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Review Article

Innate type 1 immune response, but not IL-17 cells control tuberculosis infection

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ABSTRACT

The role of the innate immune response and host resistance to *Mycobacterium tuberculosis* infection (TB) is reviewed. Based on our data and the abundant literature, an early type 1 immune response is critical for infection control, while ILC3 and Th17 cells seem to be dispensable. Indeed, in *M. tuberculosis* infected mice, transcriptomic levels of *Il17*, *Il17ra*, *Il22* and *Il23a* were not significantly modified as compared to controls, suggesting a limited role of IL-17 and IL-22 pathways in TB infection control. Neutralization of IL-17A or IL-17F did not affect infection control either. Ongoing clinical studies with IL-17 neutralizing antibodies show high efficacy in patients with psoriasis without increased incidence of TB infection or reactivation. Therefore, both experimental studies in mice and clinical trials in human patients suggest no risk of TB infection or reactivation by therapeutic IL-17 antibodies, unlike by TNF.

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). It is caused by the bacillus *Mycobacterium tuberculosis* (*M tuberculosis*), which is spread when people who are sick with TB expel bacteria into the air by coughing. It typically affects the lungs (pulmonary TB), and other organs (extrapulmonary TB). About a quarter of the world's population

is infected with MTB and thus at risk of developing TB disease (<https://www.who.int/tb/global-report-2019>). Exposure to virulent MTB causes lung, but also disseminated organ infection [1]. The bacilli are contained in a latent form due to a protective immune response with granuloma formation [2]. Indeed, 90–95% of infected people will not display clinical symptoms and will not be contagious, while having mycobacteria in their lungs. Appearance of clinical symptoms can occur in an

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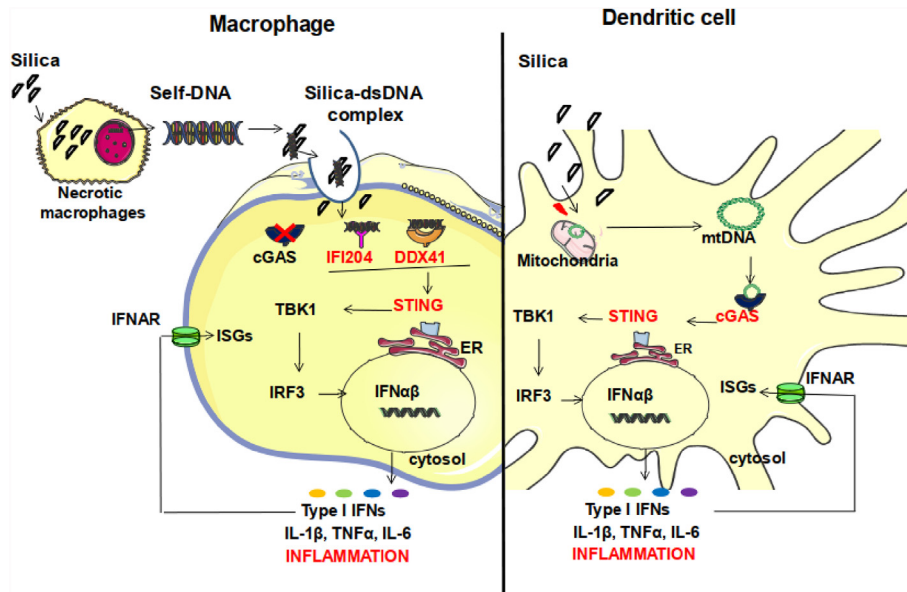


Fig. 1 Scheme of the DNA sensing pathway in cGAS-STING in dendritic cells and macrophages. In dendritic cells silica induces mitochondrial stress with the release of mtDNA activating the cGAS-STING pathway and release of type I interferons (IFNI), IL-1 β , TNF α and IL-6 causing inflammation. In macrophage cell-free DNA released by phagocytosis of dead cells in response to silica particles activate in addition to cGAS, alternative DNA sensors such as IFI284 and DDX41, with the release of inflammatory mediators as reported [54].

estimated 5–15% of cases, predominantly within the first five years following initial infection [3] and risks are considerably increased for host presenting a weakened immune system (primary or acquired immunodeficiency due to immunosuppressive or radiation therapy, silica particle exposure, chemotherapy or HIV infection) with severe disease in case of latent TB reactivation [4]. Recent work revealed that a coordinated innate and adaptive immune responses including T cells, macrophages, and the expression of mediators such as type II IFN, TNF, IL-1, IL-12p40, nitric oxide, reactive oxygen and nitrogen intermediates, are required to efficiently control *M. tuberculosis* infection. TNF and IL-1 are major mediators involved in severe inflammatory diseases against which therapeutic neutralizing antibodies are developed [2]. However, neutralizing TNF antibody therapy for autoimmune inflammatory disease cause TB reactivation [5].

Here we focus on a critical role of type 1 innate and adaptive immunity to control *M. tuberculosis* infection, which are independent of type IL-17/IL-22 response based on our experimental and published data. The potential risk on TB control by therapeutic Th17 cytokine antibody blockade is reviewed in human patients with psoriasis and related diseases.

Role of cytokines and chemokines

In TB infection, several inflammatory cytokines and chemokines are upregulated and may have a protective role to control infection [2,6]. We review the major players largely based on experimental rodent studies, which will address selected aspects of this broad field of research.

Tumor necrosis factor (TNF)

We and others identified a critical role for TNF family members to control of acute infection [5,7]. Absence of TNF and TNFR in mice or administration of neutralizing antibodies results in severe inflammation and uncontrolled infection in mice as well as reactivation of latent TB infection [8–11]. TNF α accumulates at the site of infection [12,13], triggers *M. tuberculosis* killing by activating phagocytosis in macrophages, promotes dendritic cells maturation and is responsible for the formation and maintenance of granulomas [14,15]. Further, myeloid-derived TNF allowed for early control of bacterial growth and myeloid-derived TNFR1 is critical to orchestrate the host immune response during acute TB infection [16]. In humans, TNF neutralization is often associated with TB reactivation: rheumatoid arthritis patients treated with anti-TNF can indeed display activation of an ignored latent TB, requiring systematic diagnosis before any anti-TNF administration [17–19].

Thus, TNF plays a major role in TB host defense and the data from mice predicted the risk of the use of neutralizing TNF antibody for the treatment of rheumatoid arthritis [20], which may reactivate latent tuberculosis [21]. Moreover, the TNF/TNFR1 pathway seems to be critical in innate myeloid cells, but not in T-cells, for early control of *M. tuberculosis* infection.

Interleukin-1 (IL-1)

We found that IL-1 α and IL-1 β and its shared receptor are involved in the control of *M. tuberculosis* infection [22]. We

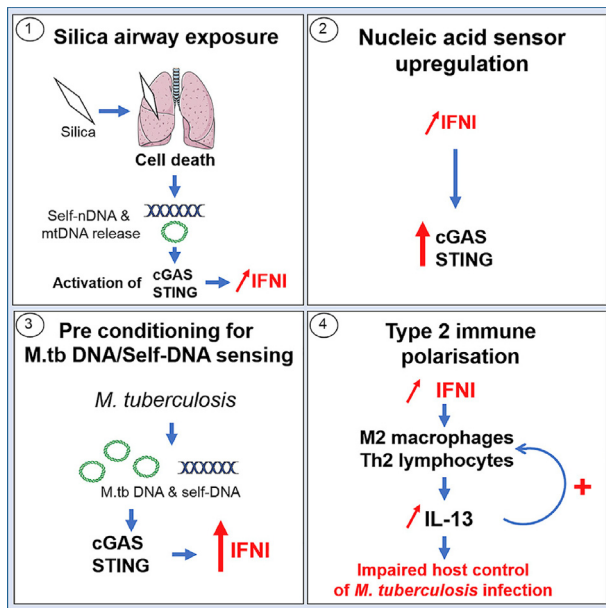


Fig. 2 Activation of the cGAS-STING pathway by silica induced a type 1 interferon (IFN-I) response which activates a type 2 response with M2 macrophages and Th2 lymphocyte. A subsequent *M. tuberculosis* infection results in a reduced protective response in the primed host [32].

reported that IL-1 α double deficient mice have uncontrolled *M. tuberculosis* infection with increased bacterial burden, exacerbated lung inflammation, high IFN γ and reduced IL-23p19 expression, which is also observed in IL-1R1-deficient mice [23]. However, single-deficient IL-1 α or IL-1 β mice only partially control acute *M. tuberculosis* infection, with restrained bacterial burden and lung pathology, in conditions where TNF deficient mice succumbed within 4 weeks with overwhelming infection. Therefore, either IL-1 α or IL-1 β exert some control of acute *M. tuberculosis* infection, which may have implications for anti-inflammatory therapy with IL-1 β neutralizing antibodies in patients [22].

Another study reported that IL-1 α or IL-1 β is sufficient to control infection, and here regulation by innate and adaptive type I interferons of IL-1 α and IL-1 β is of potential interest [23]. Further, an interdependence between IL-1 and TNF regulating TNF-dependent control of infection has been suggested [24].

IFN-I cGAS STING

The critical role of interferon- γ , type 2 interferon (IFN-II), in host response to bacterial including TB infection is established [25,26].

We recently focused on interferon- α/β , known as type 1 interferons (IFN-I), which are involved in viral defense control. Cell/tissue stress, injury and infection cause nuclear and mitochondrial disruption with the release of DNA in the cytosol and extracellular space. This self-DNA engages a novel DNA sensing pathway leading to cGAS and STING activation with IFN-I dependent inflammation and immunity [27–29] [Fig. 1].

We reviewed the role of STING in bacterial infection [30]. TB infection in mice caused the release of extracellular DNA with activation of cGAS and STING in dendritic cells, but cGAS or STING deficient mice controlled acute TB infection [31]. However, we found a silica-driven exacerbation of TB infection associated with raised type 2 immunity. In fact, silica pre-exposure primes a pulmonary Th2 cell and M2 macrophage responses, while reducing type 1 immunity to TB infection. Thus, silica-induced self-DNA primes the host response to TB-derived nucleic acids, which increases type 2 immunity while reducing type 1 immunity, crucial for controlling *M. tuberculosis* infection [32]. This data contribute to the understanding of the well known high susceptibility to TB infection of mine workers and patients with silicosis [Fig. 2].

Thus, pre-exposure to silica or potentially other particles primes STING with type 1 IFN response in the host. Subsequent mycobacterial infection activates a type 2 immune response with exacerbated mycobacterial infection relying on bacterial DNA and STING activation. Moreover, a crosstalk between IL-1 and type I interferon has been reported (Mayer-Barber et al., 2014) showing that IL-1 confers host resistance through the production of eicosanoids limiting excessive IFN-I production thereby contributing to bacterial containment. These data provide understanding in how the IL-1 pathway is essential in the immunological host response to *M. tuberculosis* infection and support the fact that innate immunity is crucial for TB control.

Chemokines

Chemokines are central in the inflammatory process. They attract myeloid and other immune cells to inflammatory sites to induce a protective host response [33]. TB infection increased the expression of the beta-chemokines CCL3, CCL4, and CCL5, and their receptor CCR5, in the lungs [34]. However, CCR5-knockout mice recruited immune cells, formed lung granulomas, developed a Th1 response and controlled infection [35]. By contrast, CCR2 expression is critical to control experimental TB infection [36]. However, a full review of the different chemokines that contributes to immune activation in TB infection is beyond the scope of this review and the most recent update is given.

Innate lymphoid cells (ILC) and Th17 cells

Innate lymphoid cells (ILC)

ILCs induce a rapid innate immune response to pathogens and other challenges of the host preceding a sustained adaptive T cell response. ILCs differentiate into the key T cells lineage lymphocytes, Th1, Th2 and Th17 [Fig. 3], share features with both adaptive and innate immune cells and comprise of three main subsets known as ILC1s, ILC2s and ILC3s [37].

ILC1s produce interferon (IFN)- γ and include natural killer (NK) cells and non-cytotoxic, non-NK type 1 ILCs. Group 2 ILCs, which produce IL-4, IL-5 and IL-13, are involved in inflammatory-linked airway hyperreactivity, tissue repair and helminth clearance. ILC3s produce IL-17 and/or IL-22, and

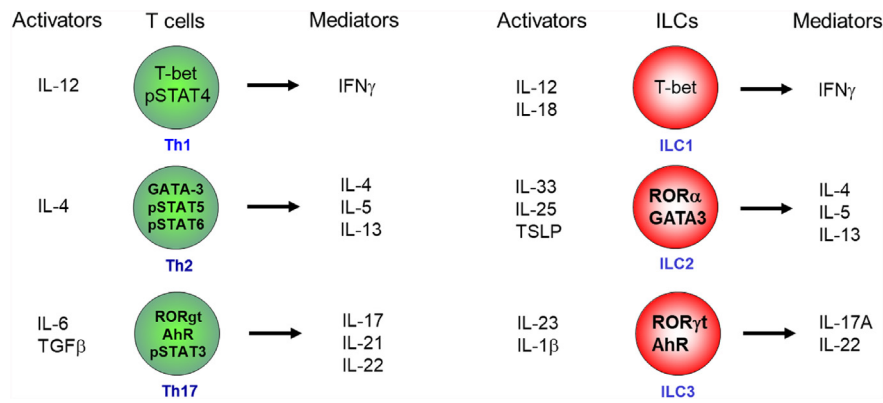


Fig. 3 Innate lymphoid cells (ILC) and adaptive T lymphocytes. The immediate immune response to injury and pathogens is effected by innate lymphoid cells (ILC1, 2 or 3) activation of cell-specific transcription factors and the release of the corresponding cytokines. The innate immune response is followed the differentiation of Th1, Th2 and Th17 cells and associated cytokine production.

participate in the inflammatory and host defence responses [37,38].

ILCs in TB infection

The contribution of ILCs in TB infection has been extensively reviewed recently [39]. Innate immune cells may be involved in the host resistance since ILC3s cytokines are upregulated [40–42]. However, whether *M. tuberculosis* infection is ILC3/IL-17 dependent is not yet resolved. A recent report showed that group 3 ILCs mediate early protective immunity against tuberculosis. Patients with pulmonary TB presented a depletion of circulating ILC subsets from the blood, which was restored upon drug treatment. Furthermore, TB infection increased accumulation of ILC subsets in the human lung, coinciding with a robust transcriptional response to infection, including a role of ILC3s in orchestrating the recruitment of immune subsets in a CXCR5 and CXCL13 dependent manner [43].

We investigated the transcriptome of TB infected mice [16] and found transcriptional signatures corresponding to CD4+ T, CD8+ T cells, $\gamma\delta$ T cells, NK cells, macrophages, monocytes and neutrophils were increased after infection. Transcriptional changes at day 28 were associated with modulation of genes associated with host–pathogen interactions such as macrophage activation and host–antimycobacterial activities. Further, selected transcripts of cytokines and chemokines were upregulated such as *Cxcl1*, *Cxcl2*, *Cxcl5*, *Cxcl10*, *Ccl2*, *Tnf*, *Fasl*, *Ifng*, *Il1a*, *Il1b*, *Ilrn*, *Il1r2*, *Il6*, *Il10*, *Il12b* and *Il13ra1* genes in response to *M. tuberculosis* infection at day 28. In contrast, only minor changes were observed for expression of *Il17*, *Il17ra*, *Il22* and *Il23a* or lineage specific transcription factors on day 28 of infection in mice [16].

We further demonstrated that absence of TNFR1 on myeloid cells, but not on lymphoid cells, leads to an increased recruitment of granulocytes expressing IL-12p40 in the lung, strongly suggesting a critical role of Th1 immunity that needs to be regulated by a functional TNF pathway particularly in innate myeloid cells [16]. Therefore, our transcriptome data do

not support an ILC3 or Th17 polarisation, but rather a critical role of innate type 1 immune cells and Th1 cells as discussed below.

Th1 versus Th17 immune responses

Present knowledge suggests that a Th1 reponse is protective, while a Th2 reponse is permissive for TB infection.

It was reported that humans and mice with loss of function via mutation of ROR γ t, have a profound reduction of IL-17A, IL-17F and IL-22 producing leukocytes and exhibit defective control of *Mycobacterium bovis* BCG and *M. tuberculosis* infection [44]. However, the susceptibility associated with a RORC mutation was attributed to a selective defect in a *M. tuberculosis*-specific IFN γ response unrelated to IL-17RA and IL-17F [44], which is in contrast to a recent report suggesting that innate ILC3 responses activated by TB infection in human and mice may contribute to host resistance [43].

Based on the two reports we revisited our data on the role of a Th17 lymphocyte response in the host response to experimental TB infection using IL-17RA, IL-22 and TNF KO mice as well antibody blockade of IL-17A, IL-17F and TNF over 4 weeks or 6 months [45]. We compared the effect neutralizing IL-17A, IL-17F or TNF antibodies on murine host responses to TB infection by evaluating lung transcriptomic, microbiological and histological analyses [45]. Coinciding with a significant increase of mycobacterial burden and pathological changes following TNF blockade, gene array analyses of infected lungs revealed major changes of inflammatory and immune gene expression signatures 4 weeks post-infection. Specifically, gene expression associated with host–pathogen interactions, macrophage recruitment, activation and polarization, host–antimycobacterial activities, immunomodulatory responses, as well as extracellular matrix metalloproteinases, were markedly modulated by TNF α blockade. IL-17A or IL-17F neutralization elicited only mild changes of a few genes without impaired host resistance four weeks after TB infection, while absence of TNF implied drastic changes consistent with the lethal phenotype of TNF KO mice

(see above). The minimal effect of anti-IL-17A treatment on *Ccl2* and rather a slightly decreased gene expression of *Zc3h12a* in lung tissue (indicative of monocyte recruitment and macrophage M2 polarization, respectively) suggest a dispensable role for IL-17A at this stage of the infection.

Further, the absence of both IL-17RA and IL-22 pathways in genetically deficient mice did not profoundly compromise host control of TB infection over a 6-months period, ruling out potential compensation between these two pathways, while TNF-deficient mice succumbed rapidly [Fig. 4].

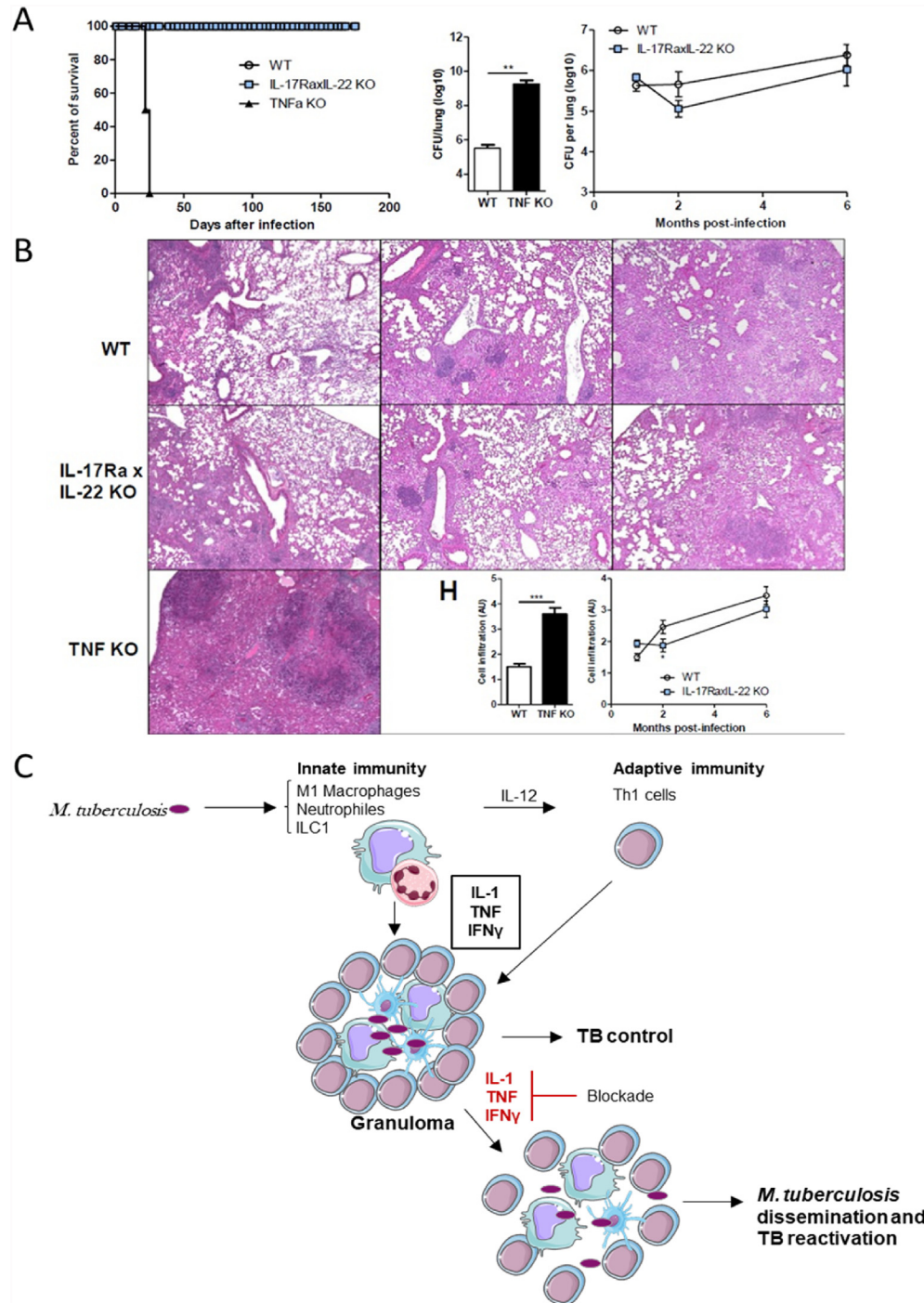


Fig. 4 Type 1 immune response controls host resistance to TB infection independent of Th17 immunity. Mice deficient for IL-17 and IL-22 pathways (IL-17RA x IL-22 KO) were infected with *M. tuberculosis* and monitored over 6 months for bodyweight, lung CFU and histology (A and B). Survival and lung pathology was similar to wild type mice, suggesting that IL-17 and IL-22 pathways are dispensable for the control of *M. tuberculosis* infection. Our extensive study deciphering TNF pathway in myeloid versus lymphoid cells showed a central role of innate immune cells in the establishment and maintain of a strong immunity against *M. tuberculosis* [16,45].

These results, in accordance with clinical data, provide experimental confirmation of the low clinical risk of mycobacterial infection under anti-IL-17A therapy, in stark contrast to anti-TNF α treatment.

Moreover, it is well known that the activity of Tregs and Th17 cells are closely linked. A recent review studied the role of Tregs in a context of *M. tuberculosis* infection, and stated that further research should focus on analyzing not just the regulatory response against *M. tuberculosis*, but rather its equilibrium with the pro-inflammatory response, especially. Indeed, the balance between pro- and anti-inflammatory responses to *M. tuberculosis* is clearly essential regarding the development of TB disease [46]. Our present data showing that the Th17 pathway is dispensable for *M. tuberculosis* control suggest that the immunosuppressive role of Treg cells seems to target other inflammatory pathways, therefore contributing to the integrity of lung tissue in TB infection.

Clinical data on Th17 targeting in psoriasis

Therapeutic antibody targeting IL-17A or its receptor IL-17RA show unprecedented efficacy in the treatment of autoimmune diseases such as psoriasis. These therapies, neutralising critical mediators of immunity, may increase susceptibility to infections. However, several reports from clinical studies targeting either IL-17A [47–49], IL-17A and IL-17F [50] show no increased incidence of TB infection or reactivation. However, the resistance to fungal infection such as candidiasis is reduced and needs to be followed [42,51,52].

Conclusions - host resistance to TB infection

Cytokine blockade of either TNF, IL-1 α and β or IFN γ is associated with reduced resistance and often associated with reactivation of extrapulmonary TB infection [53]. By contrast, both IL-17A, IL-17F and IL-22 are largely dispensable for the control *M. tuberculosis* infection.

In view of the clinical efficacy of several IL-17 antibodies in patients with psoriasis and related diseases, it is important to address whether neutralization of IL-17 reduces host resistance to infection in patients. There is no evidence that the Th17 pathway is essential to control host resistance to TB infection in patients, but it may affect the control of fungal infections and periodontitis [51]. Therefore, with proper monitoring, therapeutic IL-17 antibody blockade in Th17 driven inflammatory diseases might be considered for those patients who had a history of tuberculosis.

Open questions

- Functional role of ILC1 for protective immunity
- Contribution of type III interferon versus type II interferon is critical to control infection
- The role of type I interferon needs more investigations
- Role regulatory T cell in TB control
- To what extent can human PBMC cultured cells predict protection

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Conflicts of Interest

The authors declare no conflict of interest.

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