Regulation of Host Response to Mycobacteria by Type I Interferons

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Mycobacterial Infection and Tuberculosis

Mycobacteria are slow growing, facultative intracellular bacilli that primarily reside in macrophages. The *Mycobacterium* genus comprises more than 100 different species. Among them are the pathogenic species *Mycobacterium tuberculosis* and *M. leprae*, causing tuberculosis (TB) and leprosy, respectively. This chapter will discuss mainly on the role of type I interferons (IFNs) in *M. tuberculosis* infection, which is the focus of the majority of recent studies. TB is one of the major infectious diseases worldwide [1]. Two billion people are infected with *M. tuberculosis*, 10 % of whom will eventually develop active TB disease [2]. Annually, more than eight million people develop TB, which is responsible for over 1.3 million deaths, figures still grossly underestimated due to failures in reporting and detection [1, 3]. Once considered to be on its way to extinction, *M. tuberculosis* is posing a significant threat to global health due to the emergence of multi-drug resistant strains [3]. *M. bovis* Bacillus Calmette–Guérin (BCG), the only TB vaccine available for humans, is ineffective in protecting adults against pulmonary TB [4]. Therefore understanding the immune responses to the pathogen may lead to improved vaccination and therapy.

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Host Immune Response to *M. tuberculosis*

Host control of *M. tuberculosis* infection in both humans and mice depends on cell-mediated immunity [5, 6]. Interestingly however, despite the development of an adaptive immune response, some bacilli resist killing and survive within macrophages in granulomas [7, 8]. Mycobacterial granulomas are typically composed of lymphocytes and infected macrophages. The former cell population is thought to provide cytokine mediators necessary for macrophage activation and restriction of intracellular growth of mycobacteria [6, 9]. Importantly, defects in lymphocyte recruitment and retention or effector function during chronic infection can lead to a breakdown of immunity and result in progressive infection [10, 11].

Resistance to mycobacteria is critically dependent on the T helper 1 (Th1) response [5, 6]. Thus, patients and animals deficient in IFN-γ, IL-12, STAT1, or T-cells show significantly increased susceptibility to mycobacterial infections [12]. In addition to $CD4^+$ lymphocytes, natural killer (NK) cells also contribute to cytokine production in *M. tuberculosis* infection [13]. Critically, host control of *M. tuberculosis* infection requires intact IFN-γ receptor signaling in both hematopoietic and non-hematopoietic components [14]. It is believed that the key effector function of IFN-γ is to activate infected macrophages to produce antimicrobial mediators, such as nitric oxide and p47 immunity-related GTPases [15]. But, emerging evidence from recent studies indicates that this long-held concept may represent an over-simplified view. For example, in addition to impaired bacterial control, *M. tuberculosis*-infected *Ifng*$^{-/-}$ mice show severe pulmonary pathology associated with dramatically increased accumulation of neutrophils [13, 16]. Together, these findings suggest that IFN-γ plays a broader role in inflammation and infection beyond its proposed function in bacterial killing.

Mycobacterial Virulence Mechanisms

Following infection, avirulent mycobacteria are effectively cleared by host defence mechanisms and are unable to persist in the host. In contrast, virulent mycobacteria establish persistent infection in the infected host. The ability of *M. tuberculosis* to avoid host antimicrobial strategies is well documented [17–21]. One strategy involves the action of the *M. tuberculosis* mannose-capped lipoarabinomannan that is incorporated into lipid rafts of the plasma membrane, thereby executing arrest in phagosomal maturation [22–25]. The bacterium is known to block fusion of lysosomes as well as inhibit phagosomal acidification [26]. This prevents the activation of a number of pH-dependent antimicrobial compounds, such as maturation of cathepsin D [22], which are required for destroying intracellular bacteria.

It has been assumed that because *M. tuberculosis* is broadly equipped to combat phagosomal maturation via inhibition of Golgi-trafficking, phagosome acidification

and lysosomal fusion, that an operational phagosome would be effective in clearing infection [27]. However, the identification of bacterial strategies that allow the survival of *M. tuberculosis* mutants in fully mature phagosomes challenges this assumption. These strategies include the ability to deactivate reactive oxygen species (ROS) and protect against NOS2 damage [8]. Thus, it is unlikely that *M. tuberculosis* causes definitive arrest of phagosomal maturation, but rather delays it [28]. This may be a temporary measure to allow the bacteria to adapt and initiate transcription in response to the intracellular environment [28]. Recent studies suggest that rather than using the mycobacterial phagosome as a replicative niche, as traditionally believed, the mycobacterially-altered phagosomes act as a preparation and "waiting room" for escape of the bacteria into the cytosol [29]. This suggestion has significant ramifications, both for bacterial survival and the host defence mechanisms involved.

In a seminal study, van der Wel et al. [30] report that virulent *M. tuberculosis* but not heat-killed mycobacteria or vaccine strain *M. bovis* BCG are present within the cytosol of macrophages 2 days after infection. This translocation is dependent upon the bacterial secretion system, early secretory antigenic target 6 system 1 (ESX-1) apparatus transcribed by the region of difference-1 (RD-1) genes that are present only in virulent mycobacteria including *M. tuberculosis* [31, 32]. However, interestingly, permeabilization of the phagosomal membrane and cytosolic access to bacterial pathogen-associated molecular patterns (PAMPs) may occur within hours of infection under certain conditions [28], long before complete translocation of bacilli into the cytosol occurs. This may allow bacterial components access to the cytosol and avoid their sensing by endosomal Toll-like receptors (TLRs) [33]. Indeed, *M. tuberculosis* β-lactamase catalytic activity occurs in the cytosol progressively, from less than 2 days post infection [29]. These observations suggest that release of bacterial products precedes complete escape of the pathogen. Regardless of the sequence of events, this "phagosomal escape" represents a newly characterized virulence mechanism of *M. tuberculosis*, although whether RD-1 mediates this purported partial permeabilization of the membrane [34] or allows complete translocation of the bacilli into the cytosol [31] remains unclear. Finally, this phagosomal-cytosolic access hypothesis is further supported by studies demonstrating the ability of virulent (RD-1 competent) *M. tuberculosis* to prime $CD8^+$ T cell responses [35] and activate the inflammasome [36, 37] since both processes require the access of microbial products to cytosolic immune pathways.

Type I IFN Production and IFN Signature

In the case of mycobacterial infections, type I IFNs are produced in vitro by *M. tuberculosis*-infected murine macrophages [38, 39], as well as human monocyte derived macrophages [17], dendritic cells [40], and differentiated monocytic THP-1 cells [41]. Importantly type I IFNs are induced during infection with virulent but not avirulent mycobacteria such as with *M. bovis* BCG [17, 21, 42], indicating that type I IFN induction is unique to virulent mycobacteria.

In mice, type I IFNs and their inducible genes are detected in *M. tuberculosis*-infected tissues [21, 43]. Similarly, in humans IFN-β is expressed in leprosy skin lesions [44]. Although type I IFN cytokine genes are undetectable in peripheral blood of infected human subjects, a large set of IFN-inducible genes are readily detected in the same cells. In a seminal study, Berry et al. [45] identified the presence of a 393 transcript gene signature in whole blood of active TB patients. Further analysis revealed that 86-transcripts can distinguish active TB from other types of inflammatory conditions, such as systemic lupus erythematosus (SLE), which is known to be associated with an enhanced type I IFN gene signature [46–48]. Interestingly, 10–25 % of latently infected subjects also displayed the IFN signature [45]. Considering that approximately 10 % of latent *M. tuberculosis*-infected individuals will eventually develop active TB in their lifetime, it would be interesting to examine whether the IFN gene signature detected in latently infected individuals could be predictive for disease progression.

This type I IFN-induced gene signature, which includes the transcription factors IRF1, IRF7, Oct-1, and proteins of the STAT family, has been confirmed in patients with active TB in multiple recent reports [49–52]. Importantly, these transcriptional profiles are also observed in experimental models of *M. tuberculosis* infection in mice and in vitro in human cell lines [49, 50], providing an avenue to investigate these observations in more detail at a functional level. A study examining the expression of interferon regulated genes (IRGs) in cattle infected with *M. bovis* (the causative agent of bovine TB) found an increase in type I and type II IFN regulated genes such as *CXCL10*, *STAT1*, *IFI16*, *IRF7*, and *OAS1* [53], suggesting that similar virulence mechanisms may be conserved across mycobacterial species.

Leprosy is another major human mycobacterial disease in which a type I IFN gene signature is associated with severe disease outcome. Leprosy has traditionally been classified into two major types; tuberculoid and lepromatous. Historically, the self-healing tuberculoid leprosy is believed to be associated with Th1 responses whereas disseminated lepromatous leprosy, which is characterized by uncontrolled infection and increased tissue pathology, is driven by a strong Th2 response. Interestingly, a recent study demonstrated that lepromatous leprosy is associated with an IFN-β-dependent gene signature [44], providing a novel mechanism for uncontrolled bacterial growth associated with this severe form of the disease. Together, studies in both *M. tuberculosis* and *M. leprae* infections have clearly established that the presence of an IFN-inducible gene signature is associated with disease progression and more severe clinical manifestations, although the issue as to whether the observed gene signature is driven by type I, type II, or both remains unclear.

One of the major challenges in TB management is to effectively distinguish latent infection from active disease and to monitor treatment efficacy. To date, no laboratory test is available for these purposes. Therefore, the identification of the whole blood IFN signature associated with active TB disease has generated considerable interest in the clinical and basic TB research communities because of its potential in diagnosing and monitoring TB disease progression [54, 55]. However, the practical impact of the discovery remains unclear, as multiple recent studies have demonstrated that the IFN-inducible gene signature is also associated with

other diseases. For example, melioidosis, a disease caused by the intracellular bacterium *Burkholderia pseudomallei*, also contains the 86-gene IFN signature [52]. Another example is sarcoidosis, a lung disease associated with pulmonary lesions similar to TB, in which the blood IFN gene signature has 80 % overlap with that of active TB patients enrolled in the same study [51] and in the study published by Berry et al. These data suggest that while the IFN signature is associated with acute inflammatory conditions it is not specific for mycobacterial infection and TB.

Regulation of Host Resistance to Mycobacterial Infection by Type I IFN Signaling

The hypervirulence of clinical isolates of *M. tuberculosis* correlates with the enhanced synthesis of endogenous type I IFN. Mice deficient in the receptor for these cytokines display significantly reduced bacterial loads when chronically infected with *M. tuberculosis* [21, 38, 56]. More recently, mice deficient in interferon regulatory factor 3 (IRF3), a key molecule required for type I IFN production, were shown to display significantly increased survival and decreased bacterial load relative to their wild-type counterparts following *M. tuberculosis* infection [34]. Interestingly, in the absence of IFN-γ signaling, type I IFNs play a protective role in *M. tuberculosis* infection as mice deficient in both *Ifngr* and *Ifnar* display increased pathology and mortality than *Ifngr* single deficient mice [57]. Therefore, it appears the detrimental effect of type I IFN is dependent on the presence of an IFN-γ response to *M. tuberculosis*.

Conversely, *M. tuberculosis*-infected mice with elevated type I IFN levels show reduced survival and increased bacillary burden compared to control mice. Intranasal administration of poly:ICLC, a compound that stimulates high-level production of type I IFN, exacerbates pulmonary TB in wild-type but not in type I IFN receptor deficient mice [58]. In addition, increased mycobacterial burden is reported in a mouse model of influenza A virus and *M. tuberculosis* co-infection [59]. Importantly, the impaired host resistance is dependent on type I IFN signaling, suggesting that concurrent viral infection can exacerbate TB by triggering type I IFN production.

Compared to animal studies, the effect of type I IFN on resistance to mycobacterial infection in humans is less clear. Increased incidence of TB disease has been reported in patients with active autoimmune diseases or on treatment with recombinant IFN-α. For example, it is established that type I IFNs play a key role in disease pathogenesis of SLE and an IFN-inducible gene signature is observed in patients with severe disease [46–48, 60, 61]. In this case, increased incidence of TB disease in SLE patients has been reported [62–64]. However, the causal role for SLE in TB disease progression is difficult to establish, as SLE patients are also more susceptible to other bacterial infections [65, 66]. This may be a consequence of the immunosuppressant therapy administered to SLE patients, rather than a direct exacerbation of TB by type I IFN signaling. It would be informative to examine whether TB/SLE patients displaying the IFN gene signature can benefit from combination therapy with the IFN-α blocking antibody currently being evaluated in clinical trials [67].

Type I IFN therapy is used frequently for the treatment of multiple sclerosis, hepatitis C virus, and a number of cancers [68]. The effect of type I IFN therapy on *M. tuberculosis* infection remains controversial, since both beneficial and detrimental effects have been reported [69–74]. In a number of cases administration of IFN-α alone or in combination with standard anti-mycobacterial regimen enhanced mycobacterial control in TB patients. In one study, aerosolized IFN-α lead to earlier resolution of infection and was associated with lower levels of IL-1β, IL-6, and TNF-α in bronchoalveolar lavage fluid [75]. In a second case, inclusion of IFN-β to a four drug regimen of mycobacterial antibiotics resulted in rapid resolution of a previously difficult-to-treat infection [76]. Together, these conflicting clinical data make it difficult to conclude the effect of type I IFNs on *M. tuberculosis* infection and TB disease in humans, although it is plausible that type I IFNs are detrimental to *M. tuberculosis* control in certain circumstances but beneficial in others.

Innate Sensing for Type I IFN Induction

Mycobacteria are complex microorganisms that primarily interact with cells of the phagocyte lineage (macrophages and dendritic cells). Recognition of mycobacterial products by surface and cytosolic pathogen recognition receptors (PRRs) leads to the activation of multiple innate pathways.

Cell surface sensing of *M. tuberculosis* 19 kDa lipoprotein occurs through TLR2 in association with TLR1 or TLR6 [77, 78]. However, these TLRs lack TRIF signaling adaptors and are unable to transduce signals culminating in IRF3 activation and IFN production [79]. In infected DCs, sensing of mycobacterial unmethylated CpG-DNA by TLR9 in the endosomal compartment is inhibited by the mycobacteria [80]. Consequently, TLR signaling is not necessary for *M. tuberculosis-mediated* induction of type I IFNs [19, 21, 42, 81, 82].

Virulent mycobacteria capable of causing damage to the phagosomal membrane can trigger type I IFN production in infected macrophages, suggesting that cytosolic sensing could be responsible for mycobacterium-induced type I IFN production. Damage to the phagosomal membrane is accomplished by the ESX-1 secretion system [21]. Known cytosolic receptors for muropeptides, components of the bacterial cell wall, are the nucleotide-binding oligomerization domain-containing protein (NOD) receptors [42, 43, 83]. In *M. tuberculosis* infection, bacterially derived *N*-glycolyl-muramyl dipeptides (MDPs) in the cytosol have been reported to activate the NOD2 sensor, which leads to the induction of type I IFN production in macrophages [42, 84] along with other functions in the innate and adaptive response [85]. In this model, NOD2 recognition of *M. tuberculosis* MDP triggers the ubiquitination of the receptor-interacting protein kinase 2 (RIP2), which subsequently activates TANK binding kinase 1 (TBK1) to stimulate IRF5 leading to the transcription of type I IFN genes (Fig. 1).

However, a distinct sensing mechanism has been proposed recently. Cox and colleagues have demonstrated that induction of type I IFN genes in murine cells

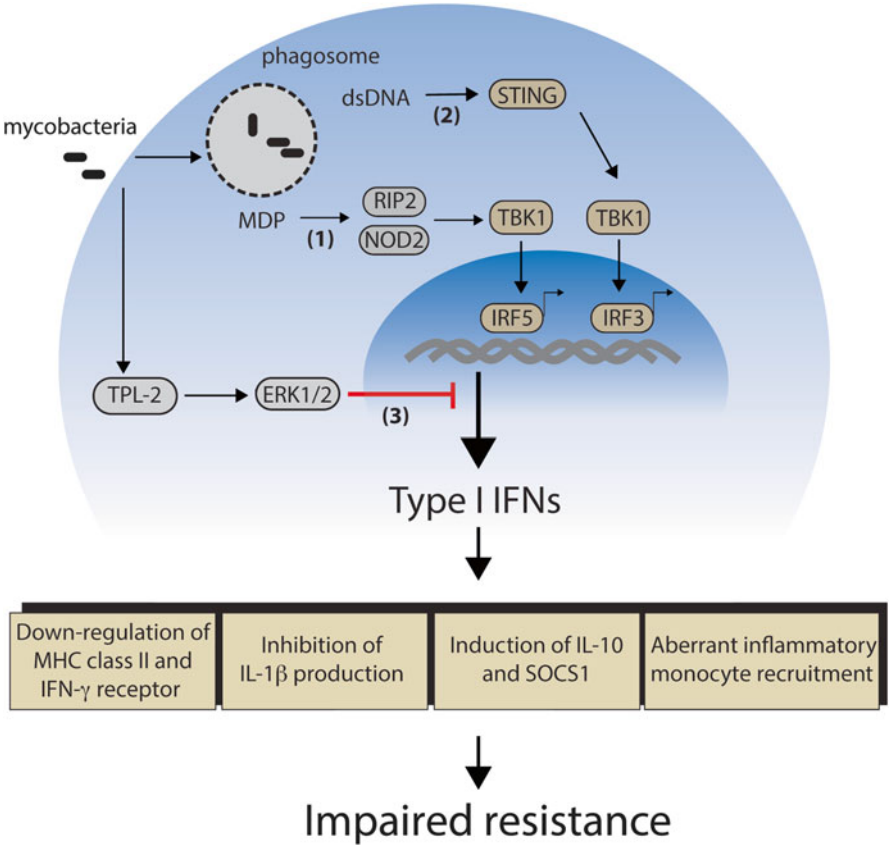

Fig. 1 The postulated mechanisms underlying the induction and function of type I IFN in mycobacterial infection. Phagosomal damage caused by ESX-1, a mycobacterial secretion system present only in virulent mycobacteria, and subsequent cytosolic translocation of microbial products initiates the innate cascades for type I IFN production in mycobacterial-infected macrophages. Although both avirulent and virulent mycobacteria can activate NF-κB (not depicted) and MAPK pathways through surface expressed pattern recognition receptors, only virulent mycobacteria activate cytosolic innate mechanisms leading to type I IFN production. It is postulated that mycobacterial MDP recognized by NOD2 triggers a TBK1 and IRF5-dependent pathway **(1)** whereas mycobacterial double-stranded DNA activates a STING, TBK1, and IRF3-dependent mechanism **(2)**. Both pathways are not effectively triggered by BCG or other RD1-deficient mycobacteria, which lack the ESX-1 secretion system. Finally, activation of the TPL-2/ERK pathway is capable of limiting *M. tuberculosis* induced type I IFN production **(3)** (indicated in *red line*). The production of type I IFN has been associated with increased susceptibility to mycobacterial infection. The cytokines inhibit known antimicrobial effector mechanisms, such as IFN-γ-induced MHC class II upregulation, IFN-γ receptor expression and IL-1β production. Type I IFNs also induce IL-10 and SOCS1 to suppress host protective Th1 response to the pathogen. Finally, over-production of type I IFN exacerbates *M. tuberculosis* infection by recruiting immature myeloid cells that are incompetent in killing intracellular bacteria

requires the activation of the Stimulator of IFN genes (STING) by cytosolic mycobacterial products and subsequent phosphorylation of TBK1 and IRF3 [34]. Due to the fact that the pathway plays a key role in sensing bacterial DNA [86–89], the finding implies that mycobacterial DNA is a cytosolic PAMP for type I IFN induction. Indeed, *M. tuberculosis* DNA is detected in the cytosolic fraction of infected macrophage lysates [34].

Cytosolic cyclic-di-GMP is a molecule unique to bacterial but not mammalian cells [82]. Due to its bacterial specificity, c-di-GMP represents an important target for innate immune recognition, and has been shown to induce potent activation of cytosolic pathways [90]. *Listeria monocytogenes* c-di-AMP is known to induce type I IFN production [91] by binding to the cytosolic DNA sensor STING [92, 93]. However, unexpectedly, mycobacterial c-di-GMP and c-di-AMP are not involved in stimulating type I IFN production in infected murine macrophages [34] although mutations in c-di-GMP signaling within mycobacteria has been linked to impaired infectivity of *M. tuberculosis* [94, 95].

Function of Type I IFN in Mycobacterial Infection

While the mechanisms of action by which type I IFN increase mycobacterial virulence are still being investigated, some studies have provided important insights as to how the cytokines negatively affect anti-mycobacterial immunity (summarized in Fig. 1).

Recent work has demonstrated that type I IFNs regulate the production of IL-1β, a critical cytokine in host resistance to *M. tuberculosis* infection. Novikov et al. [17] demonstrate that exogenous and *M. tuberculosis*-induced type I IFNs are able to suppress *IL1B* gene transcription in human macrophages. Although the exact molecular mechanism responsible for the suppression has yet to be defined, a separate study found that the type I IFN-dependent IL-1β inhibition could be partially restored by blocking IL-10 activity [96]. In addition, IFN-β-dependent IL-10 suppresses IFN-γ-dependent antimicrobial mechanisms in *M. leprae*-infected human macrophages and is associated with the development of lepromatous leprosy [44]. IL-10 is an anti-inflammatory cytokine known to inhibit Th1 responses and macrophage antimicrobial effector functions. Importantly, the cytokine has been shown to exacerbate murine mycobacterial infection in some settings [97–99]. It is, therefore, possible that IL-10 induction by type I IFNs is one of the general mechanisms contributing to the pro-bacterial effect of type I IFNs.

In addition to inducing IL-10, type I IFNs upregulate negative regulators of IFN signaling including suppressor of cytokine signaling 1 (SOCS1) [100, 101]. *Socs*1 gene expression is elevated in infection with *M. tuberculosis* strains, particularly those of high virulence and associated with high IFN-α/β stimulating activity [39]. SOCS molecules are also found to be increased in active human TB cases and appear to correlate with disease severity [102, 103]. Experimentally, mouse macrophages deficient in type I IFN receptor demonstrated reduced *Socs1* gene induction

after mycobacterial infection [104]. *Socs1* deficient macrophages displayed reduced bacterial numbers compared to wild-type macrophages and, importantly, this effect was dependent on the inhibition of IFN-γ signaling thereby providing a mechanism by which type I IFNs suppress the antimicrobial activities of IFN-γ [104]. In addition, it is well established that type I IFNs can down-regulate the expression of IFN-γ receptor [105, 106]. This down-regulation has also been observed in *M. tuberculosis* infection when infected mice were treated with the synthetic type I IFN inducer poly:ICLC [58]. Limiting the expression of cell surface IFN-γ receptor would likely impair IFN-γ-dependent effector functions in macrophages, such as induction of NOS2.

While multiple mechanisms have been postulated to explain the pro-bacterial function of type I IFNs in mycobacterial infection in vitro, the exact function of the cytokines in vivo is poorly understood. Type I IFN has been shown to down-regulate the Th1 response in one study [38] but not others [56, 58]. Interestingly, the detrimental effect of poly:ICLC treatment in *M. tuberculosis*-infected mice is linked to the dramatically increased accumulation of immature inflammatory monocytes [107]. Flow cytometric sorting experiments reveal that immature myeloid cells harbor significantly more bacteria than their mature counterparts. Therefore, type I IFNs may contribute to host susceptibility to *M. tuberculosis* infection by supplying a niche for mycobacterial growth and survival. The mechanisms that regulate type I IFN production in vivo are also not well defined. However, a recent study demonstrated that mice deficient in tumor progression locus-2 (TPL-2) show increased levels of IFN-β in the serum and bacillary loads in lungs compared to wild-type controls following infection with *L. monocytogenes* and *M. tuberculosis*. It is postulated that the activation of TPL-2 and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways, possibly by TLR signals, prevents excessive production of type I IFN during the infections [108].

Concluding Remarks

Increasing evidence suggests that type I IFNs negatively regulate host resistance to intracellular pathogens including mycobacteria. There is an urgent need for a better understanding of the cytokines' biological functions in infection, as well as identification of the host and mycobacterial factors required for the cytokine production. While the question as to whether an IFN-inducible gene signature will assist in identifying TB cases and latently infected individuals who are at high risk of developing active disease needs to be carefully examined in longitudinal studies, it is clear that type I IFN inducing agents should be used with caution in people with mycobacterial infection. Finally, it would be interesting to examine whether therapeutic blockade of some components of the type I IFN signaling pathway could promote bacterial clearance and reduce TB reactivation and transmission in humans.

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