IFN-β: A Contentious Player in Host–Pathogen Interaction in Tuberculosis

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Abstract: Tuberculosis (TB) is a major health threat to the human population worldwide. The etiology of the disease is Mycobacterium tuberculosis (Mtb), a highly successful intracellular pathogen. It has the ability to manipulate the host immune response and to make the intracellular environment suitable for its survival. Many studies have addressed the interactions between the bacteria and the host immune cells as involving many immune mediators and other cellular players. Interferon-β (IFN-β) signaling is crucial for inducing the host innate immune response and it is an important determinant in the fate of mycobacterial infection. The role of IFN-β in protection against viral infections is well established and has been studied for decades, but its role in mycobacterial infections remains much more complicated and debatable. The involvement of IFN-β in immune evasion mechanisms adopted by Mtb has been an important area of investigation in recent years. These advances have widened our understanding of the pro-bacterial role of IFN-β in host–pathogen interactions. This pro-bacterial activity of IFN-β appears to be correlated with its anti-inflammatory characteristics, primarily by antagonizing the production and function of interleukin 1β (IL-1β) and interleukin 18 (IL-18) through increased interleukin 10 (IL-10) production and by inhibiting the nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome. Furthermore, it also fails to provoke a proper T helper 1 (Th1) response and reduces the expression of major histocompatibility complex II (MHC-II) and interferon-γ receptors (IFNGRs). Here we will review some studies to provide a paradigm for the induction, regulation, and role of IFN-β in mycobacterial infection. Indeed, recent studies suggest that IFN-β plays a role in Mtb survival in host cells and its downregulation may be a useful therapeutic strategy to control Mtb infection.

Keywords: Mycobacterium tuberculosis (Mtb); interferon-β (IFN-β); nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3); interleukin-1β (IL-1β); fate of infection

1. Introduction

Tuberculosis remains a major global health threat to both human and animal populations. The disease is caused by Mycobacterium tuberculosis complex (MTBC), a group of highly related intracellular pathogens, and is a major cause of human morbidity and mortality worldwide [1]. Current estimations show that one-third of the world’s population is latently infected with Mtb. However, only 5–10% of infected people develop active tuberculosis (TB) in their lifetime [2]. It is the leading infectious cause of deaths, exceeding HIV/AIDS, and resulted in approximately 1.3 million human deaths in 2016 [3]. Host innate immune response is one of the most important determinants in the outcome of Mtb infection. The possible outcomes of an infection by a pathogen depend upon a complex interplay between virulence factors produced by the invading microbe and the immune responses mounted by the host defense system. These immune responses are characterized by an
upregulation of many cytokines, chemokines, and products having direct or indirect antimicrobial activity [4,5]. However, many pathogens, for their survival, have evolved strategies to suppress and misdirect their host’s immune responses [6–10]. In this regard, Mtb has evolved multiple mechanisms for eluding or suppressing the host cell immune response and thus has become a successful intracellular pathogen.

Several cytokines have been shown to participate in the innate host response against Mtb, where they function either to enhance host resistance or aggravate the infection [11]. The critical role of inflammatory cytokines such as IL-1β has been demonstrated in the control of Mtb activity because the cytokines increase the antimicrobial function of macrophages [12]. On the other hand, IFN-β, an important cytokine, has been reported to have pro-bacterial activity and in many studies with animal models and humans has been associated with the development of TB [13–16]. Interferons (IFNs) have three major types: type I, II, and III. IFN-β is a member of type I IFN, a family of structurally related cytokines in humans and mice that includes several IFN-α (represented by several partially homologous genes) and one IFN-β (represented by a single gene) [17]. On the other hand, there is only one type II IFN, known as IFN-γ [18–20]. Type III IFN is the most recently discovered member of the IFN family [21–24].

IFN-β is a pleiotropic cytokine that is produced in response to a variety of pathogens including viruses, bacteria, and protozoa [25–28], and plays a crucial role in the stimulation of the innate and adaptive immune responses [29,30]. In general, type I IFN signals through type I IFN receptor (IFNAR), which consists of two subunits: IFN receptor 1 (IFNAR1) and IFN receptor 2 (IFNAR2) [31]. IFNAR depends on Janus kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2) to phosphorylate signal transducer and activator of transcription 1 (STAT1) and 2 (STAT2) [32]. Phosphorylated STAT1 and STAT2 then lead to the formation of the transcriptional complex IFN-stimulated gene factor-3 (ISGF3) complex that translocates into the nucleus to induce gene expression [33]. Another transcriptional complex, the STAT1/STAT2 heterodimer, results in transcription of ISG15, ISG54, and IFI6 genes [34,35]. These transcription factor functions are regulated by interferon regulatory factor 2 (IRF-2) and arginine methylation of STAT1 [36–38]. On the other hand, negative regulatory factors limiting type I IFN-mediated signaling include suppressor of cytokine signaling 1 (SOCS1), protein tyrosine phosphatase non-receptor type 6 (PTPN6), and ubiquitin-specific peptidase (UBP) [39–43].

Induction and regulation of IFN-β in Mtb infection is complex and has been vastly studied in recent years. In contrast to the established protective role of IFN-β in anti-viral immunity, it has been demonstrated that Mtb has evolved certain mechanisms to use IFN-β to enhance its intracellular survival [8,9]. Recent studies have shown that this pro-bacterial activity of IFN-β is correlated with its anti-inflammatory properties [13,44]. This is because IFN-β antagonizes the production and function of IL-1β and IL-18 through increased IL-10 production and inhibits the NLRP3 inflammasome [45]. This reduced IL-1β secretion is correlated with increased host susceptibility in Mtb infection [46,47]. IFN-β may also indirectly suppress the activation of the NLRP3 inflammasome via induction of interleukin 27 (IL-27) [48,49]. Similarly, type I IFN production was associated with reduced secretion of IL-12 and TNFα in both L. monocytogenes and M. tuberculosis inflammasome via induction of interleukin 27 (IL-27) [48,49]. Therefore, IL-1 inhibition by type I IFNs can impair host resistance in TB [51,52]. Furthermore, IFN-β fails to initiate appropriate Th1 response with reduced expression of the MHC-II and IFNGR [53]. The general role of type I IFN as an immune regulator has been previously reviewed [54], so this review will focus on the detailed interplay between IFN-β and Mtb infection, including induction and regulation of IFN-β and its role in the fate of infection. Indeed, recent developments suggest that IFN-β plays a role in Mtb survival in host cells and is detrimental to host immunity. Therefore, its downregulation in Mtb infection may be a useful therapeutic approach for better control and treatment of TB.
2. Induction and Regulation of interferon-β (IFN-β) in Tuberculosis

Induction of IFN-β by Mtb and other members of the MTBC group is an important step for activation of innate immunity. This process is mediated by the activation of pattern-recognition receptors (PRR) such as Toll-like receptors (TLR) and cytosolic receptors such as retinoid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) [55–57]. Infection of various human and mouse cell types with Mtb activates interferon regulatory factors (IRFs) like IRF-3, IRF-5, and nuclear factor-κB (NF-κB), and leads to the expression of IFN-β [58–61]. IFN-β induction is mainly controlled at the level of gene transcription wherein a family of transcription factors and interferon regulatory factors (IRFs) play a central role [62]. Several studies on IRFs have provided new paradigms of how genes are ingeniously regulated during immune responses [59,63].

A comparison of gene expression profiles in mouse macrophages infected with virulent mycobacterial strains versus an avirulent mutant with an inactive early secretory antigenic target 6 (ESAT-6) system 1 (ESX-1) revealed the selective induction of IFN-β-associated genes by virulent, but not the avirulent, bacteria [64]. This virulence-associated IFN-β response was found to be independent of the TLR adaptor TIR-domain-containing adapter-inducing interferon-β (TRIF) and the receptor interacting protein-2 (RIP-2) but required Tank-binding kinase 1 (TBK1), a kinase also necessary for IFN-β induction by invading viruses and bacteria [15]. While partly confirming the above results, another report disagreed [65] and described that N-acetyl muramyl dipeptide 1 (Nod1), Nod2, and RIP-2 are required for IFN-β induction by virulent mycobacterial strains. The authors suggested that the role of ESX-1 in virulence determination is to facilitate bacterial Nod ligands getting in close contact with these host cytoplasmic receptors. It is tempting to assume that Mtb has evolved some mechanisms to use its own chromosomal DNA to provoke IFN-β response, as these cytokines are not only produced during in vivo infections [66] but also in active human disease [13]. Wassermann et al. [67] demonstrated that cyclic GMP–AMP synthase (cGAS) is an innate mycobacterial DNA sensor and have also provided some insight into how ESX-1 controls the activation of specific intracellular recognition pathways that lead to IFN-β and IL-1β production. Many other studies [68,69] have reported that cGAS is required for activating IFN-β production via the stimulator of interferon genes (STING)/TBK1/IRF3 pathway during Mtb and Legionella pneumophila infection of macrophages. Upon sensing cytosolic DNA, cGAS also activates cell-intrinsic antibacterial defenses, leading to an increased autophagic response against Mtb. Other researchers [15,70] have also reported that IFN-β response against Mtb requires ESX-1 activation, which contributes to the pathogenesis of the disease.

Previous investigations have shown indirect evidence implicating cytosolic mycobacterial DNA in triggering these IFN-β inducing pathways [67,70]. However, in a very recent study, Wiens et al. [71] described the role of mitochondrial dynamics and reported that host mitochondrial DNA (mtDNA), not mycobacterial DNA, contributes to IFN-β induction. Different strains of MTBC differentially induced IFN-β, though the strains did not differ in their access to the host cytosol and IFN-β induction by each strain required simultaneous stimulation of STING and cGAS. Treating macrophages with a mitochondria-specific antioxidant resulted in a reduced level of cytosolic mtDNA and inhibition of IFN-β induction by some strains. Furthermore, the variation in the role of mtDNA in IFN-β induction by different MTBC strains suggest that some additional mechanisms are also responsible for IFN-β signaling in Mtb infection. In addition, we have unveiled that another DNA sensor of interferon-inducible protein 204 (IFI204) plays an important role in IFN-β release in macrophages exposed to M. bovis [72].

Besides this, some studies [68,73] support a model in which Mtb triggers the STING/TBK1 pathway using the ESX-1 production system to interrupt phagosomal membranes and thereby allowing bacterial DNA access to cGAS in the cytosol. These results reveal that the mechanism of IFN-β induction in mycobacterial infection is more complex than the already established models suggest. Although the in vivo situation is certainly much more complex and the possible role of additional DNA sensors (which may work in close coordination with cGAS to activate the innate immune response)
still remains unclear, it is believed that cGAS is a major player in the IFN-β signature associated with active TB [13,47].

3. IFN-β Regulating Signaling Pathways

3.1. IRF3 Pathway

The induction of type I IFN is controlled mainly at the transcriptional level, wherein a group of transcription factors known as interferon regulatory factors (IRFs) plays a pivotal role. Studies on most of the genes that encode IRFs have shown that IRFs have distinctive roles in the maturation and function of immune cells [62,74]. This IRF family of transcription factors comprises nine members, named consecutively from IRF1 to IRF9 [75,76]. Out of these nine IRF members, IRF3 and IRF7, which are structurally highly homologous, have gained much more attention as key regulators of type I IFN gene expression. It has been previously reported that IRF3 is a transcriptional factor responsible for stimulation of the IFN-β gene. IRF3 resides and is constitutively expressed in its inactive form. It undergoes phosphorylation and nuclear translocation upon viral and bacterial infection [77,78]. Although IRF7 also forms a homodimer or a heterodimer with IRF3 and acts on type I IFN gene family members, IRF3 is more potent in mediating the IFN-β gene, whereas IRF7 activates type I IFN genes [79,80].

The requirement of IRF3 and IRF7 transcription for IFN-β induction has been widely studied [81,82]. In early studies, IRF3 was reported to be responsible for the initiation of IFN-β gene induction by signals that induce the cooperative binding of IRF3 with other transcription factors; namely NF-κB and c-Jun/ATF-2 to the IFN-β promoter. This theory is supported by several lines of evidence [83].

It has also been described that IFN-α gene induction is affected in murine embryonic fibroblasts (MEFs) from mice deficient in IFN-β [84]. These results suggest that type I IFN gene induction occurs sequentially, wherein the initial IFN-β induction by IRF3 mediates the positive-feedback regulation of the gene induction mediated by the IFN-inducible IRF7 that can activate type I IFN genes. Unlike IRF3, IRF7 is downregulated in most cell types but it is strongly mediated by type I IFN signaling [80,81]. Stockinger et al. [85] reported that the cytosolic recognition of bacterial DNA results in IFN-β gene activation through the TBK1–IRF3 pathway, as proved by the absence of IFN-β induction in macrophages from TBK1−/− or IRF3−/− mice. In another study, it was shown that L. monocytogenes extracts that were pretreated with DNAase had an impaired ability to induce IFN-β, indicating an important role of cytosolic bacterial DNA in IFN-β gene induction [30]. Furthermore, the transfection of cells with dsDNA derived from either a pathogen or a host has been reported to induce type I IFN genes as well as many IFN-inducible genes via a TLR-independent mechanism [86,87]. This type I IFN gene induction mechanism requires TBK1 as well as IRF3. IRF3 is activated in response to lipopolysaccharides (LPS) in a MyD88 (myeloid differentiation primary response protein 88)-independent manner. It is involved in the LPS-induced MyD88-independent pathway and activated by the TLR3 ligand [88,89]. It is known that after stimulation with TLR4 and TLR3 ligands, LPS and dsRNA can induce IFN-β expression and subsequently lead to the induction of a set of IFN-inducible genes independently of MyD88, indicating that another adaptor protein may have a pivotal role in inducing IFN-β expression [90,91].
3.2. IFN-Stimulated Gene Factor-3 (ISGF3) Complex Pathway

An essential transcriptional complex is ISGF3. IFN-α/β binds to IFNAR1 and IFNAR2 and signals through receptor-bound Janus protein tyrosine kinases and STATs [31,32]. Activated STAT1/STAT2 link with interferon regulatory factor 9 (IRF9) to form ISGF3, which binds to IFN-stimulated response elements (ISREs) and upregulates IFN-β-stimulated genes (ISGs) [18]. These ISREs are found in the promoters of certain genes such as promyelocytic leukemia (PML), ISG15 ubiquitin-like modifier, IFN-induced protein with tetratricopeptide repeat 2, and IFN-α-inducible protein 6 (IFI6) [92–94]. This mature ISGF3 complex does not undergo further tyrosine phosphorylation, and is responsible for the activation of the IRF7 gene. Similar to IRF3, IRF7 resides in the cytosol and, on activation, undergoes serine phosphorylation in its C-terminal region allowing its dimerization and nuclear translocation. IRF7 forms a homodimer or a heterodimer with IRF3 and each of these different dimers differentially act on the type I IFN gene family. Due to its susceptibility to ubiquitin-dependent degradation, IRF7 has a very short half-life (0.5–1 h) [95]. This labile nature of IRF7 represents a possible mechanism to control the IFN gene induction process to inhibit the overexpression of IFNs that may be injurious to the host.

3.3. NF-κB Pathway

NF-κB is a heterodimeric protein composed of different combinations of members of the Rel family of transcription factors. The Rel/ NF-κB family of transcription factors is involved mainly in stress-induced, immune, and inflammatory responses [96]. NF-κB is also an important regulator in cell fate decisions, such as programmed cell death and proliferation control, and it is critical in tumorigenesis [97]. The recognition of bacterial and viral products by TLRs on cells of the innate immune system also results in NF-κB induction, leading to the production of pro-inflammatory cytokines and the activation of antigen presenting cells (APCs). Type I IFN expression can be mediated by pathogens through endosomal membrane-bound TLRs, including TLR3, TLR7/8, and TLR9 [98,99]. Through MyD88 or TRIF adaptors, TLRs activate the kinases NF-κB, TBK1, and inducible IκB kinase (IKK) [100,101]. These kinases become phosphorylated and lead to activation of IRF3 and IRF7, which are critical for the induction of type I IFN [100]. IRF3 is constitutively expressed and plays a role in IFN-β expression following activation-induced dimer formation, while IRF7 expression is mediated through IFN feed-forward signaling and it is crucial for type I IFN expression [79,80].

The promoter of IFN-β contains NF-κB binding sites and two ISREs recognized by phosphorylated IRF3/7 [102]. Previous studies have shown that the activity of cooperating regulatory proteins recruited to DNA binding transcription factors plays an important role in the regulation of gene expression [103,104]. It was demonstrated that activation of IP10 (interferon-inducible protein-10), but not the MCP-1 promoter, both of which contain NF-κB binding sites differing in one and two nucleotides, requires IRF3 as a co-activator following LPS stimulation [105]. This suggests that the binding site sequence composition has an influence on the type of cooperative proteins that are recruited to complex with the NF-κB dimer. More recently, it has also been shown that glucocorticoid receptors can selectively trans-repress the transcription of a subset of genes (such as Scyb9) with promoters that use IRF3 as an essential co-activator of NF-κB binding upon LPS stimulation [106]. Besides these signaling pathways, an autocrine/paracrine feedback loop is also present, augmenting the induction of type I IFNs (Figure 1). This feedback loop is instigated by type I IFNs and leads to ISGF3 complex formation. The binding of this ISGF3 complex to the ISREs in the ISRE-containing genes results in amplified type I IFN production [107].
Figure 1. Interferon-β (IFN-β) signaling pathways and autocrine/paracrine loop. IFN-β signaling pathways may be MyD88-independent (TRIF or TLR3-4 pathways) or MyD88-dependent pathways. The pathway that is mainly triggered by TLR3 and TLR4 requires the adaptor protein TRIF, which leads to the production of type I IFNs. TRIF engages TNF receptor associated factor 3 (TRAF3) and NAP-1 (nucleosome assembly protein-1) to activate TBK1 and IKK. TBK1 and IKK lead to the induction of the transcription factor IRF3 inducing type I IFNs. On the other hand, stimulation of TLR7/8 or TLR9 leads to recruitment of MyD88 protein, IRAK4, TRAF3, and TRAF6 and results in activation of IRAK1, IKK-α, and transcription factors IRF5/IRF7, leading to the induction of type I IFNs. Once produced, IFN-β can also enhance the activation of IRF5/IRF7, leading to augmented type I IFN induction. In addition to these main pathways associated with the production of type I IFNs, there is also an autocrine/paracrine feedback loop amplifying the production of type I IFNs. This feedback loop is initiated by type I IFNs and leads to the formation of the ISGF3 complex. Binding of this ISGF3 complex to the IFN-stimulated response element (ISRE) within the ISRE-containing genes results in type I IFN induction.

4. The Role of IFN-β in Tuberculosis

IFN-β signaling is crucial for host resistance against different pathogens [108]. Several Mtb-induced genes have key transcription factor binding sites for STATs, IRF-1, and IRF-7 leading to activation of the innate immune response [66]. Like other types of interferons, IFN-β has a ubiquitously expressed heterodimeric receptor composed of two chains, IFNAR1 and IFNAR2, which signal through Tyk2 and Jak1. This results in recruitment of STAT1 to receptor-bound STAT2 and production of STAT1–STAT2 heterodimers that detach from the receptors and migrate into the nucleus, leading to the activation of transcriptional factors [27]. Recently, it has been reported that IFN-β can signal through IFNAR1 independent of IFNAR2, and it is able to initiate a non-canonical signaling mechanism that controls the expression of a distinct set of genes [109]. IFN-β is capable of inducing many pathways in almost all cell types including immune cells where, on the one hand, it leads to increased...
secretion of certain cytokines such as interleukin-10 (IL-10) and interleukin-6 (IL-6) and, on the other hand, to blocked production and/or function of others like interleukin-17 (IL-17), interleukin-1 (IL-1), and IFN-γ [14].

The role of IFN-β has been well established in viral infections and hundreds of IFN-β-stimulated genes (ISGs) have been reported to have direct or indirect participation in antiviral immunity [110–116]. However, its protective or deleterious role in Mtb infection is much more complex and debatable [14]. As reported in another study, the continuous infusion of IFN-β to mice infected with M. avium resulted in increased resistance, as evidenced by a ten-fold reduction in hepatic and splenic bacterial loads [117]. However, in recent studies on Mtb infection in animal models and humans, endogenous IFN-β led to an increase in bacterial load and a reduced survival rate of the host [11,13–15,44,68,118]. In addition, a related pathogen, M. bovis, was shown to enhance replication rates in macrophages pre-treated with IFN-β [119]. The same pro-bacterial activity of IFN-β has been reported in mice infected with Listeria [120]. Furthermore, hypervirulence of a mycobacterial strain has been linked with enhanced IFN-β production, which is associated with impaired Th1 immune responses [16,68,121]. Later, it was reported that IFN-β receptor–deficient mice, chronically infected with a variety of different mycobacterial strains, demonstrated significantly reduced bacterial loads as compared to wild-type animals, while Mtb infected mice treated with IFN-β showed aggravated lung pathology and mycobacterial burden [122]. Dorhoi et al. [123] also demonstrated that IFN-β triggers immunopathological responses in TB-susceptible mice by modulating lung phagocyte dynamics. They reported that mice lacking IFNAR1 were protected and experienced reduced death rates upon aerosol infection with Mtb.

In a very recent study, de Toledo-Pinto et al. [124] identified many genes involving type I IFN that are differentially expressed in M. leprae-infected primary human Schwann cells. The gene encoding 2′-5′ oligoadenylate synthase-like (OASL) showed the greatest upregulation and was also upregulated in M. leprae infected human macrophages and primary monocytes. OASL knockdown was associated with decreased viability of M. leprae occurring in parallel to upregulation of either antimicrobial peptide expression or autophagy levels. M. leprae-mediated OASL expression was dependent on cytosolic DNA sensing mediated by STING. The addition of M. leprae DNA enhanced nonpathogenic M. bovis Bacillus Calmette-Guérin (BCG) intracellular survival, downregulated antimicrobial peptide expression, and increased monocyte chemoattractant protein-1 (MCP-1) secretion. Bouchonnet et al. [119] evaluated the effects of type I IFN on mycobacterial growth in human macrophages in vitro. They reported that type I IFN impairs the ability of human macrophages to control the growth of M. bovis BCG. Exogenous type I IFN resulted in increased mycobacterial growth because type I IFN has direct pleiotropic effects on the differentiation and functional activities of macrophages. These results indicate that type I IFN could directly stimulate mycobacterial growth in patients harboring these organisms. In another study, Auerbuch et al. [50] reported that mice lacking IFNAR1 are resistant to L. monocytogenes as compared to wild-type mice. Mariotti et al. [125] found that Mtb diverts type I IFN-induced monocyte differentiation from dendritic cells (DCs) into immuno-privileged macrophages. They reported that in the presence of type I IFN, Mtb might impede the renewal of potent antigen presenting cells (APCs) such as DCs, generating a safe habitat for intracellular growth. The study further suggested that Mtb has the ability to interfere specifically with monocyte differentiation. This ability may represent an effective Mtb strategy for eluding immune surveillance and persisting in the host.

Taken together, the reports mentioned above show that, in contrast to the critical role played by IFN-β in anti-viral immune response, its induction during mycobacterial infection seems to be detrimental to the host by eluding and directing the host immune response towards a niche that permits and facilitates the intracellular survival of the pathogen (Figure 2). This pro-bacterial activity of IFN-β is related to its anti-inflammatory properties, not only because it antagonizes IL-1β’s production and function but also, in part, due to its failure to elicit a proper Th1 response and expression of MHC-II and interferon-γ receptors (IFNGRs) [121,122]. The pathways for regulating IFN-β in mycobacterial
infection and the mechanism(s) by which it suppresses host resistance are currently active areas of investigation in the field of innate immunity.

**Figure 2.** Role of IFN-β in host–pathogen interaction in Mtb infection. Mtb gains access to the host cytosol and leads to mitochondrial stress and release of mtDNA. This mtDNA and some other unknown factors indicated by “?” trigger the cGAS–STING–TBK1–IRF3–IFN-β pathway. On the other hand, Mtb also induces NLRP3 and AIM2 inflammasomes resulting in IL-1β synthesis. These two pathways have opposite roles and outcomes in the host defense against Mtb. In addition to direct inhibition of IL-1β, IFN-β can also inhibit or diminish the production of IL-1β through inhibition of NLRP3 inflammasomes and the augmented induction of IL-10. Reciprocal inhibition of IFN-β has been reported through IL-1β-induced PGE2. A recent study demonstrated that AIM2 could also inhibit IFN-β induction by interfering with the STING–TBK1 pathway [72]. IL-1β is recognized as beneficial for host cells with anti-mycobacterial activity while IFN-β is considered largely detrimental for host cells having pro-bacterial and replication-promoting properties.

Furthermore, many studies have demonstrated that type I IFNs can have an immunosuppressive role in the chronic phase of infection with *M. tuberculosis* and *M. leprae* in mice and humans [11,61,126]. Increased IL-10-mediated type I IFNs also contribute to the exacerbation of disease in a mouse model of *M. tuberculosis* infection [68]. Similarly, type I IFNs have primarily a suppressive role in chronic disseminated lepromatous leprosy lesions in patients infected with *M. leprae* [44]. Immunosuppressive pathways include for example the induction of IL-10 and programmed death-ligand 1 (PDL1), which antagonize the IFN-γ-induced antimicrobial response that drives pathogen clearance and disease resolution in self-healing tuberculoid lesions [44,127]. These studies provide a roadmap for future investigations on type I IFN blocking therapy to enhance specific immunity and facilitate clearance of chronic infections.
4.1. Immune Regulation by IFN-β in Tuberculosis

After its induction, type I IFN stimulates the formation of STAT-1 homodimers and ISGF3 [32,33]. In active Mtb infection, blood-based profiling has identified many genes induced by IFN-β [13]. It has been suggested that the expression of these immunologically important genes in Mtb-infected macrophages is independent of both TLR2 and TLR4, but it is dependent on IFNAR and STAT1 [128]. Results presented in another study indicate that production of host-protective cytokines such as tumor necrosis factor α (TNF-α), IL-12, and IL-1β is inhibited by exogenous type I IFN, whereas production of immunosuppressive IL-10 is promoted in an IL-27–independent manner [129]. Furthermore, much of the ability of type I IFN to inhibit cytokine production is mediated by IL-10, corroborating the idea that these IFNs inhibit the immune response during tuberculosis. Antonelli and his colleagues [122] treated pathogen-exposed mice intra-nasally with polyinosinic–polycytidylic acid condensed with poly-L-lysine and carboxymethylcellulose (poly-ICLC), an agent designed to stimulate prolonged, high-level production of type I IFN. Drug-treated Mtb–infected wild-type (WT) mice, but not mice lacking IFNAR1, displayed marked elevations in lung bacillary loads, accompanied by widespread pulmonary necrosis without detectable impairment of Th1 effector function. The above findings suggest that poly-ICLC treatment detrimentally affects the outcome of Mtb infection by promoting the accumulation of a permissive myeloid population in the lung.

Nevertheless, activation of mycobacterial infection is not a recognized adverse effect associated with the therapeutic use of recombinant type I IFN. As reported in earlier studies, administration of aerosolized IFN-α to patients receiving antimicrobial treatment for pulmonary tuberculosis led to a more rapid decrease in the number of bacilli identified in sputum and earlier resolution of fever and some radiographic abnormalities [130,131]. These immune-modulatory roles of IFN-α may be responsible for this salutary effect. The net effect of type I IFN on immune and inflammatory responses in humans and in murine models has been, however, quite variable in different situations [132,133]. The administration of type I IFN to mice infected with Mtb appears to impair the development of Th1 responses [134], which is thought to be necessary for protection against mycobacterial infection. There are also some indications that type I IFN may exert negative effects on mycobacteriostatic activity. Several case reports describing the appearance of mycobacterial infections in patients receiving IFN-α have been published [135,136], and the administration of type I IFN to mice infected with Mtb has been shown to enhance mycobacterial growth [134]. The extent to which an increase in type I IFN production influences mycobacterial replication in vivo still requires further investigations. These findings suggest that agents that stimulate type I IFNs should be used with caution in patients with active mycobacterial disease. On the other hand, Prabhakar et al. [137] reported that Mtb could inhibit IFN-α signaling by blocking type I IFN stimulated tyrosine phosphorylation of STAT-1. Infection with M. bovis BCG does not inhibit type I IFN-stimulated tyrosine phosphorylation of STAT-1, formation of homodimers, or transcription of genes regulated by STAT-1 homodimers, suggesting that inhibition of the response to type I IFN is related to the pathogenicity of Mtb.

4.2. IFN-β Suppresses IL-1 Production and Inflammasome Activation

IL-1 is an important and well-known cytokine with antibacterial properties [12]. It plays a pivotal role in the induction of the inflammatory and immune response against virulent mycobacterial strains but is suppressed by type I IFN [47,51]. IFN-β-induced inhibition of IL-1 production has been reported by Guarda et al. [45] and Ma et al. [138] through two distinct pathways. IFN-β signaling via the STAT1 transcription factor repressed the activity of NLRP1 and NLRP3 inflammasomes, hence suppressing caspase-1-dependent IL-1β maturation. In addition, IFN-β induced IL-10 in a STAT1-dependent manner, and then IL-10 via autocrine action led to reduced production of pro-IL-1α and pro-IL-1β through STAT3 signaling. Mayer-Barber et al. [47] reported that IFN-β inhibited IL-1 production by both subsets, while CD4+ T cell-derived IFN-γ suppressed IL-1 expression selectively in inflammatory monocytes. This data provided cellular evidence for the anti-inflammatory effects and pro-bacterial functions of IFN-β during mycobacterial infection. In another report by the same
author [52], it was revealed that IL-1/prostaglandin E2 (PGE2) is another important pathway by which IFN-β antagonizes IL-1 production during mycobacterial infection. The absence of IFN-β, signaling resulted in increased PGE2 and IL-1β and decreased IL1Ra. Mtb-infected wild-type bone marrow-derived macrophages (BMDM) produced significantly less PGE2 when exogenous IFN-β was present. Novikov et al. [47] demonstrated that IFN-β selectively limits the production of IL-1β. This regulation occurs at the level of IL-1β mRNA expression, rather than caspase-1 activation or autocrine IL-1 amplification, and this regulation is only evident with the virulent mycobacterial strains, as avirulent strains fail to trigger the same response. Reciprocal control of type I IFNs by the IL-1/PGE2-mediated pathway has also been reported, and PGE2 treatment led to reduced production of type I IFNs and increased protection against Mtb infection [28,52]. Briken et al. [139] reviewed the role of IFN-β after its induction by mycobacterial infection, showing it could suppress NLRP3-inflammasome activation while increasing the action of AIM2 (absent in melanoma 2) inflammasomes. The suppressive effects of IFN-β on NLRP3 inflammasome activation have been reported by other researchers [47,51].

AIM2-inflammasome induction by mycobacterial infection was demonstrated in a previous study in which non-tuberculous mycobacteria (NTM) such as M. smegmatis (Msme), but not virulent mycobacteria, were reported to induce AIM2 inflammasomes in an IFN-β-dependent manner [64]. Moreover, Mtb was able to inhibit AIM2 inflammasome activation induced by Msme or by transfected dsDNA depending upon the ESX-1 secretion system, because an ESX-1-deficient Mtb mutant failed to inhibit AIM2 activation. The ESX-1 system is also important for the escape of Mtb from autophagy [140,141]. In contrast, a recent study by our research group [72] reported that M. bovis-induced AIM2 inflammasome activation decreases autophagy in primary and immortalized cells. Furthermore, we showed that the AIM2 cytosolic DNA sensor may conjugate competitively with cytosolic M. bovis DNA to restrict M. bovis-induced STING–TBK1-dependent autophagy activation and IFN-β secretion.

The role of IFN-β signaling in inducing AIM2 inflammasomes has been reported for macrophages infected with F. tularensis and L. monocytogenes [142,143]. Some studies have revealed that IFN-β acts at the transcription and translation levels of AIM2 in order to enhance the AIM2 inflammasome activity [143,144]. However, in another report, researchers failed to detect changes in protein levels of AIM2 after infection with F. tularensis [145]. This enigma requires further investigation to determine the molecular mechanism of interaction among the ESX-1 system of virulent mycobacteria, the AIM2 inflammasome, and IFN-β signaling. Comparing Mtb with NTMs may help reveal the inhibitory abilities of Mtb with respect to host cell death [146] and host cell autophagy [140,141]. It can be inferred that Mtb has adapted the methods to exploit the pathogen-beneficial functions of IFN-β to aggravate the disease.

4.3. Cross-Talk between Type I and Type II IFNs in Mycobacterial Infection

IFN-γ-induced Th1 responses have a critical role against mycobacterial infection. Therefore, one of the suggested mechanisms for type I IFN-mediated loss of Mtb control is the inhibition of Th1 responses [121]. It is well known that type I IFNs induce the immunosuppressive cytokine IL-10, which leads to loss of protection against Mtb [129]. Similarly, in M. leprae infection of humans, an IL-10-mediated suppression of IFN-γ signaling by type I IFNs has been linked to the lepromatous rather than the better-controlled tuberculoid form of the disease [44]. This study revealed an inverse correlation between type I IFNs and IFN-γ gene expression, and suggested that the differential production of IFNs contributes to protection versus pathogenesis in mycobacterial infections. Another study depicted antagonistic effects of type I IFNs on IFN-γ and as a result increased host susceptibility to bacterial infections [147]. These results support a previous study [53] in which it was also demonstrated that type I IFNs increase host susceptibility to L. monocytogenes whereas IFN-γ activates macrophages to resist the infection. The studies described that these opposing immunological effects of type I IFNs and IFN-γ occur because of cross-talk between the respective signaling pathways.
Such cross-talk leads to dominance of type I IFN immune responses and may play a role in the beneficial effects of IFN-γ treatment against inflammatory diseases.

4.4. Role of Type I IFNs in Mycobacterial and HIV Co-Infection

It has been established that viral infections are potent stimuli for the production of type I IFNs [148,149]. Some studies have proposed the idea that increased type I IFN production mediated by certain viral infections could contribute to the increased susceptibility of patients to TB. An increased growth rate of Mtb in HIV type 1 (HIV-1)-infected macrophages has been demonstrated, although the mechanism by which viral-induced type I IFNs led to increased susceptibility to tuberculosis has not been explored [150]. On the other hand, transcription from the long terminal repeat of HIV-1 is highly increased in macrophages from convalescent HIV-1-infected individuals with active mycobacterial infections, resulting in increased viral replication [151]. Thus, in the human population having combined infections with both pathogens, a malevolent cycle might be established that is beneficial for the replication of both mycobacteria and HIV-1.

5. Conclusions and Future Prospects

Tuberculosis is the second major cause of morbidity and mortality, after HIV, in the human population worldwide. Infection with Mtb leads to a complex host–pathogen interaction involving up- and downregulation of many inflammatory and immune-regulatory cytokines. IFN-β is one of the most important cytokines and the mechanism for its induction and function in mycobacterial infection is complex. Although some other factors remain undiscovered, it is believed that cGAS, an innate sensor of mycobacterial infection, is a major player contributing to the IFN-β signature associated with active disease in humans. The immune-suppressive and pro-bacterial roles of IFN-β are revealed by its ability to downregulate IL-1β and IL-18, and upregulate IL-10. IL-1β has a protective role against virulent mycobacterial strains and it is downregulated through distinct pathways. IFN-β signaling, via the STAT1 transcription factor, represses the activity of the NLRP1 and NLRP3 inflammasomes, leading to the suppression of caspase-1-dependent IL-1β maturation. In addition, IFN-β promotes IL-10 induction and inhibits IFN-γ- and IL-12-mediated anti-bacterial activity of immune modulating cells. The reciprocal inhibition of IFN-β is mediated through the IL-1–PGE2 pathway. AIM2-inflammasome signaling during infection by virulent and avirulent mycobacteria and its interaction with IFN-β has been reported, but the findings are not in accord with each other. Therefore, the interaction of the ESX-1 secretion system, IFN-β, and the AIM2 inflammasome in Mtb infection remains an important question for future investigations.

It can be concluded that in contrast to the pivotal role played by IFN-β in anti-viral immune response, its induction during mycobacterial infection seems to be injurious to the host. The above findings implicate IFN-β as a downregulator of protective immune responses in mycobacterial infection. Furthermore, recognition of the multiple points of innate immune regulation, including the cGAS–STING–TBK1–IRF3–IFN-β, NLRP3/AIM2/IL-1β, and IL-1β/PGE2/IFN-β pathways, provides potential therapeutic targets. We expect that the information presented in this review about the induction and regulation of IFN-β, and its subsequent role in immune modulation in mycobacterial infection, will be helpful for better understanding host–pathogen interactions in TB. Furthermore, it will also help in the design of future strategies to confine the intracellular activities of this deadly pathogen for better control and treatment of the disease.

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