Type I interferons in tuberculosis: Foe and occasionally friend

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Tuberculosis remains one of the leading causes of mortality worldwide, and, despite its clinical significance, there are still significant gaps in our understanding of pathogenic and protective mechanisms triggered by *Mycobacterium tuberculosis* infection. Type I interferons (IFN) regulate a broad family of genes that either stimulate or inhibit immune function, having both host-protective and detrimental effects, and exhibit well-characterized antiviral activity. Transcriptional studies have uncovered a potential deleterious role for type I IFN in active tuberculosis. Since then, additional studies in human tuberculosis and experimental mouse models of *M. tuberculosis* infection support the concept that type I IFN promotes both bacterial expansion and disease pathogenesis. More recently, studies in a different setting have suggested a putative protective role for type I IFN. In this study, we discuss the mechanistic and contextual factors that determine the detrimental versus beneficial outcomes of type I IFN induction during *M. tuberculosis* infection, from human disease to experimental mouse models of tuberculosis.

Introduction

Although cytokines play critical roles in host defense and immune homeostasis, they can also be key mediators of inflammatory pathology. This paradoxical aspect of cytokine biology is perhaps best exemplified in the dichotomous functions of type I IFN in health and disease. The type I IFN family is a multigene cytokine family that encodes numerous partially homologous IFN-α subtypes, a single IFN-β, and several other poorly defined single genes products (Pestka et al., 2004). All type I IFN share a ubiquitously expressed heterodimeric receptor composed of the subunits IFNAR1 and IFNAR2, which signal through STAT1 and STAT2 to activate a broad family of IFN-stimulated genes (ISGs; Pestka et al., 2004; Ivashkiv and Donlin, 2014). Dominant IFNAR1 expression has been shown to favor IFN-β ligation and activation of the protein kinase B (also known as Akt) pathway over the classical JAK–STAT pathway (de Weerd et al., 2013). ISGs either stimulate or inhibit immune function and in so doing have host-protective or detrimental effects. Thus, although type I IFN is well known for its antiviral activity and stimulation of effector T cell responses (Yan and Chen, 2012; Crouse et al., 2015), it has also been implicated in autoimmune diseases (Hall and Rosen, 2010) and exacerbation of bacterial and even certain viral infections (Decker et al., 2005; Trinchieri, 2010; Davidson et al., 2015; McNab et al., 2015).

The host beneficial protective effects of type I IFN have been most thoroughly studied in viral infections where these cytokines stimulate the production of innate antiviral proteins and promote effector CD8^{+} T cell responses (Crouse et al., 2015). The deleterious effects of type I IFN seen in autoimmune diseases such as lupus or in the genetically based interferonopathies appear to stem largely from dysregulated cytokine synthesis (Banchereau and Pascual, 2006; Crow, 2015). Nevertheless, cytokine overproduction does not provide a unifying explanation for the deleterious activity of type I IFN in infections with bacteria such as *Listeria monocytogenes*, *Brucella abortus*, and *Staphylococcus aureus* (McNab et al., 2015; Stifter and Feng, 2015).

The present review focuses on the role of type I IFN in the immune response to *Mycobacterium tuberculosis.* This topic has received great attention (O'Garra et al., 2013; Mayer-Barber and Sher, 2015; Donovan et al., 2017; Sabir et al., 2017) both because of the global public health importance of this pathogen and the now numerous studies linking type I IFN expression with tuberculosis. However, recent data suggest that even in the prominent example of tuberculosis, the "foe"-like properties of type I IFN are not ironclad and the same cytokines can display "friendly" protective functions under different settings of host–pathogen encounter. Deciphering the mechanisms underlying these opposing activities of type I IFN in tuberculosis should

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contribute enormously to our understanding of the pathogenesis of this important disease while providing new insights into how this major cytokine pathway can be manipulated to ensure beneficial rather than deleterious outcomes for the host.

Role of cytokines in the immune response in tuberculosis

Despite being one of the oldest diseases, tuberculosis remains a devastating public health problem. Worldwide, 6.3 million new cases and 1.67 million deaths (of which 0.37 million were in HIV-positive coinfected individuals) were reported in 2016 alone (World Health Organization, 2017). Although most individuals exposed to *M. tuberculosis* generate an effective immune response and remain clinically asymptomatic (latent infection), ~10% of the infected individuals will progress to active disease at some stage of their lifetime, presenting with clinical signs and symptoms of tuberculosis and, in a significant proportion of patients, cultivable *bacilli* in the sputum (Lawn and Zumla, 2011; O'Garra et al., 2013; Getahun et al., 2015). Several mechanisms have been described that result in the development of a protective immune response that controls infection (Flynn and Chan, 2001; North and Jung, 2004; Cooper, 2009; O'Garra et al., 2013); however, the host immune mechanisms underlying progression to active disease remain poorly understood.

The role of cytokines in host protection against *M. tuberculosis* infection is well established and was first demonstrated in experimental mouse models of infection that established critical roles for IFN-γ (Cooper et al., 1993; Flynn et al., 1993), TNF-α (Flynn et al., 1995a), and IL-12 (Cooper et al., 1995, 1997; Flynn et al., 1995b) in controlling infection. Importantly, these early discoveries were corroborated by studies of human tuberculosis establishing the requirement of the same cytokines for protection. Patients with rheumatoid arthritis or Crohn's disease who were latently infected with *M. tuberculosis*, when treated with anti–TNF-α antibodies or soluble receptor for TNF, showed an increased rate of progression to active tuberculosis (Keane et al., 2001), corroborating a critical role for TNF-α in human tuberculosis. Moreover, human Mendelian susceptibility to mycobacterial disease resulting from deficient IL-12 or IFN-γ signaling confers high susceptibility to *M. tuberculosis* and other mycobacterial infections (Newport et al., 1996; Altare et al., 1998; de Jong et al., 1998; Jouanguy et al., 1999; Fortin et al., 2007). Finally, it is well known that HIV-positive individuals with reduced CD4+ T cells, the main source of IFN-γ during *M. tuberculosis* infection, also display increased susceptibility to tuberculosis (Post et al., 1995). The mechanisms underlying the role of these cytokines was later described as an IL-12/IFN-γ axis in which IL-12, produced early in infection by APCs, promotes the differentiation of CD4+ T helper 1 (Th1) cells and IFN-γ production. IFN-γ further activates macrophages to produce TNF-α and other protective cytokines, promoting intracellular killing of the pathogen through the production of reactive oxygen and nitrogen species (Flynn and Chan, 2001; North and Jung, 2004; Cooper, 2009; O'Garra et al., 2013).

Type I IFN–inducible transcriptional signature in human tuberculosis

In contrast to the now well-established protective function of IFN-γ, the pathogenic role of type I IFN in tuberculosis has only recently been appreciated. The first evidence revealing a role for type I IFN in the pathogenesis of human tuberculosis was provided a few years ago by a transcriptomic study of patients with active disease and latently infected or healthy individuals from the UK and South Africa (Berry et al., 2010). Blood transcriptional profiles of patients with active tuberculosis were dominated by a type I IFN-inducible gene signature that correlated with the extent of lung radiographic disease and diminished with successful treatment (Berry et al., 2010). Several other studies have since verified these findings in additional patient cohorts from different geographic regions with diverse host genetic and tuberculosis epidemiological backgrounds (Maertzdorf et al., 2011a,b, 2012; Bloom et al., 2012, 2013; Ottenhoff et al., 2012; Cliff et al., 2013; Roe et al., 2016; Zak et al., 2016; Sambarey et al., 2017b; Singhania et al., 2017; Esmail et al., 2018; Table 1). In addition, integration and meta-analysis of diverse human tuberculosis datasets confirmed the reproducibility of the type I IFN–inducible blood transcriptional signature in human tuberculosis (Joosten et al., 2013; Blankley et al., 2016; Sambarey et al., 2017a; Singhania et al., 2017; Table 1). Analysis of purified cells from the blood of patients with active disease showed overexpression of IFN-inducible genes in neutrophils and monocytes, but not in CD4+ or CD8+ T cells (Berry et al., 2010; Bloom et al., 2013), suggesting that overactivation of monocytes and neutrophils by type I IFN during infection may contribute to disease pathogenesis.

Similar findings have since been observed in other mycobacterial infections. In human leprosy, caused by *Myobacterium leprae*, type I IFN and their downstream genes, were preferentially expressed in lesions of the disseminated and progressive lepromatous form at the site of disease, whereas IFN-γ and its downstream genes were preferentially expressed in the lesions from patients with the self-healing tuberculoid form (Teles et al., 2013). Overexpression of IFN-inducible genes in blood has also been reported in patients with other pulmonary diseases such as sarcoidosis and acute influenza infection but has not been detected in other bacterial infections (Berry et al., 2010; Maertzdorf et al., 2012; Bloom et al., 2013; Singhania et al., 2017). However, distinct gene patterns have been detected between tuberculosis and sarcoidosis (Bloom et al., 2013) and tuberculosis and influenza infection (Singhania et al., 2017).

In tuberculosis, overexpression of IFN response genes, including *STAT1*, *IFITs*, *GBPs*, *MX1*, *OAS1*, *IRF1*, and other genes, were also detected early in tuberculosis contacts who progressed to active disease (Zak et al., 2016; Scriba et al., 2017; Singhania et al., 2017; Esmail et al., 2018), suggesting that peripheral activation of the type I IFN response precedes the onset of active disease and clinical manifestations of tuberculosis. These changes apparently preceded the up-regulation of other innate immune responses and down-regulation of genes associated with specific lymphocyte cell populations (Scriba et al., 2017; Singhania et al., 2017), although this conclusion requires more detailed studies. The type I IFN–inducible signature was also present in 10–25% of latently infected patients who are asymptomatic (Berry et al., 2010; Singhania et al., 2017), suggesting that these patients may be at the highest risk to progress to active disease.

Several clinical studies have reported reactivation of tuberculosis in patients undergoing IFN-α based therapy for chronic

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Table 1. Type I IFN–inducible blood transcriptional signature in human tuberculosis

Original study	Geographic location	Sample type	Cohort size	● Type I IFN signature shown in original study			o Type I IFN signature reported in subsequent analysis			
				Active disease	Correlated radiographical disease	Treatment response	Joosten et al., 2013	Blankley et al., 2016	Sambarey et al., 2017a	Singhania et al., 2017
Jacobsen et al., 2007	Germany	PBMCs	Active TB ($n=9$); LTBI ($n=9$)				o			
Mistry et al., 2007	South Africa	Whole blood	Active, recurrent, or cured TB; LTBI ($n=10$/group)				o			
Berry et al., 2010[a]	UK	Whole blood (and sorted cells)	Active TB ($n=21$); LTBI ($n=21$); HCs ($n=12$)	●	●	●	o	o	o	o
	South Africa	Whole blood	Active TB ($n=20$); LTBI ($n=31$)	●			o	o	o	o
Maertzdorf et al., 2011a	South Africa	Whole blood	Active TB ($n=46$); LTBI ($n=25$); HC ($n=37$)	●			o		o	
Maertzdorf et al., 2011b	The Gambia	Whole blood	Active TB ($n=33$); LTBI ($n=34$); HC ($n=9$)	●			o			
Bloom et al., 2012	South Africa	Whole blood	active TB ($n=33$); LTBI ($n=34$); HC ($n=9$)	●		●		o	o	
Maertzdorf et al., 2012	Germany	Whole blood	Active TB ($n=8$); LTBI ($n=4$); HC ($n=14$)	●			o		o	
Ottenhoff et al., 2012	Indonesia	PBMCs	Active TB over time during treatment ($n=23$); HC ($n=23$)	●		●	o		o	
Cliff et al., 2013	South Africa	Whole blood	Active TB over time during treatment ($n=27$)	●		●	o	o	o	
Bloom et al., 2013	UK	Whole blood (and sorted cells)	Active TB ($n=35$); HCs ($n=113$)	●				o	o	o
Kaforou et al., 2013	South Africa, Malawi	Whole blood	Active TB (HIV-/+; $n=195$); LTBI (HIV-/+; $n=167$)					o		o
Cai et al., 2014	China	PBMCs	active TB ($n=9$); LTBI ($n=6$); HC ($n=6$)					o		
Anderson et al., 2014	Kenya	Whole blood	Active TB ($n=79$); LTBI ($n=14$)					o		
	South Africa, Malawi		Active TB ($n=110$); LTBI ($n=54$)					o		
Roe et al., 2016	UK	Whole blood	Active TB ($n=46$); postrecovery ($n=31$)	●	●					
Zak et al., 2016	South Africa	Whole blood	Progressors ($n=40$); nonprogressors ($n=104$)	●						o
Sambarey et al., 2017b	India	Whole blood	Active TB ($n=19$); LTBI ($n=13$); HCs ($n=15$)	●						
Singhania et al., 2017	UK	Whole blood	Active TB ($n=53$); LTBI ($n=49$); HCs ($n=50$)	●						
Esmail et al., 2018	South Africa	Whole blood	Active TB ($n=15$); subclinical TB ($n=10$); latent TB ($n=25$)	●						

Type I IFN signature reported in original study (●) and/or in subsequent analysis by others (o). HC, healthy control; LTBI, latent tuberculosis infection; PBMC, peripheral blood mononuclear cell; TB, tuberculosis.

[a]Original study providing the first data in human disease to support a role for type I IFN in the pathogenesis of tuberculosis.

viral hepatitis (Sabbatani et al., 2006; Farah and Awad, 2007; Telesca et al., 2007; Belkahla et al., 2010; Guardigni et al., 2012; Abutidze et al., 2016; de Oliveira Uehara et al., 2016; Matsuoka et al., 2016). In addition, a very recent study showed that impaired type I IFN signaling due to a rare East Asian functional mutation in the *IFNAR1* gene was associated with increased resistance to tuberculosis (Zhang et al., 2018). As the control population consisted of healthy individuals, it is presently unclear whether this

polymorphism influences susceptibility to infection as opposed to disease progression in latent infected individuals. In contrast, patients with an inherited deficiency in the gene encoding ISG15, who displayed immunological and clinical signs of enhanced type I IFN responses (Zhang et al., 2015), were shown to be more susceptible to mycobacterial infections (Bogunovic et al., 2012). Together, these findings provide strong evidence that type I IFN signaling correlates with impaired control of *M. tuberculosis* and

other mycobacterial infections and underlies an increased risk of tuberculosis in humans.

Foe-like pathogenic role of high and sustained type I IFN in tuberculosis: Evidence from mouse models

Following on from the observations in human tuberculosis, whole-genome blood transcriptional profiling in animal models of tuberculosis have since shown up-regulation of type I IFN response related genes in response to *M. tuberculosis* infection in both nonhuman primates (Gideon et al., 2016) and mice (Domaszewska et al., 2017). However, different effects of type I IFN in either protection or pathogenesis in experimental models of tuberculosis have been reported as we discuss herein. Several studies have reported reduced bacterial loads (Ordway et al., 2007; Stanley et al., 2007; Mayer-Barber et al., 2011; Dorhoi et al., 2014) and/or improved host survival (Manca et al., 2005; Dorhoi et al., 2014; Kimmey et al., 2017) upon *M. tuberculosis* infection of IFNAR-deficient (*Ifnar1−/−*) mice compared with WT controls although this phenotype has not been universally observed (Cooper et al., 2000; Antonelli et al., 2010; Desvignes et al., 2012; McNab et al., 2013; Redford et al., 2014; Moreira-Teixeira et al., 2016, 2017). The reasons underlying the discrepancies in the results of these studies (summarized in Table 2) are presently unclear but may relate to differences in the *M. tuberculosis* strains used for challenge, host genetic background of the different colonies of *Ifnar1−/−* mice used, or environmental differences.

Elevated production of type I IFN has been associated with the virulence of *M. tuberculosis* strains and increased host susceptibility. Studies of infection with hypervirulent *M. tuberculosis* clinical isolates (e.g., HN878 and BTB 02–171) compared with the less virulent laboratory strain (H37Rv) showed a positive correlation between increased levels of type I IFN and increased mycobacterial virulence (Manca et al., 2001, 2005; Ordway et al., 2007; Carmona et al., 2013). However, similar bacterial loads and survival were reported in *Ifnar1−/−* and WT controls in the *M. tuberculosis*–resistant C57BL/6 genetic background (McNab et al., 2013; Moreira-Teixeira et al., 2017). IFNAR deficiency in mice with a *M. tuberculosis*–susceptible genetic background (A129, 129S2) enhanced host survival following infection with not only the hypervirulent strain HN878 (Manca et al., 2005) but also the less virulent H37Rv strain (Dorhoi et al., 2014). A stronger up-regulation of type I IFN response related genes has recently been reported in the blood of the highly susceptible 129S2 mouse strain compared with the resistant C57BL/6 mouse strain early after infection with the *M. tuberculosis* strain H37Rv (Domaszewska et al., 2017). This increased expression of type I IFN–inducible genes detected in 129S2 compared with C57BL/6 mice is consistent with the results showing that the detrimental effect of type I IFN during *M. tuberculosis* (laboratory strain H37Rv) infection is more pronounced in the highly susceptible 129S2 strain than the resistant C57BL/6 strain (Dorhoi et al., 2014). However, a transient protective effect of type I IFN has also been observed during *M. tuberculosis* (Erdmann strain) infection using the 129 strain (Cooper et al., 2000). Differing findings may relate to the genetic variation among 129 substrains (Simpson et al., 1997; Festing et al., 1999) in addition to *M. tuberculosis* strain type and the host environment. Experiments in

which *Ifnar1−/−* mice of either susceptible or resistant genetic backgrounds are studied side by side are needed to investigate the basis of the discrepancy across all the studies.

Robust evidence for the role of high and sustained levels of type I IFN in *M. tuberculosis* persistence and disease pathogenesis has been further provided by experimental models of type I IFN overexpression. Direct instillation of purified murine IFN-α/β into the lungs of *M. tuberculosis*–infected B6D2/F1 mice resulted in increased lung bacterial loads and reduced survival of infected mice (Manca et al., 2001). Prolonged induction of high levels of type I IFN by intranasal administration of the TLR3 ligand poly-ICLC during *M. tuberculosis* infection impaired control of bacterial growth and exacerbated pulmonary immunopathology in WT mice, but not in *Ifnar−/−* mice (Antonelli et al., 2010; Mayer-Barber et al., 2014). Host coinfection with influenza A virus, another well-known inducer of type I IFN, has also been shown to reduce host resistance to *M. tuberculosis* infection via the action of type I IFN, because this was observed in WT, but not in IFN AR-deficient, mice (Redford et al., 2014). Likewise, abrogation of negative regulators of type I IFN signaling leading to elevated levels of type I IFN resulted in impaired *M. tuberculosis* clearance (McNab et al., 2013; Dauphinee et al., 2014). Specifically, deletion of the MAPK kinase kinase 8 (MAP3K8; also known as TPL2), a negative regulator of type I IFN induction downstream of TLR, resulted in increased bacterial loads upon *M. tuberculosis* or *L. monocytogenes* infection, which was not observed in the absence of IFNAR (McNab et al., 2013). Impaired control of the bacterial loads in the absence of TPL2 was correlated with type I IFN–dependent induction of IL-10 and suppression of IL-12 production during infection (McNab et al., 2013). Mice carrying a loss-of function mutation within the *ubiquitin-specific peptidase 18* (*Usp18*) gene, which results in increased levels of type I IFN production and hyperactivation of type I IFN signaling during bacterial infection, were also shown to be more susceptible to *M. tuberculosis* infection, showing increased bacterial burdens and decreased survival (Dauphinee et al., 2014). Collectively, these studies performed in experimental mouse models of *M. tuberculosis* infection point to a detrimental role of high and sustained levels of type I IFN in exacerbating tuberculosis.

Mechanisms of type I IFN induction in *M. tuberculosis* infection

Because type I IFN has been associated with disease pathogenesis, identifying mechanisms regulating type I IFN induction during *M. tuberculosis* infection has been an active area of research (Donovan et al., 2017; Sabir et al., 2017). In vitro studies in human and murine cells have shown that distinct mycobacterial molecules and signaling pathways may be involved in the induction of this family of cytokines during *M. tuberculosis* infection (Fig. 1). High levels of type I IFN are preferentially induced by virulent strains of *M. tuberculosis* (Manca et al., 2001, 2005; Novikov et al., 2011; Carmona et al., 2013), and this property seems to depend on the well-known mycobacterial virulence factor ESX-1 protein secretion system (Stanley et al., 2007; Manzanillo et al., 2012; Wassermann et al., 2015).

Recognition of mycobacterial products in the cytosol, such as peptidoglycan fragments, by the cytosolic sensor

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Table 2. **Summary of outcomes reported following aerosol infection with *M. tuberculosis* in *Ifnar*$^{-/-}$ mice**

Mtb strain	Dose (CFU)	Mouse background	Bacterial loads[a]		Lung pathology[a]	Survival[a]	Reference
			Lung	Spleen			
H37Rv	100	C57BL/6 (R)	Increased (day 28 p.i.)	—	—	—	Antonelli et al., 2010
H37Rv	100–150	C57BL/6 (R)	Decreased (day 28 p.i.)	—	—	—	Mayer-Barber et al., 2011
H37Rv	100	C57BL/6 (R)	Transiently decreased (day 18 p.i.) but similar at day 25 p.i.	—	—	Similar (day 70 p.i.)	Desvignes et al., 2012
H37Rv	50–150	C57BL/6 (R)	Similar (day 27 p.i.)	—	—	—	Redford et al., 2014
H37Rv	100–150	C57BL/6 (R)	—	—	—	Similar (day 80 p.i.)	Mayer-Barber et al., 2014
H37Rv	500 (200 for survival)	C57BL/6 (R)	Decreased (day 42 p.i.)	—	—	Similar (day 80 p.i.)	Dorhoi et al., 2014
	200	129S2 (S)	Decreased (day 21 p.i.)	—	Decreased (day 21 p.i.)	Increased	
H37Rv	50–100	KO 129 (S); WT C57BL/6 (R)	Decreased (chronic phase, > day 75 p.i.)	—	—	—	Ordway et al., 2007
Erdman	10^6 (i.v.)	C57BL/6 (R)	Similar (days 10, 21 p.i.)	Decreased (days 10, 21 p.i.)	—	—	Stanley et al., 2007
Erdman	100	C57BL/6 (R)	Transiently decreased (day 7 p.i.) but similar at days 21, 77, 100, 245 p.i.	Transiently decreased at day 77 p.i. but similar at other time points	Similar (days 100, 275 p.i.)	Increased	Kimmey et al., 2017
Erdman	100	B6/129 (S)	Transiently increased (days 10, 20, 40 p.i.) but similar by day 80 p.i.	—	—	—	Cooper et al., 2000
Erdman	50–100	KO 129 (S); WT C57BL/6 (R)	Decreased (> day 25 p.i.)	—	—	Similar (day 200 p.i.)	Ordway et al., 2007
CSU93	50–100	KO 129 (S); WT C57BL/6 (R)	Decreased (> day 25 p.i.)	—	—	Similar (day 200 p.i.)	Ordway et al., 2007
HN878	100–200	C57BL/6 (R)	Similar (days 28, 60 p.i.)	—	—	—	Moreira-Teixeira et al., 2017
HN878	30	C57BL/6 (R)	Similar (day 48 p.i.)	—	—	—	McNab et al., 2013
HN878	100–200	129 (S)	—	—	—	Increased	Manca et al., 2005
HN878	50–100	KO 129 (S); WT C57BL/6 (R)	Decreased (> day 50 p.i.)	—	—	Similar (day 200 p.i.)	Ordway et al., 2007
BTB 02-171	30	C57BL/6 (R)	Similar (day 56 p.i.)	—	—	—	McNab et al., 2013
BTB 02-171	100–200	C57BL/6 (R)	Similar (days 20, 24, 27 p.i.)	—	Similar (day 27 p.i.)	Similar (> day 200 p.i.)	Moreira-Teixeira et al., 2016

Dashes indicate no data reported. *Mtb*, *M. tuberculosis*; p.i., postinfection; (R), *M. tuberculosis*–resistant mouse strain; (S), *M. tuberculosis*–susceptible mouse strain.
[a]Compared with WT mice.

nucleotide-binding oligomerization containing protein 2 (NOD2) has been shown to induce type I IFN expression by infected murine macrophages (Leber et al., 2008; Pandey et al., 2009). NOD2 activates the downstream serine/threonine-protein kinase (TBK1)–IFN regulatory factor 5 (IRF5) signaling pathway, leading to the production of type I IFN (Pandey et al., 2009). Three independent studies have identified a central role for the cytosolic DNA sensor nucleotidyltransferase cyclic GMP-AMP synthase (cGAS) in the detection of mycobacterial DNA in the host cytosol and induction of type I IFN transcription in macrophages (Collins et al., 2015; Wassermann et al., 2015; Watson et al., 2015). The sensing of DNA by cGAS leads to the synthesis of the second messenger cyclic di–GMP-AMP

(cGAMP), which activates the stimulator of IFN genes (STING) and the downstream TBK1–IRF3 signaling pathway, culminating in the transcription of type I IFN (Manzanillo et al., 2012; Collins et al., 2015; Wassermann et al., 2015; Watson et al., 2015). Mycobacterial DNA in the host cytosol can also be sensed by absent in melanoma 2 (AIM-2) protein, which partially contributes to the activation of the NLRP3-inflammasome, promoting the maturation of the protective cytokine IL-1β (Shah et al., 2013; Wassermann et al., 2015). This AIM-2–IL-1β signaling pathway has been recently reported to negatively regulate the STING-dependent type I IFN production in macrophages and dendritic cells (DCs) by inhibiting the association between STING and TBK1 (Yan et al., 2018).
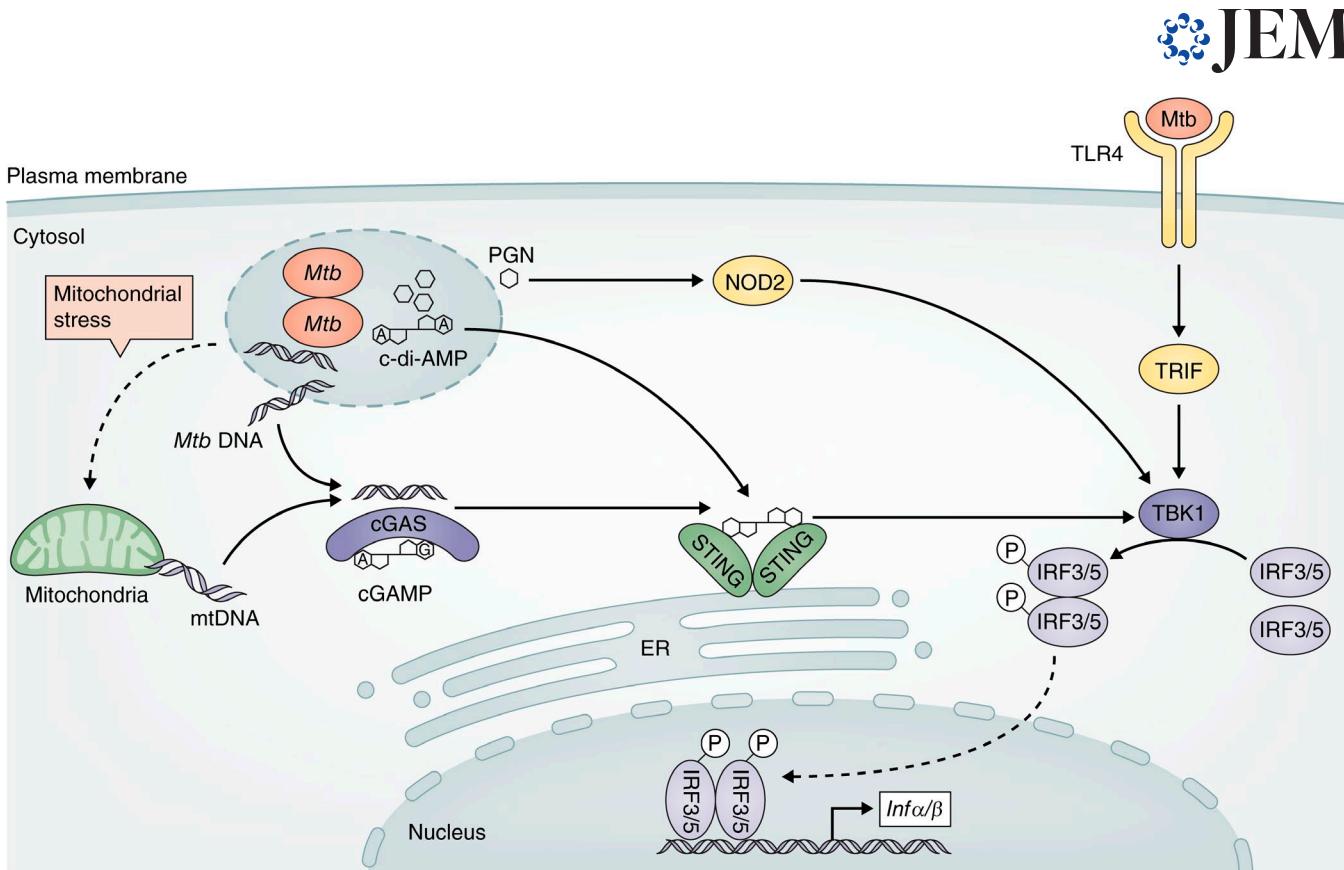
Figure 1. **Alternative pathways of type I IFN induction during *M. tuberculosis* infection.** Recognition of mycobacterial products by a range of cell surface and cytosolic PRR, including TLR4, NOD2, and STING, activates the kinase TBK1 leading to phosphorylation (P) and dimerization of IRF3 or IRF5, which translocates into the nucleus and promotes transcription of type I IFN genes. Release of mycobacterial or mitochondrial DNA in the cytosol activates cGAS, which synthesizes cGAMP. Host-derived cGAMP and/or mycobacterial-derived c-di-AMP activates the STING pathway and the downstream TBK1–IRF3 signaling axis. Peptidoglycan fragments can be sensed by NOD2 in the cytosol, activating the TBK1–IRF5 signaling pathway. Detection of extracellular *M. tuberculosis* and/or its products by TLR4 triggers TRIF-TBK1-IRF3–dependent induction of type I IFN by certain strains. Mtb, *M. tuberculosis;* mtDNA, mitochondrial DNA; PGN, peptidoglycan.

A more recent study suggested that cGAS/STING–dependent type I IFN induction in macrophages can also be triggered by mitochondrial DNA released into the cytosol due to mitochondrial stress caused by *M. tuberculosis* infection (Wiens and Ernst, 2016). Production of cyclic di-AMP (c-di-AMP) by *M. tuberculosis* has also been shown to promote type I IFN induction in a STING-dependent but cGAS-independent mechanism (Dey et al., 2015). STING-dependent induction of type I IFN can be regulated by mycobacterial and host phosphodiesterases, which inhibit STING activation and consequent induction of type I IFN by hydrolysis of both mycobacterial-derived c-di-AMP and host-derived cGAMP (Dey et al., 2017).

TLRs are another set of pattern recognition receptors (PRRs) that are important for sensing *M. tuberculosis* infection (Stamm et al., 2015). Whereas some *M. tuberculosis* strains activate mainly TLR2, others also activate TLR4 and the downstream MyD88-independent TIR domain–containing adapter-inducing IFN-β (TRIF), resulting in different macrophage responses characterized by varying production of type I IFN (Carmona et al., 2013; Moreira-Teixeira et al., 2016). Sensing of *M. tuberculosis* infection by C-type lectin receptors has also been reported to induce type I IFN production by B cells (Benard et al., 2017) and to amplify type I IFN responses in DCs (Troegeler et al., 2017). In B cells, induction of type I IFN during *M. tuberculosis* infection

has also been shown to require the STING signaling pathway and to be negatively regulated by MyD88 (Benard et al., 2017).

These studies indicate that different *M. tuberculosis* strains can induce type I IFN by triggering multiple cell surface and cytosolic PRR and downstream signaling pathways (Fig. 1), which may contribute to the differential levels of type I IFN and virulence induced by distinct strains. Further studies are required to determine the relative importance of each of these pathways in vivo and determine how widely they function in different cell types, as they could provide novel targets for tuberculosis prevention and therapy.

Pathogenic effects of type I IFN signaling during *M. tuberculosis* infection

Studies performed in patients and mouse models of infection collectively point to a harmful role of high and sustained type I IFN in tuberculosis (discussed above). However, the mechanisms by which type I IFN signaling exacerbates *M. tuberculosis* infection are not yet fully understood (Mayer-Barber and Sher, 2015; McNab et al., 2015; Donovan et al., 2017; Sabir et al., 2017). Early studies with hypervirulent strains of *M. tuberculosis* associated the induction of higher levels of type I IFN with the suppression of proinflammatory cytokines and impaired antibacterial Th1 responses (Manca et al., 2001, 2005; Ordway et al., 2007). The

A Early and/or low level of type I IFN signalling
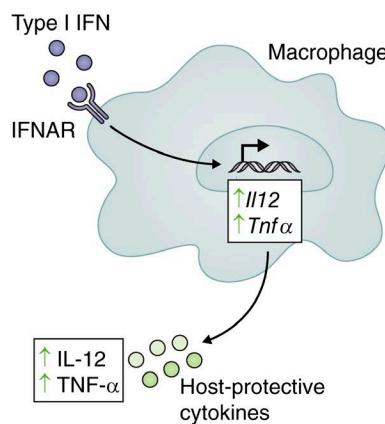
B Late and high level of type I IFN signalling
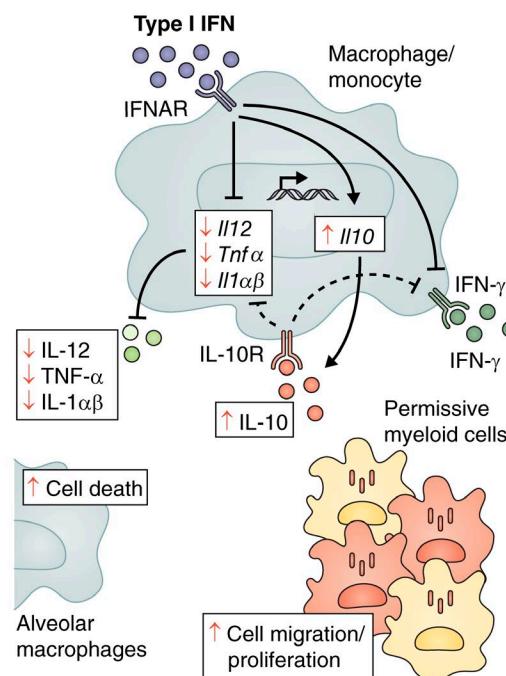
C In the absence of IFN-γ receptor
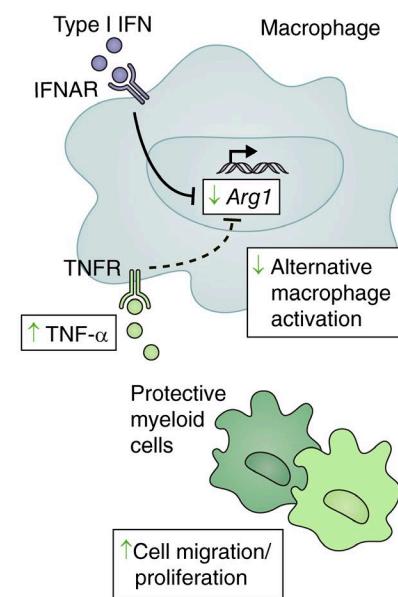
Figure 2. **Foe- and friendly-like effects of type I IFN during *M. tuberculosis* infection.** Type I IFN has been reported to play both negative (red arrows) and positive (green arrows) functions during *M. tuberculosis* infection. **(A)** Tonic levels of autocrine type I IFN signaling prime the production of protective cytokines IL-12 and TNF-α. **(B)** However, high and sustained levels of type I IFN promote the production of IL-10 and inhibit the production of protective cytokines IL-12, TNF-α, IL-1α, and IL-1β. IL-10 mediates a suppressive feedback loop, contributing to the decreased production of IL-12 and TNF-α. Type I IFN also inhibits myeloid cell responsiveness to IFN-γ by both IL-10–dependent and independent mechanisms, suppressing IFN-γ–dependent host-protective immune responses. In addition, type I IFN can promote cell death in alveolar macrophages and accumulation of permissive myeloid cells at the site of infection. **(C)** In the absence of the IFN-γ receptor, type I IFN inhibits *Arg1* expression directly or indirectly by increasing TNF-α levels, thus regulating macrophage activation toward a more protective phenotype. Type I IFN signaling can also promote the recruitment, differentiation, and/or survival of protective myeloid cells that control pathology at the site of infection. *Arg1*, arginase 1; IFNγR, IFN-γ receptor; IL-10R, IL-10 receptor; TNFR, TNF-α receptor.

inhibition of host-protective cytokines and innate cell responsiveness in addition to IFN-γ–driven antibacterial effects by type I IFN has since been verified by several other studies both in human cells (Mayer-Barber et al., 2011; Novikov et al., 2011; de Paus et al., 2013; Teles et al., 2013) and mouse models (Mayer-Barber et al., 2011; McNab et al., 2013, 2014; Dorhoi et al., 2014). In addition, type I IFN has also been shown to promote early cell death of alveolar macrophages (Dorhoi et al., 2014) and boost the local accumulation of permissive myeloid cells, which contribute to the spread of infection and pulmonary inflammation (Antonelli et al., 2010; Dorhoi et al., 2014), underlining the complex role of type I IFN during *M. tuberculosis* infection (Fig. 2).

Type I IFN has been reported to inhibit the production of IL-1α and IL-1β, which are critical for host defense against *M. tuberculosis* infection (Mayer-Barber et al., 2010, 2011), both in vitro in infected human (Mayer-Barber et al., 2011; Novikov et al., 2011; de Paus et al., 2013) and mouse myeloid cells (Mayer-Barber et al., 2011; McNab et al., 2014) and in vivo in mouse models (Mayer-Barber et al., 2011; Dorhoi et al., 2014). Prostaglandin E2 (PGE2) has been shown to be a critical downstream mediator of IL-1–dependent host resistance, and accordingly, type I IFN has been shown to limit PGE2 in vitro in human and mouse cells and in vivo (Mayer-Barber et al., 2014). PGE2 is known to prevent necrosis of *M. tuberculosis*–infected macrophages by promoting

apoptosis, a cell death modality that contains the pathogen, limiting its dissemination (Chen et al., 2008; Divangahi et al., 2009). Thus, an additional mechanism by which type I IFN could enhance *M. tuberculosis* infection and disease is through promotion of necrosis as a consequence of PGE2 inhibition.

In turn, it has recently been demonstrated that there is a reciprocal control of type I IFN regulation by IL-1β through a PGE2-mediated mechanism (Mayer-Barber et al., 2014). Increasing the levels of PGE2 during *M. tuberculosis* infection, by direct administration of this prostanoid or by increasing its level through 5-lipoxygenase blockade with zileuton, limited type I IFN induction and conferred host resistance to infection in mice (Mayer-Barber et al., 2014). These findings suggest zileuton as a drug that could be used for host-directed therapy of tuberculosis by limiting detrimental type I IFN overproduction.

The production of other proinflammatory cytokines such as TNF-α and IL-12 has also been shown to be negatively affected by the addition of exogenous IFN-α or IFN-β to human monocytes (de Paus et al., 2013) and murine macrophages (McNab et al., 2014) in in vitro cultures. Type I IFN has also been reported to induce the production of the immunosuppressive cytokine IL-10 in vitro in macrophages (Mayer-Barber et al., 2011; McNab et al., 2014) and in vivo in CD4+ T cells (Moreira-Teixeira et al., 2017), which has been shown to increase susceptibility to *M.*

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tuberculosis infection (Redford et al., 2011). In addition, the increased susceptibility of *M. tuberculosis*–infected mice given the double-stranded RNA homologue poly-ICLC, which led to enhanced type I IFN production, was shown to be dependent on IL-10 production (Mayer-Barber et al., 2014). The inhibitory effect of type I IFN on the production of IL-12 and TNF-α by *M. tuberculosis*–infected macrophages is abrogated in the absence of IL-10 (McNab et al., 2014). However, the inhibitory effect of type I IFN on IL-1β production is only slightly affected by IL-10 deficiency (Mayer-Barber et al., 2011; McNab et al., 2014), indicating that type I IFN suppresses the macrophage response to *M. tuberculosis* infection by both IL-10–dependent and –independent mechanisms.

In addition, type I IFN has been shown to repress macrophage/monocyte responsiveness to the antibacterial effects of IFN-γ during mycobacterial infections (de Paus et al., 2013; Teles et al., 2013; McNab et al., 2014). In both mouse and human cells, type I IFN has been shown to suppress the ability of monocytes and macrophages to up-regulate antimycobacterial effector molecules and to restrict bacterial growth in response to both *M. tuberculosis* and *M. leprae* (Teles et al., 2013; McNab et al., 2014). This inhibitory effect of type I IFN on the antimycobacterial activity of IFN-γ in human macrophages has shown to be mediated by IL-10 (Teles et al., 2013). However, the inhibition of IFN-γ–induced cytokine production by type I IFN in murine macrophages seems to be mediated by both IL-10–dependent and –independent mechanisms (McNab et al., 2014). Down-regulation of IFN-γ–driven inducible nitric oxide synthase and IL-12/23 p40 by type I IFN has also been reported in lung myeloid cells during *M. tuberculosis* infection in vivo (Mayer-Barber et al., 2011; Mayer-Barber and Sher, 2015). Although induction of IL-10 by type I IFN has been reported during *M. tuberculosis* infection in vivo (Moreira-Teixeira et al., 2017), it is not yet clear whether IL-10 is responsible for the suppressive effects of type I IFN on IFN-γ function in vivo.

Friendly protective functions of type I IFN in tuberculosis
Although a role for type I IFN in the pathogenesis of tuberculosis is strongly supported by studies in both human tuberculosis (Zhang et al., 2018) and studies in experimental mouse models of *M. tuberculosis* infection (Antonelli et al., 2010; McNab et al., 2013; Dorhoi et al., 2014; Mayer-Barber et al., 2014; Redford et al., 2014), there is also evidence that type I IFN can display protective functions under specific conditions. Several clinical case reports have described improved clinical symptoms and decreased bacterial burden after coadministration of IFN-α together with antimycobacterial chemotherapy to patients with active tuberculosis who were not responsive to conventional treatment and/or had recurrent disease (Giosué et al., 1998; Palmero et al., 1999; Giosuè et al., 2000; Mansoori et al., 2002; Zargoulidis et al., 2012). These clinical studies of IFN-α adjunct therapy were designed before the now numerous studies linking type I IFN expression with active tuberculosis, and the mechanisms underlying the beneficial effects of IFN-α administration in these patients remain unclear. Therapeutic effects of IFN-α have also been reported in young patients suffering from mycobacterial infections with complete or partial IFN-γ receptor

(IFNGR) signaling deficiencies when administered together with antimycobacterial chemotherapy (Ward et al., 2007; Bax et al., 2013).

A protective role for type I IFN in the absence of IFN-γ signaling has also been proposed in mouse models of *M. tuberculosis* infection (Desvignes et al., 2012; Moreira-Teixeira et al., 2016), suggesting that the dominant suppressive effect of type I IFN on IFN-γ antimycobacterial activity may mask potentially protective functions of this family of cytokines (Fig. 2). These studies reported increased pulmonary pathology and early mortality following *M. tuberculosis* infection in mice deficient in both type I IFN and IFN-γ receptors (*Ifngr1⁻/⁻ Ifnar1⁻/⁻*) compared with single IFNGR-deficient mice (*Ifngr1⁻/⁻*; Desvignes et al., 2012; Moreira-Teixeira et al., 2016). In contrast to what has been reported in the immunocompetent host, where type I IFN signaling may promote local accumulation of permissive myeloid cells that contribute to the spread of infection and pulmonary inflammation (Antonelli et al., 2010; Dorhoi et al., 2014), in the absence of IFN-γ signaling, type I IFN may facilitate the recruitment, differentiation, and/or survival of myeloid cells that control pathology (Desvignes et al., 2012). Although no difference in the lung bacterial burden was observed during infection with the less virulent laboratory strain H37Rv (Desvignes et al., 2012), infection with the hypervirulent strain BTB 02–171, shown to induce high levels of type I IFN (Carmona et al., 2013), revealed the ability of type I IFN to also control bacterial replication (Moreira-Teixeira et al., 2016). Following infection with BTB 02–171, increased lung bacterial loads were observed in double *Ifngr1⁻/⁻Ifnar1⁻/⁻* mice, which are deficient in both type I IFN and IFN-γ receptors, compared with single *Ifngr1⁻/⁻* mice. Increased control of bacterial replication in the absence of IFN-γ signaling correlated with suppression of alternative macrophage activation by type I IFN, likely by direct regulation of macrophage activation as well as by regulation of cytokine expression in the infected lungs (Moreira-Teixeira et al., 2016). These findings may help to explain some of the mechanisms underlying the beneficial effects of IFN-α treatment, at least in patients with compromised IFN-γ responses, and provide new avenues for host-directed therapies in tuberculosis.

Type I IFN has also been reported to increase host resistance in mouse models of infection against avirulent mycobacterial strains, such as *Mycobacterium smegmatis* (Ruangkiattikul et al., 2017), *Mycobacterium avium* (Denis, 1991), and *Mycobacterium bovis* bacillus Calmette-Guérin (BCG; Kuchtey et al., 2006). In addition, it has been suggested that type I IFN may improve the immunogenicity of BCG vaccination against *M. tuberculosis* infection in mouse and guinea pig models (Bottai et al., 2015; Gröschel et al., 2017; Rivas-Santiago and Guerrero, 2017). Recombinant expression of the ESX-1 protein secretion system in the attenuated BCG vaccine has been shown to increase the protective effect of vaccination against *M. tuberculosis* infection (Bottai et al., 2015; Gröschel et al., 2017). This increased protection correlated with enhanced IFN-β production by macrophages infected with recombinant ESX-1–expressing BCG (Gröschel et al., 2017). However, the contribution of type I IFN in the protection conferred by ESX-1–expressing BCG vaccine

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still requires investigation. In support for a role of type I IFN in increasing BCG vaccine efficacy, an independent study has shown that administration of IFN-α during BCG vaccination promotes the production of host-protective cytokines (e.g., IFN-γ, TNF-α, and IL-12) and confers increased protection against *M. tuberculosis* infection over that observed with BCG alone (Rivas-Santiago and Guerrero, 2017). These findings suggest that type I IFN may play a friendly protective role in the context of BCG-induced immunity and could be targeted to improve preventive vaccination against tuberculosis.

In vitro experiments in human peripheral blood cells have shown that treatment with type I IFN can increase DC maturation and IL-12 production following BCG infection, which then promotes T cell priming and production of IFN-γ (Giacomini et al., 2009), and may help to explain the positive effects of type I IFN during vaccination. Whereas addition of IFN-β at the time of infection has been shown to negatively affect proinflammatory cytokine production via IL-10–dependent and –independent mechanisms (Mayer-Barber et al., 2011; McNab et al., 2014), basal type I IFN signaling has been shown to be required for maximal production of IL-12 and TNF-α by macrophages in response to *M. tuberculosis* infection (McNab et al., 2014). Indeed, *Ifnar1*$^{-/-}$ macrophages have been shown to produce lower levels of IL-12 and TNF-α in response to *M. tuberculosis* infection compared with WT macrophages (McNab et al., 2014). Tonic type I IFN signaling has also been reported to be important for optimal IL-12 production by macrophages (Howes et al., 2016) and DCs (Gautier et al., 2005) in other contexts. Moreover, pretreatment of WT macrophages with IFN-β for >8 h before *M. tuberculosis* infection enhanced the production of IL-12 and TNF-α (McNab et al., 2014), indicating that the timing of type I IFN signaling may be important in determining the effects of type I IFN during *M. tuberculosis* infection. Thus, these findings suggest that early tonic type I IFN signaling can elicit friendly functions during *M. tuberculosis* infection by priming innate immune cells for the production of proinflammatory host-protective cytokines (Fig. 2).

Closing remarks

Members of the type I IFN family were first discovered for their ability to interfere with viral replication and are well known for their antiviral responses (Yan and Chen, 2012; Crouse et al., 2015). Unlike their largely protective role in viral infections, this family of cytokines plays a less predictable role in bacterial infection (Trinchieri, 2010; McNab et al., 2015; Stifter and Feng, 2015; Mayer-Barber and Yan, 2017). Over the past decade, numerous studies have uncovered a foe-like pathogenic role of type I IFN in tuberculosis. Patients with active tuberculosis have a blood transcriptional gene signature dominated by type I IFN–related genes that is correlated with disease severity and is down-regulated following successful treatment (Table 1). In experimental models, elevated levels of type I IFN are associated with the virulence of *M. tuberculosis* strains and increased host susceptibility. Several mechanisms underlying the pathogenic role of type I IFN in tuberculosis have been described, including induction of IL-10 and negative regulation of the IL-12/IFN-γ and IL-1β/PGE2 host-protective responses. However, there is also evidence that type I IFN may play a friendly role in certain contexts, highlighting the complex role of type I IFN in tuberculosis (Fig. 2). Although high levels of type I IFN have negative effects during the course of *M. tuberculosis* infection, tonic I IFN signaling or low levels of type I IFN in the context of low mycobacterial loads may in turn have positive effects by priming host-protective responses. This may explain the protective effects of IFN-α therapy together with anti-mycobacterial drugs in patients with active disease. Thus, it is likely that a balanced induction of this family of cytokines is required for optimal protection. Various signaling pathways have been described to induce type I IFN production in response to *M. tuberculosis* infection (Fig. 1). Differential activation of these pathways and/or high or low engagement of these signaling pathways during infection may contribute to the induction of distinct levels of type I IFN and the differential virulence of *M. tuberculosis* strains. In addition, potential differences in temporal and spatial induction of individual IFN-α subtypes and IFN-β during infection could contribute to variations in disease outcome and determine foe or friend features of the type I IFN response. A further unexplored area is the possible differential role of IFNAR subunits (IFNAR1 and IFNAR2) in determining the outcome of type I IFN signaling. Dominant IFNAR1 expression has been shown to favor IFN-β ligation and activation of the protein kinase B (also known as Akt) pathway over the classical JAK–STAT pathway (de Weerd et al., 2013). Therefore, differential expression of IFNAR subunits on the relevant responding cells during *M. tuberculosis* infection could be another factor regulating detrimental versus protective activities of type I IFN signaling during infection. Deciphering the mechanisms underlying the differential induction of type I IFN and what determines the outcome of type I IFN signaling during *M. tuberculosis* infection, from induction of IL-10 to the regulation of the IL-12/IFN-γ and IL-1β/PGE2 host-protective responses, may offer new avenues for host-directed therapies for tuberculosis. In addition, such research may yield important basic information about type I IFN induction and function that will enhance our broader understanding of how this major cytokine family impacts on disease outcomes.

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