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PERSPECTIVE

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IFNγ-producing CD4$^+$ T lymphocytes: the double-edged swords in tuberculosis

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Abstract

IFNγ-producing CD4$^+$ T cells (IFNγ$^+$CD4$^+$ T cells) are the key orchestrators of protective immunity against *Mycobacterium tuberculosis* (*Mtb*). Primarily, these cells act by enabling *Mtb*-infected macrophages to enforce phagosome-lysosome fusion, produce reactive nitrogen intermediates (RNIs), and activate autophagy pathways. However, TB is a heterogeneous disease and a host of clinical and experimental findings has also implicated IFNγ$^+$CD4$^+$ T cells in TB pathogenesis. High frequency of IFNγ$^+$CD4$^+$ T cells is the most invariable feature of the active disease. Active TB patients mount a heightened IFNγ$^+$CD4$^+$ T cell response to mycobacterial antigens and demonstrate an IFNγ-inducible transcriptomic signature. IFNγ$^+$CD4$^+$ T cells have also been shown to mediate TB-associated immune reconstitution inflammatory syndrome (TB–IRIS) observed in a subset of antiretroviral therapy (ART)-treated HIV- and *Mtb*-coinfected people. The pathological face of IFNγ$^+$CD4$^+$ T cells during mycobacterial infection is further uncovered by studies in the animal model of TB–IRIS and in *Mtb*-infected PD-1$^{-/-}$ mice. This manuscript encompasses the evidence supporting the dual role of IFNγ$^+$CD4$^+$ T cells during *Mtb* infection and sheds light on immune mechanisms involved in protection versus pathogenesis.

Keywords: Tuberculosis, Protection, Pathogenesis, IFN-gamma, CD4$^+$ T cell, TB–IRIS, Macrophage, Neutrophil, Necrosis, Matrix metalloproteinase, Granuloma

Background

Tuberculosis (TB) continues to be one of the major causes of morbidity and mortality worldwide [1]. *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB, mainly resides in host macrophages and modulates their cellular physiology to support its own growth and duplication. Although macrophages are armed with a battery of antimicrobial mechanisms, elimination of the intracellular bacilli from these cells is largely dependent on activation signals arising from CD4$^+$ T lymphocytes [2]. A key role in CD4$^+$ T cell-mediated macrophage activation can be attributed to IFNγ, which helps in *Mtb* clearance by inducing iNOS expression and enforcing phagosome-lysosome fusion [2]. T_H1-polarized CD4$^+$ T cells are the main source of IFNγ during mycobacterial infections. Significantly enhanced susceptibility to TB in people suffering from HIV/AIDS or inherited IFNγ deficiencies underlines the critical role of IFNγ-producing CD4$^+$ T cells (IFNγ$^+$CD4$^+$ T cells) in host resistance to *Mtb* [2].

The protective role of IFNγ$^+$CD4$^+$ T cells against *Mtb*, however, is one side of the story. With advancements in TB immunobiology, a host of studies has emerged to show that IFNγ$^+$CD4$^+$ T cells are directly or indirectly involved in TB pathogenesis. It has been observed that active TB patients mount a heightened T_H1 type of CD4$^+$ T cell responses against *Mtb* antigens [3]. T_H1 type of CD4$^+$ T cell response can also be observed in latently infected people, but its aggravation commonly precedes the reactivation of latent TB into the active disease [3]. Similar aggravation of T_H1 type of antimycobacterial immunity also occurs in TB–associated immune reconstitution inflammatory syndrome (TB–IRIS) observed in a subset of antiretroviral therapy (ART)-treated HIV- and *Mtb*-coinfected people [4]. Studies in both human patients and the animal models have attributed the pathogenesis of TB–IRIS to hyperactive IFNγ$^+$CD4$^+$ T cell responses [3, 5].

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The present manuscript elaborates on the clinical and experimental findings demonstrating the protective versus the pathological role of IFNγ$^+$CD4$^+$ T cells during *Mtb* infection. It further sheds light on the underlying mechanisms of IFNγ$^+$CD4$^+$ T cell-mediated protection against TB and TB pathogenesis. Besides broadening individual's perspective of TB immunobiology, this manuscript will prompt the TB vaccinologists to retrospect their strategies to combat this age-old disease.

Protective role of IFNγ$^+$CD4$^+$ T cells against *Mtb*

Nearly one-third of the world's population is infected with *Mtb* [6]. However, most of the latently infected people never develop active TB, demonstrating the competence of their immune system to contain the bacilli [2]. Both human and animal studies have established that IFNγ$^+$CD4$^+$ T cells are the key mediators of protective immunity against *Mtb*. It has been shown that mice deficient in IFNγ are unable to control low-dose *Mtb* infection and succumb to the progressive disease [7–9]. As CD4$^+$ T lymphocytes are the most important source of IFNγ during mycobacterial infection, animals deficient in CD4$^+$ T cells have also been found to be susceptible to low-dose *Mtb* infection. Other lymphocyte subsets such as CD8$^+$ T cells, natural killer (NK) cells, CD1-restricted T cells and γδ T cells also secrete IFNγ in response to *Mtb* infection, but they are unable to compensate for the lack of CD4$^+$ T lymphocytes as a source of this cytokine [2]. Mounting of IFNγ$^+$CD4$^+$ T cell responses relies on IL-12 secretion by antigen-presenting cells. Consistently, animals deficient in IL-12 are also unable to control *Mtb* infection and die of the progressive disease [10, 11].

The importance of IL-12/IFNγ axis in protection against human TB is illustrated by people having mutations in the genes encoding these cytokines [2]. Such people exhibit Mendelian susceptibility to mycobacterial disease (MSMD) and are predisposed to progressive infection with BCG and environmental non-tuberculous mycobacteria [12, 13]. Similarly, lack of IFNγ receptor 1 (IFNγR1) has been shown to cause fatal lepromatoid BCG infection and disseminated non-tuberculous mycobacterial disease [13, 14]. Since IFNγ production depends on IL-12, deficiency in IL-12 receptor β1 (IL-12Rβ1) has also been shown to result in severe primary TB in the affected individuals [2, 15, 16].

One of the most important evidence supporting the protective role of CD4$^+$ T cells against human TB is provided by people suffering from HIV/AIDS. Infection with HIV leads to selective deletion of CD4$^+$ T lymphocytes, which in turn results in the significantly enhanced susceptibility to TB [17]. Owing to the unrestricted growth of the bacilli, TB frequently affects extrapulmonary sites in HIV/AIDS patients, and can also occur in disseminated form in the severe cases. Similar to the case of HIV/AIDS, idiopathic CD4$^+$ T cell lymphocytopenia has also been shown to increase TB susceptibility and its associated mortality [18, 19].

Mechanisms of IFNγ$^+$CD4$^+$ T cell-mediated protection against *Mtb*

Despite the long known role of IFNγ$^+$CD4$^+$ T cells in protection against *Mtb*, its underlying mechanisms are not completely understood. Studies aimed at elucidating the mechanisms of IFNγ-mediated protection against *Mtb* have largely focused on its effect on the infected macrophages. These studies have revealed that IFNγ-activated macrophages eliminate the intracellular bacilli primarily by: (i) producing reactive nitrogen intermediates (RNIs), (ii) enforcing phagosome-lysosome fusion, and (iii) activating the autophagy pathway.

Nitric oxide and other RNIs help in the clearance of the intracellular bacilli by inflicting oxidative damage on to them [20]. *Mtb*-infected macrophages, however, did not produce copious amounts of RNIs in the absence of activating signals. IFNγ promotes iNOS expression in *Mtb*-infected macrophages which catabolizes L-arginine into nitric oxide (NO), which in turn is used as the substrate to generate other RNIs [20, 21]. The indispensable role of RNIs in protection against TB is demonstrated by the enhanced susceptibility of iNOS$^{-/-}$ mice to *Mtb* [22]. Besides having a direct effect on intracellular *Mtb*, RNIs can also reduce the bacillary load by inducing apoptotic cell death in infected macrophages [21]. Apoptosis of infected macrophages is a protective response and is associated with diminished *Mtb* survival. As *Mtb*-containing apoptotic bodies are readily phagocytosed by dendritic cells, it also augments *Mtb*-specific immunity [23].

One of the important strategies evolved by *Mtb* and other pathogenic mycobacteria to survive within infected macrophages is to inhibit phagosome maturation. By excluding vacuolar H$^+$-ATPase, pathogenic mycobacteria inhibit phagosome acidification and escape the degradative action of lysosomal acid hydrolases [24]. Studies with *Mtb*-infected macrophages have shown that IFNγ signalling can activate these cells to enforce phagosome maturation and eliminate the intracellular bacilli [25]. Transcription of pH-responsive genes in IFNγ-activated macrophages and attenuation of the acid-susceptible *Mtb* strains in the infected animals shows that IFNγ signalling enables the infected macrophages to overcome phagosomal maturation block both in vitro and in vivo [26, 27].

Autophagy was initially described as a cell survival mechanism during starvation. A plethora of recent studies has demonstrated that autophagy also plays a key role in protection against the intracellular

pathogens including *Mtb* [28]. Antimycobacterial effects of autophagy have been attributed to enhanced killing of mycobacteria within the infected cells and reduced inflammation in the affected tissues [29, 30]. The genetic link between autophagy, inflammatory conditions, and TB susceptibility provides an important support to the role of anti-inflammatory and bactericidal properties of autophagy in protection against human TB [31, 32]. IFNγ is a potent autophagy inducer in the *Mtb*-infected macrophages and produces the cellular effects similar to that of starvation [33]. Studies by Matsuzawa et al. have shown that IFNγ-induced macrophage autophagy is mediated by JAK1/2, PI3K, and p38MAPK and is independent of STAT1 [34]. Interestingly, T_H2 cytokines IL-4 and IL-13 have been shown to hamper IFNγ-induced autophagy in macrophages, suggesting an alternate mechanism for their deleterious effects on anti-*Mtb* immunity [35].

Pathological role of IFNγ$^+$CD4$^+$ T cells during *Mtb* infection

Despite their protective role against *Mtb*, IFNγ$^+$CD4$^+$ T cells have been implicated in TB pathogenesis by a number of studies. This section presents the clinical and experimental findings demonstrating the involvement of IFNγ$^+$CD4$^+$ T cells in TB pathogenesis. Notably, the pathological character of IFNγ$^+$CD4$^+$ T cells is predominantly manifested in a subset of *Mtb*-infected immunocompetent adults and TB–IRIS patients, wherein these cells exhibit excessive responsiveness to mycobacterial antigens [3]. In immunocompetent adults, active TB develops from the reactivation of latent infection and primarily affects lung tissue. An overly intense IFNγ$^+$CD4$^+$ T cell response is the most important immunological parameter distinguishing the active disease from latent infection in these people [27]. On the contrary, the incompetence of host immune system to contain the bacilli is responsible for TB pathogenesis in young children and immunodeficient people [3].

Classical evidence supporting the pathological role of IFNγ$^+$CD4$^+$ T cells during *Mtb* infection is provided by tuberculin skin testing (TST)—a diagnostic test to examine *Mtb* exposure. TST involves the intradermal injection of purified *Mtb* antigens, followed by monitoring for the delayed-type hypersensitivity (DTH) reaction seen as local skin induration. As DTH is mediated by T_H1-polarized CD4$^+$ T cells, a larger area of skin induration in TB patients demonstrates a strong association between IFNγ$^+$CD4$^+$ T cells and the active disease [36]. In latently infected people, the area of skin induration has been found to correlate with the future risk of active TB [37]. Therefore, an intense tuberculin reaction is considered as more serious and indicates the likelihood of the concomitant active disease or its future risk [38]. However, it should be noted that lack of reactivity or anergy to *Mtb* antigens does not predict the resistance to active TB. As it signifies the lack of T_H1 response to mycobacteria, anergy to mycobacterial antigens is associated with enhanced risk of morbidity and mortality in the infected people [39].

Studies aimed at characterizing the host immune response during *Mtb* infection further suggest the involvement of IFNγ$^+$CD4$^+$ T cells in TB pathogenesis. These studies have shown the heightened levels of IFNγ in lung tissue, broncho-alveolar lavage (BAL) fluid, pleural effusion, and lymph nodes of active TB patient [2]. BAL fluid IFNγ levels in active TB patients have been found to directly correlate with the disease severity and subsided with its successful treatment [40]. These findings are supported by transcriptomic analysis of whole blood cells from TB patients and healthy controls by Berry et al. [41]. The authors have observed an enhanced transcription of IFNγ-inducible genes in active TB patients, compared with latently infected people and healthy controls. Consistent with enhanced IFNγ levels, increased frequency of IFNγ-producing CD4$^+$ T cells during active TB has been reported by several studies [42–45]. Although most of these studies have shown the polyfunctionality of CD4$^+$ T cells in active TB patients, the specific role of IFNγ$^+$CD4$^+$ T cells in TB pathogenesis is evident from animal studies.

Unequivocal support for the pathological role of IFNγ-producing CD4$^+$ T cells during *Mtb* infection is provided by TB–associated immune reconstitution inflammatory syndrome (TB–IRIS). Affecting a subset of antiretroviral therapy (ART)-treated HIV- and *Mtb*-coinfected people, TB–IRIS occurs in diverse manifestations and poses a major challenge in the clinical management of HIV in these people. Mechanistically, the ART-mediated decline in the viral load allows for the rapid expansion of *Mtb*-specific CD4$^+$ T cells [4, 46]. Both terminally-differentiated and effector memory CD4$^+$ T cells with specificity to *Mtb* antigens have been shown to expand in ART-treated HIV- and *Mtb*-coinfected people [47, 48]. Exaggeration of antimycobacterial immunity (with CD4$^+$ T cell expansion) in the ART-treated HIV- and *Mtb*-coinfected people is evidenced by their conversion from a 'negative' TST status to a strongly 'positive' one [49]. Interestingly, ART-treated people who develop TB–IRIS demonstrate a more strong T_H1 type of CD4$^+$ T cell response to *Mtb* antigens, compared with those who do not experience this condition [46, 50]. Evidently, immunological parameters in TB–IRIS patients pint out an active participation of IFNγ$^+$CD4$^+$ T cells in TB pathogenesis.

Direct involvement of IFNγ$^+$CD4$^+$ T cells in TB–IRIS development is confirmed by a mouse model, wherein

the human disease has been mimicked by adoptively transferring naïve $CD4^+$ T cells into *M. avium*-infected, T cell-deficient ($TCR\alpha^{-/-}$) mice [5]. It has been shown that adoptively transferred $CD4^+$ T lymphocytes rapidly acquired T_H1 phenotype and led to the failure of lung function, wasting and eventual death of host animals. The authors have further noted that ability of the donor lymphocytes to cause lung pathology was lost in IFNγ-deficient $CD4^+$ T cells [5]. Thus, both human and animal studies attribute the pathogenesis of TB–IRIS to *Mtb*-specific $IFN\gamma^+CD4^+$ T cells.

Studies in PD-$1^{-/-}$ mice and a macaque model further confirm the direct involvement of $IFN\gamma^+CD4^+$ T cells in TB pathogenesis [51]. PD-1 is present on T lymphocytes and its engagement by PD-L1 results in the negative regulation of T cell functions [2]. As PD-L1 was found to be abundant in TB patients, researchers wondered over the outcome of PD-1 signalling during *Mtb* infection and examined it using knockout mouse strains [51, 52]. Surprisingly, it was observed that instead of developing resistance to *Mtb*, PD-$1^{-/-}$ mice exhibited significantly enhanced susceptibility to mycobacterial infection. Further analysis of TB pathogenesis in PD-$1^{-/-}$ mice revealed that these animals mount an exaggerated $IFN\gamma^+CD4^+$ T cell response to the bacilli [51]. Besides PD-1, $CD4^+CD25^+FoxP3^+$ T regulatory (T_{reg}) cells can also suppress the exaggerated $IFN\gamma^+CD4^+$ T cell response during mycobacterial infection [53, 54]. In macaque model of TB, higher frequency of T_{reg} cells has been observed in the animals who would develop the latent infection, compared with those that would develop the active disease [55]. These findings in PD-$1^{-/-}$ mice and the macaque model demonstrate that aggravated $IFN\gamma^+CD4^+$ T cell response is the key mediator of TB pathology and that its inhibition prevents the reactivation of latent infection into the active disease.

It is evident from the above-discussed findings that protective versus pathological character of $IFN\gamma^+CD4^+$ T cells is defined by the degree of their responsiveness to *Mtb*. A hyperactive $IFN\gamma^+CD4^+$ T cell response to *Mtb* is pathological in nature and is frequently observed in adult TB patients. After initial exposure, most of the immunocompetent adults would contain *Mtb* infection without developing any disease symptom. This condition of asymptomatic *Mtb* infection, referred to as latent TB, represents the state of protection against the bacilli. Latent TB persists lifelong in most, but nearly 10% of the infected people who would develop active TB in their lifetime. As discussed above, reactivation of latent infection into the active disease can be attributed to aggravated anti-*Mtb* $IFN\gamma^+CD4^+$ T cell responses. Similar aggravation of *Mtb*-specific $IFN\gamma^+CD4^+$ T cell responses is to blame for TB–IRIS development in a subset of HIV- and *Mtb*-coinfected people. In contrast to immunocompetent adults and TB–IRIS patients, most young children and immunodeficient people mount a hypoactive $IFN\gamma^+CD4^+$ T cell response to *Mtb*, which is inefficient in containing the bacilli. Therefore, *Mtb* infection in these people leads to primary TB, frequently affecting the extrapulmonary sites. The protective versus pathological role of $IFN\gamma^+CD4^+$ T cells during *Mtb* infection is summarized in Fig. 1.

Mechanisms of $IFN\gamma^+CD4^+$ T cell-mediated TB pathogenesis

Preferential expression of IFNγ-inducible genes in neutrophils (and to some extent in monocytes) during active TB indicates the involvement of these cells in IFNγ-mediated TB pathogenesis [56]. Neutrophils are frequently infected by *Mtb* and are abundant at the site of active disease. Although these cells may help in the containment of the bacilli during the initial phase of infection, their involvement in TB pathogenesis is supported by a number of studies. It has been shown that the frequency of neutrophils at the site of active disease correlates with the disease severity [57]. Higher neutrophil count (neutrophilia) is associated with low sputum conversion and poor TB prognosis [57, 58]. Increased frequency of neutrophils at the affected site has also been demonstrated in susceptible mouse strains and their depletion from these animals resulted in the enhanced resistance to *Mtb* [59]. Interestingly, IFNγ has been shown to increase neutrophil lifespan which may

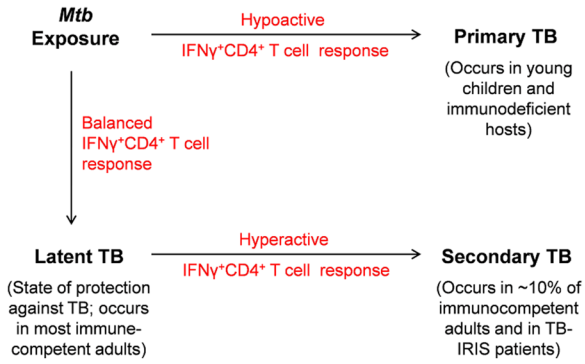

Fig. 1 Protective versus pathological role of $IFN\gamma^+CD4^+$ T cells during *Mycobacterium tuberculosis* (*Mtb*) infection. *Mtb* exposure in most young children and immunodeficient people evokes a hypoactive $IFN\gamma^+CD4^+$ T cell response, which is inefficient in containing the bacilli. Therefore, *Mtb* infection in these people results in primary TB, frequently affecting the extrapulmonary sites. In contrast, most of the immunocompetent adults mount a balanced immune response to *Mtb* and contain it in the form of latent TB. With the course of time, $IFN\gamma^+CD4^+$ T cell response would aggravate in nearly 10% of latently infected people, leading to the development of active TB in them. Similar aggravation of $IFN\gamma^+CD4^+$ T cells is to blame for TB–IRIS development in a subset of ART-treated, HIV- and *Mtb*-coinfected people

potentially contribute to neutrophilia in the infected animals. Besides, the functional activity of neutrophils is also bolstered by IFNγ [60].

Mtb-infected neutrophils and macrophages are the potent producers of toxic molecules and matrix degrading enzymes, including elastases, myeloperoxidases, collagenases, and serine proteases. MMP-1 is a key collagenase up-regulated in TB patients and its enhanced levels have been shown to be associated with increased lung pathology in a transgenic mouse model [61]. MMP-9, which has been implicated in the pathogenesis of many inflammatory diseases, is also abundant in active TB patients and is associated with poor prognosis of the disease [62]. Interestingly, a heightened $IFN\gamma^+CD4^+$ T cell response has been shown to be associated with enhanced MMP production [63]. Additionally, $IFN\gamma^+CD4^+$ T cell-activated neutrophils and macrophages produce copious amounts of reactive nitrogen intermediates (RNIs) and reactive oxygen species (ROS) which can damage the healthy tissue [64]. A combined action of tissue-digesting enzymes and RNI/ROS can result in the dismantling of granuloma and progression of latent infection into active TB. Supporting this, higher neutrophil and inflammatory monocyte frequency, elevated serum nitrate levels, and enhanced MMP expression have been observed in the *Mtb*-infected animals, wherein pathology was mediated by $IFN\gamma^+CD4^+$ T cells [5, 63].

Necrotic cell death of neutrophils and macrophages also plays a key role in TB pathogenesis. The pathological role of necrotic cell death in TB has been demonstrated elegantly in the zebrafish model, wherein increased production of LXA4 (an inducer of necrosis) resulted in reduced host resistance to mycobacterial infection [65]. These findings are relevant in human TB, for polymorphisms in *Alox5* and *Ita4h*, which regulate necrosis versus apoptosis, has been shown to define TB susceptibility [65, 66]. Although IFNγ promotes the necrosis in *Mtb*-infected macrophages [67], its effect on neutrophils is not clear. It is probable that increased oxidative stress in the presence of IFNγ could direct *Mtb*-infected neutrophils to the necrotic pathway.

Another interesting mechanism of IFNγ-mediated TB pathology has been demonstrated by Aly and co-workers [68]. The authors have demonstrated that by altering the balance between angiostatic and angiogenic mediators, IFNγ disrupts the granuloma vascularization and leads to a hypoxic central core. Deprived of nutrients and oxygen supply, the core of granuloma necrotizes and undergoes caseation, resulting in the activation of latent infection into active TB [68]. It is likely that the combined action of this and above-discussed mechanisms leads to $IFN\gamma^+CD4^+$ T cell-mediated TB pathogenesis in immunocompetent adults. The individual contribution of these mechanisms to the development of TB, however, awaits further analysis.

Conclusion and future perspectives

$IFN\gamma^+CD4^+$ T cells are the key orchestrators of antimycobacterial immunity. However, with increasing recognition of TB as a heterogeneous disease [2], $IFN\gamma^+CD4^+$ T cells have also been implicated in TB pathogenesis. A more intense tuberculin reaction, which is driven by $IFN\gamma^+CD4^+$ T cells, is frequently observed in TB patients, and its intensity in latently infected people indicates the future risk of the active disease in them [27]. Active TB patients exhibit enhanced IFNγ levels in different tissues which correlate with disease severity [2, 40]. In keeping with this, increased expression of IFNγ-inducible genes has been observed in active TB patients, compared with latently infected people and healthy controls [56]. The pathological face of $IFN\gamma^+CD4^+$ T cells during *Mtb* infection is also obvious in TB–IRIS patients and its animal model [5]. Enhanced susceptibility of $PD\text{-}1^{-/-}$ mouse strains, which mount heightened $IFN\gamma^+CD4^+$ T cell responses to *Mtb*, further support the pathological role of these cells during *Mtb* infection [51]. Disrupted granuloma vascularization and/or neutrophil- and macrophage-mediated dismantling of granuloma architecture are important mechanisms of $IFN\gamma^+CD4^+$ T cell-mediated TB pathology.

Owing to earlier studies demonstrating the protective role of $IFN\gamma^+CD4^+$ T cells during *Mtb* infection, vaccinologists had been aiming to boost $IFN\gamma^+CD4^+$ T cell response as a strategy to TB immunoprophylaxis. Unfortunately, these strategies have failed to confer significant protection against human TB [69]. Failure of rationally designed vaccines against human TB and the dual role of $IFN\gamma^+CD4^+$ T cells during *Mtb* infection call for retrospection of our approach to TB vaccination. It is imperative that instead of boosting antimycobacterial immunity, researchers must attempt to dampen the $IFN\gamma^+CD4^+$ T cell responses in susceptible immunocompetent adults to prevent TB in them. Likely success of these approaches against human TB is suggested by animal studies.

Conclusively, a significant volume of scientific data demonstrates that, besides conferring protection against *Mtb*, $IFN\gamma^+CD4^+$ T cells also play a key role in TB pathogenesis in immunocompetent adults. As adult TB represents the major burden of the disease, there is an urgency of legitimate efforts to evaluate the immune-dampening approaches in these patients. Not only these approaches can improve treatment outcome against the active disease, they are also likely to help in the effective management of drug-resistant TB, which has emerged as a major challenge for the clinicians.

Abbreviations
TB: tuberculosis; *Mtb*: *Mycobacterium tuberculosis*; IFN: interferon; TB–IRIS: tuberculosis–associated immune reconstitution inflammatory syndrome; PD-1: programmed cell death protein-1; iNOS: inducible nitric oxide synthase; RNIs: reactive nitrogen intermediates; MMP: matrix metalloproteinase.

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Competing interests
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References

1. World Health Organization. Global tuberculosis report 2016. 2016
2. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP (2013) The immune response in tuberculosis. Annu Rev Immunol 31:475–527. doi:10.1146/annurev-immunol-032712-095939
3. Kumar P (2016) Adult pulmonary tuberculosis as a pathological manifestation of hyperactive antimycobacterial immune response. Clin Trans Med 5(1):38
4. Mahnke YD, Greenwald JH, DerSimonian R, Roby G, Antonelli LR, Sher A et al (2012) Selective expansion of polyfunctional pathogen-specific CD4+ T cells in HIV-1–infected patients with immune reconstitution inflammatory syndrome. Blood 119(13):3105–3112
5. Barber DL, Mayer-Barber KD, Antonelli LR, Wilson MS, White S, Caspar P et al (2010) Th1-driven immune reconstitution disease in Mycobacterium avium–infected mice. Blood 116(18):3485–3493
6. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA 282(7):677–686
7. Flynn JL, Chan J, Triebold KJ, Dalton DK, Stewart TA, Bloom BR (1993) An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. J Exp Med 178(6):2249–2254
8. Cooper AM, Dalton DK, Stewart TA, Griffin J, Russell D, Orme I (1993) Disseminated tuberculosis in interferon gamma gene-disrupted mice. J Exp Med 178(6):2243–2247
9. Green AM, DiFazio R, Flynn JL (2013) IFN-γ from CD4 T cells is essential for host survival and enhances CD8 T cell function during *Mycobacterium tuberculosis* infection. J Immunol 190(1):270–277
10. Cooper AM, Magram J, Ferrante J, Orme IM (1997) Interleukin 12 (IL-12) is crucial to the development of protective immunity in mice intravenously infected with *Mycobacterium tuberculosis*. J Exp Med 186(1):39–45
11. Cooper AM, Mayer-Barber KD, Sher A (2011) Role of innate cytokines in mycobacterial infection. Mucosal Immunol 4(3):252–260
12. Casanova J-L, Abel L (2002) Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 20(1):581–620
13. Dorman SE, Picard C, Lammas D, Heyne K, van Dissel JT, Baretto R et al (2004) Clinical features of dominant and recessive interferon γ receptor 1 deficiencies. Lancet 364(9451):2113–2121
14. Jouanguy E, Lamhamedi-Cherradi S, Altare F, Fondanèche M-C, Tuerlinckx D, Blanche S et al (1997) Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid bacillus Calmette–Guerin infection and a sibling with clinical tuberculosis. J Clin Investig 100(11):2658
15. Boisson-Dupuis S, El Baghdadi J, Parvaneh N, Bousfiha A, Bustamante J, Feinberg J et al (2011) IL-12Rβ1 deficiency in two of fifty children with severe tuberculosis from Iran, Morocco, and Turkey. PLoS ONE 6(4):e18524
16. Caragol I, Raspall M, Fieschi C, Feinberg J, Larrosa MN, Hernández M et al (2003) Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor β1 deficiency. Clin Infect Dis 37(2):302–306
17. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC et al (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 163(9):1009–1021
18. Ahmad DS, Esmadi M, Steinmann WC (2013) Idiopathic CD4 lymphocytopenia: spectrum of opportunistic infections, malignancies, and autoimmune diseases. Avicenna J Med 3(2):37
19. Socio GV, Gerli R, Menichetti F (1999) Disseminated tuberculosis and idiopathic CD4+ T-lymphocytopenia. Clin Microbiol Infect 5(10):653–654
20. Fang FC (2004) Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. Nat Rev Microbiol 2(10):820–832
21. Herbst S, Schaible UE, Schneider BE (2011) Interferon gamma activated macrophages kill mycobacteria by nitric oxide induced apoptosis. PLoS ONE 6(5):e19105
22. MacMicking JD, North RJ, LaCourse R, Mudgett JS, Shah SK, Nathan CF (1997) Identification of nitric oxide synthase as a protective locus against tuberculosis. Proc Natl Acad Sci 94(10):5243–5248
23. Behar SM, Martin CJ, Nunes-Alves C, Divangahi M, Remold HG (2011) Lipids, apoptosis, and cross-presentation: links in the chain of host defense against *Mycobacterium tuberculosis*. Microbes Infect 13(8):749–756
24. Wong D, Bach H, Sun J, Hmama Z, Av-Gay Y (2011) *Mycobacterium tuberculosis* protein tyrosine phosphatase (PtpA) excludes host vacuolar-H+–ATPase to inhibit phagosome acidification. Proc Natl Acad Sci 108(48):19371–19376
25. McKinney JD, Gomez JE (2003) Life on the inside for *Mycobacterium tuberculosis*. Nat Med 9(11):1356–1358
26. Ehrt S, Schnappinger D (2009) Mycobacterial survival strategies in the phagosome: defence against host stresses. Cell Microbiol 11(8):1170–1178
27. North RJ, Jung Y-J (2004) Immunity to tuberculosis. Annu Rev Immunol 22:599–623
28. Campoy E, Colombo MI (2009) Autophagy in intracellular bacterial infection. Biochimica et biophysica acta (BBA)-molecular. Cell Res 1793(9):1465–1477
29. Songane M, Kleinnijenhuis J, Netea MG, van Crevel R (2012) The role of autophagy in host defence against *Mycobacterium tuberculosis* infection. Tuberculosis 92(5):388–396
30. Castillo EF, Dekonenko A, Arko-Mensah J, Mandell MA, Dupont N, Jiang S et al (2012) Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation. Proc Natl Acad Sci 109(46):E3168–E3176
31. Deretic V (2014) Autophagy in tuberculosis. Cold Spring Harb Perspect Med 4(11):a018481
32. Levine B, Mizushima N, Virgin HW (2011) Autophagy in immunity and inflammation. Nature 469(7330):323–335
33. Rovetta AI, Pena D, Hernández Del Pino RE, Recalde GM, Pellegrini J, Bigi F et al (2014) IFNG-mediated immune responses enhance autophagy against *Mycobacterium tuberculosis* antigens in patients with active tuberculosis. Autophagy 10(12):2109–2121
34. Matsuzawa T, Kim B-H, Shenoy AR, Kamitani S, Miyake M, MacMicking JD (2012) IFN-γ elicits macrophage autophagy via the p38 MAPK signaling pathway. J Immunol 189(2):813–818
35. Harris J, De Haro SA, Master SS, Keane J, Roberts EA, Delgado M et al (2007) T helper 2 cytokines inhibit autophagic control of intracellular *Mycobacterium tuberculosis*. Immunity 27(3):505–517
36. North RJ, Jung Y-J (2004) Immunity to tuberculosis. Annu Rev Immunol 22(1):599–623
37. Comstock GW, Livesay VT, Woolpert SF (1974) The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 99(2):131–138
38. Doherty TM, Demissie A, Olobo J, Wolday D, Britton S, Eguale T et al (2002) Immune responses to the *Mycobacterium tuberculosis*-specific antigen ESAT-6 signal subclinical infection among contacts of tuberculosis patients. J Clin Microbiol 40(2):704–706
39. Maher J, Kelly P, Hughes P, Clancy L (1992) Skin anergy and tuberculosis. Respir Med 86(6):481–484
40. Tsao T, Huang C, Chiou W, Yang P, Hsieh M, Tsao K (2002) Levels of interferon-γ and interleukin-2 receptor-α for bronchoalveolar lavage fluid

and serum were correlated with clinical grade and treatment of pulmonary tuberculosis. Int J Tuberc Lung Dis 6(8):720–727
41. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T (2010) An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature 466(7309):973–977
42. Sester U, Fousse M, Dirks J, Mack U, Prasse A, Singh M et al (2011) Whole-blood flow-cytometric analysis of antigen-specific CD4 T-cell cytokine profiles distinguishes active tuberculosis from non-active states. PLoS ONE 6(3):e17813
43. Herrera MT, Torres M, Nevels D, Perez-Redondo CN, Ellner JJ, Sada E et al (2009) Compartmentalized bronchoalveolar IFN-γ and IL-12 response in human pulmonary tuberculosis. Tuberculosis 89(1):38–47
44. Qiu Z, Zhang M, Zhu Y, Zheng F, Lu P, Liu H et al (2012) Multifunctional CD4 T cell responses in patients with active tuberculosis. Sci Rep 2:216
45. Gerosa F, Nisii C, Righetti S, Micciolo R, Marchesini M, Cazzadori A et al (1999) CD4+ T cell clones producing both interferon-γ and interleukin-10 predominate in bronchoalveolar lavages of active pulmonary tuberculosis patients. Clin Immunol 92(3):224–234
46. Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, Gicquel B et al (2006) Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. Aids 20(2):F1–F7
47. Sutherland JS, Young JM, Peterson KL, Sanneh B, Whittle HC, Rowland-Jones SL et al (2010) Polyfunctional CD4+ and CD8+ T cell responses to tuberculosis antigens in HIV-1–infected patients before and after antiretroviral treatment. J Immunol 184(11):6537–6544
48. Wilkinson KA, Seldon R, Meintjes G, Rangaka MX, Hanekom WA, Maartens G et al (2009) Dissection of regenerating T-Cell responses against tuberculosis in HIV-infected adults sensitized by *Mycobacterium tuberculosis*. Am J Respir Crit Care Med 180(7):674–683
49. Narita M, Ashkin D, Hollender ES, Pitchenik AE (1998) Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med 158(1):157–161
50. Meintjes G, Wilkinson KA, Rangaka MX, Skolimowska K, Van Veen K, Abrahams M et al (2008) Type 1 helper T cells and FoxP3-positive T cells in HIV–tuberculosis-associated immune reconstitution inflammatory syndrome. Am J Respir Crit Care Med 178(10):1083–1089
51. Sakai S, Kauffman KD, Sallin MA, Sharpe AH, Young HA, Ganusov VV et al (2016) CD4 T cell-derived IFN-γ plays a minimal role in control of pulmonary *Mycobacterium tuberculosis* infection and must be actively repressed by PD-1 to prevent lethal disease. PLoS Pathog 12(5):e1005667
52. McNab FW, Berry MP, Graham CM, Bloch SA, Oni T, Wilkinson KA et al (2011) Programmed death ligand 1 is over-expressed by neutrophils in the blood of patients with active tuberculosis. Eur J Immunol 41(7):1941–1947
53. Burl S, Hill P, Jeffries D, Holland M, Fox A, Lugos M et al (2007) FOXP3 gene expression in a tuberculosis case contact study. Clin Exp Immunol 149(1):117–122
54. Ribeiro-Rodrigues R, Resende Co T, Rojas R, Toossi Z, Dietze R, Boom WH et al (2006) A role for CD4+ CD25+ T cells in regulation of the immune response during human tuberculosis. Clin Exp Immunol 144(1):25–34
55. Green AM, Mattila JT, Bigbee CL, Bongers KS, Lin PL, Flynn JL (2010) CD4+ regulatory T cells in a cynomolgus macaque model of *Mycobacterium tuberculosis* infection. J Infect Dis 202(4):533–541
56. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T et al (2010) An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature 466(7309):7973–7977
57. Lowe DM, Redford PS, Wilkinson RJ, O'Garra A, Martineau AR (2012) Neutrophils in tuberculosis: friend or foe? Trends Immunol 33(1):14–25
58. Barnes PF, Leedom JM, Chan LS, Wong SF, Shah J, Vachon LA et al (1988) Predictors of short-term prognosis in patients with pulmonary tuberculosis. J Infect Dis 158(2):366–371
59. Yeremeev V, Linge I, Kondratieva T, Apt A (2015) Neutrophils exacerbate tuberculosis infection in genetically susceptible mice. Tuberculosis 95(4):447–451
60. Ellis TN, Beaman BL (2004) Interferon-γ activation of polymorphonuclear neutrophil function. Immunology 112(1):2–12
61. Elkington P, Shiomi T, Breen R, Nuttall RK, Ugarte-Gil CA, Walker NF et al (2011) MMP-1 drives immunopathology in human tuberculosis and transgenic mice. J Clin Investig 121(5):1827–1833
62. Elkington PT, Ugarte-Gil CA, Friedland JS. Matrix metalloproteinases in tuberculosis. Eur Respiratory Soc; 2011
63. Tadokera R, Meintjes GA, Wilkinson KA, Skolimowska KH, Walker N, Friedland JS et al (2014) Matrix metalloproteinases and tissue damage in HIV-tuberculosis immune reconstitution inflammatory syndrome. Eur J Immunol 44(1):127–136
64. Eisenreich W, Heesemann J, Rudel T, Goebel W (2013) Metabolic host responses to infection by intracellular bacterial pathogens. Front Cell Infect Microbiol 3:24
65. Tobin DM, Vary JC, Ray JP, Walsh GS, Dunstan SJ, Bang ND et al (2010) The lta4h locus modulates susceptibility to mycobacterial infection in zebrafish and humans. Cell 140(5):717–730
66. Herb F, Thye T, Niemann S, Browne EN, Chinbuah MA, Gyapong J et al (2008) ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. Hum Mol Genet 17(7):1052–1060
67. Wong K-W, Jacobs WR (2013) *Mycobacterium tuberculosis* exploits human interferon γ to stimulate macrophage extracellular trap formation and necrosis. J Infect Dis 208(1):109–119
68. Aly S, Laskay T, Mages J, Malzan A, Lang R, Ehlers S (2007) Interferon-gamma-dependent mechanisms of mycobacteria-induced pulmonary immunopathology: the role of angiostasis and CXCR3-targeted chemokines for granuloma necrosis. J Pathol 212(3):295–305
69. Tameris MD, Hatherill M, Landry BS, Scriba TJ, Snowden MA, Lockhart S et al (2013) Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. Lancet 381(9871):1021–1028