system is very common among diabetic subjects, which makes them more prone to acquire infections and persistence of the same. World Health Organization (WHO) has recognised diabetes mellitus (DM) as a global epidemic, mostly affecting low, and middle-income counties, where 80% of all deaths from DM occur (WHO Report, 2013). Several epidemiological studies demonstrated that subjects with diabetes are three times at higher risk of getting active TB disease compared to those without diabetes, Available data suggest that in
2011 there were an estimated 61.3 million adults with DM, giving a national adult prevalence of 8.3% in persons aged 20 years and above. A further 77 million people were estimated to have had impaired glucose tolerance. In terms of absolute numbers and given the size of the population, this makes India one of the highest DM and TB burden countries.

The association between diabetes mellitus (DM) and tuberculosis and their synergistic role in causing human disease has been appreciated for a long time but has only lately become a major topic of clinical and fundamental research [12]. While tuberculosis continues to be a major disease burden in developing countries, the rise in prevalence of type 2 DM has been rapid and relentless, and the dual burden of diabetes and tuberculosis clearly represents a serious global public health concern [15]. Type-2 diabetes mellitus (T2DM) and pulmonary tuberculosis (TB) are two of the most prevalent co-morbid conditions in many parts of the world, and the convergence of diabetes and tuberculosis appears to pose a serious threat to healthcare worldwide. Indeed, a variety of clinical and epidemiological studies have identified T2DM as a risk factor for the development of active tuberculosis [13]. In fact, a recent meta-analysis of 13 observational studies on the risk for TB disease among diabetics determined that diabetic patients were 3.1 times more likely to have tuberculosis than non-diabetic individuals [13]. Moreover, T2DM also appears to be associated with a greater severity of TB disease among the infected population and to have a detrimental effect on both disease presentation and response to treatment [12, 15]. Although the clinical and public health significance posed by the dual burden of TB and DM has been increasingly recognized, data examining the immunological and metabolic basis of susceptibility to TB in diabetics remain scarce. Although enhanced susceptibility to TB in patients with DM was initially attributed to a putative immunodeficiency among those with diabetes, recent studies in both animal models and humans are not consistent with this explanation.
Enhanced susceptibility to tuberculosis in patients with diabetes mellitus has been ascribed to a several factors including those related directly to hyperglycemia and insulin resistance as well as to indirect effects on macrophage and lymphocyte function [12]. Several early studies reported reduced pro-inflammatory cytokines in patients with diabetes after infection with *Mycobacterium tuberculosis* [190,191]. Two recent studies, however, reported the elevation of Th1 type cytokines in tuberculosis-infected diabetic hosts; one was conducted in streptozocin-treated mice [192] and another in diabetic and non-diabetic tuberculosis patients [193]. In addition, we have previously shown that Type 2 diabetes mellitus in tuberculosis disease is associated with elevated frequencies of Th1 and Th17 cells and cytokines [194]. Cytokines of the innate and adaptive immune systems orchestrate the immune response to tuberculosis infection, with Type 1, Type 17 and the IL-1 family of cytokines having been implicated in protection against tuberculosis disease [195] in murine systems whereas Type 2 and anti-inflammatory cytokines along with Type 1 interferons (IFN) have been associated with either increased susceptibility to disease and/or enhanced pathology [195].