Introduction
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Tuberculosis (TB) is one of the most important infectious diseases in the world. TB, although largely a curable disease, still remains a major cause of morbidity and mortality worldwide. Although *Mycobacterium tuberculosis* (Mt) infects, 2 billion people worldwide, 90% of Mt-infected individuals are able to resist overt disease (active TB) development and manifest only latent infection [1]; the mechanism by which these individuals resist development of active disease is still not clear. The disease is caused by infection via the lung with the acid-fast bacillus *M. tuberculosis*, first identified as a pathogen by Robert Koch in 1882 [2]. TB is predominantly a disease of the lung, with pulmonary TB accounting for 70% of cases, although *M. tuberculosis* can disseminate to other organs, including lymph nodes, bone, and meninges, and cause extra-pulmonary disease [3]. *M. tuberculosis*, which infects an estimated one of three individuals of the living human population, is an outstanding example of a pathogen that successfully evades adaptive immune responses. Not only does this result in enormous human morbidity and mortality but it also poses unique challenges to the development of an efficacious vaccine to prevent infection or disease [4]. Control of the global TB epidemic has been impaired by the lack of an effective vaccine [5,6], by the emergence of drug-resistant forms of *M. tuberculosis*, and by the lack of sensitive and rapid diagnostics [7].

Protective immunity against *M. tuberculosis* is not completely understood but depends on a wide range of innate and adaptive immune mechanisms. T cell-mediated immune responses are important in the host control of *M. tuberculosis* infection. The ability of CD4+ T cells to produce interferon-γ (IFN-γ), which activates phagocytes to contain the intracellular pathogen, is central in protection. Indeed, T helper 1 (Th1) cells and the IFN-γ that they produce are crucial for protection against disease. This is evident from the increased risk of tuberculosis in individuals
with deficiencies in their IFN-γ and interleukin-12 (IL-12; which promotes Th1 cell differentiation) signaling pathways [8]. Many other CD4⁺ T cell subsets, in addition to IFN-γ producing Th1 cells, may also have a role, for example, IL-17-producing CD4⁺ T cells were shown to mediate the recruitment of protective Th1 cells to the lung upon *M. tuberculosis* challenge. Furthermore, increased frequencies of regulatory CD4⁺ T regulatory (Treg) cells during active disease may ensure that the Th1 cell response is not excessive, and this would help minimize lung damage in tuberculosis [9]. The CD8⁺ T cell response to *M. tuberculosis* is normally of a lower magnitude than the CD4⁺ T cell response; however, CD8⁺ T cells may modulate phagocyte activity or produce molecules such as granulysin that may be directly cytotoxic to the mycobacteria [10,11]. Similarly, other cytokines, in addition to IFN-γ, may also be crucial; for example, tumor necrosis factor (TNF) is important for establishing the granuloma, which is a well-organized collection of innate and adaptive cells that forms to contain the pathogen [10]. Development of TB disease results from interactions among the environment, the host and the pathogen and known risk factors include HIV co-infection, immunodeficiency, diabetes mellitus, overcrowding, malnutrition, and general poverty [7].

Diabetes mellitus (DM) has been recognized as a risk factor for Tuberculosis (TB) for decades, but although the association between Type 2 diabetes mellitus (T2DM) and TB is not new, only with the recent explosive DM pandemic has the importance of understanding the relationships between T2DM and TB emerged as a global health priority [12]. Previous reports found that patients with DM were two to eight times at higher risk for development of active TB and at approximately three times higher risk for development of pulmonary TB (PTB) as compared with patients without DM [12,13,14]. In addition to increasing the risk for reactivating latent TB infection, there is also evidence that DM is also associated with greater severity of TB
disease affecting both disease presentation and response to treatment. Overall, the data suggest that DM is associated with greater radiographic severity of TB disease, delayed sputum conversion, unfavorable outcomes and increased risk of relapse [12,15]. In addition, DM might predispose to the development of drug-resistant TB [16,17]. Despite the clinical and public health significance posed by the dual burden of TB and DM, very little is known about the immunological and biochemical mechanisms of susceptibility.