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Induction and Function of IFN β During Viral and Bacterial Infection

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Abstract

Since the discovery of the protein “interferon” over 50 years ago, IFN β , an antiviral cytokine has been well studied. In particular the pathways inducing this cytokine during viral infection have been characterized, leading to the discovery of multitude of pattern recognition receptors. IFN β is also induced during bacterial infection, following recognition of bacterial ligands by the host viral and DNA sensors. However, the function of IFN β during bacterial infection is variable and - sometimes detrimental to the host. This review discusses the currently identified receptors and pathways engaged in IFN β induction during infection with emphasis on the role of IFN β during bacterial infection.

Keywords

type I IFN; viral sensors; DNA sensors

INTRODUCTION

The existence of a host-produced viral interference factor had been observed since the last century, but the term “interferon” was first coined in 1957 by Isaacs and Lindenmann.¹ Following incubation of heated influenza virus with chick chorio-allantoic membrane a new factor was released that induced “interference” in fresh pieces of chorio-allantoic membrane to live virus. Since then, interferons have been characterized in the following decades in great detail. Of the interferons, the group known as type I IFN specifically comprises a family of cytokines that include multiple (>11) IFN α genes and a single IFN β gene. Other IFNs include type II IFNs (IFN γ), which has integral immune function and type III IFNs (IFN λ), also an antiviral cytokine family [reviewed in^{2, 3}]. It is now known that type I IFNs (IFN α and IFN β) are the major contributors in innate immunity serving as the first line of defense against viruses. They are more than just anti-virals as they play a major role in linking innate to adaptive immunity. Over the last two decades a tremendous amount of data has been generated on immune functions of type I IFNs and the pathogen recognition receptors (PRRs) involved in the induction of this important anti-viral defense. Type I IFNs are produced in response to number of viral and bacterial infections in multiple cell types including lymphocytes, macrophages, endothelial cells and fibroblasts. Leukocytes are a major source of IFN α , with plasmacytoid dendritic cells (DC) as major producers.⁴ Fibroblast/epithelial cells are major producers of IFN β , though most cell types can make the cytokine upon stimulation. Both IFN α and IFN β signal through a common receptor IFNAR that consists of IFNAR1 and IFNAR2 chains. Binding of the cytokines to the receptor leads to the activation of JAK-STAT signaling pathway, which results in direct antiviral effects of type I IFNs and expression of interferon-inducible genes and. This review is focused on IFN β , a key interferon rapidly induced following infection. Specifically, the receptors

engaged in induction of IFN β are discussed in detail. The role of IFN β during viral infection has been reviewed extensively previously.^{5–7} Therefore, the less defined role of IFN β during bacterial infection is discussed. Further, the immune functions of IFN β are reviewed in the context of an infection model to understand the disease outcomes, specifically using mice deficient for type I IFN signaling or following in vivo neutralization of IFN β . Lastly, in order to appreciate the complexities of the different signaling pathways that induce type I IFNs, the mechanisms by which viruses target these pathways are discussed.

1. THE MAJOR PATHWAYS OF TYPE I IFN INDUCTION

A multitude of intracellular pathways can lead to type I IFN induction following viral/bacterial infection. It is likely that the major driving force in evolution for existence of several redundant pathways that induce type I IFN, is viral infections. Further, viruses can target a number of these pathways by degrading or inactivating specific components of the pathway to avoid IFN-mediated killing.^{8–10} The existence of a vast array of receptors and pathways underscores the important role of type I IFN in immune defense.

A. The pathogen sensors

A number of pattern recognition receptors (PRR) exist in the cells to detect viral infections, a majority of them evolved to sense viral DNA and RNA. Here we review the receptors specifically engaged in type I IFN induction. It is important to note that some of these receptors also induce inflammatory cytokines, such as TNF α or IL-6 during infection.

1. The TLRs—The Toll-like receptors (TLRs) are type I trans-membrane receptors with a unique pathogen recognition Leucine rich repeat (LRRs), a cysteine rich domain, a transmembrane domain, and an intracellular Toll/IL-1R (TIR) motif [reviewed in^{11, 12}]. The TLRs are responsible for the recognition of unique microbe-associated molecular patterns (MAMP) and initiate an immediate cytokine response upon infection.¹³ At least 11 different TLRs are known in humans and mice, and ligands for each have been identified.¹³ The TLRs involved in type I IFN induction are schematically represented in Figure. 1. TLR4 is localized in the plasma membrane and is known to traffic between the Golgi and the plasma membrane,¹⁴ bind to LPS, and induces a potent IFN β response. TLR3 is located intracellularly in the endosomal compartment in human DCs but is expressed on the cell surface in fibroblasts¹⁵ and can bind viral dsRNA to induce IFN response. Induction of type I IFNs by cross-linking of TLR3 and TLR4 is mediated through the adaptor molecule TRIF (Toll-IL-1 receptor domain-containing adaptor inducing IFN β , also called TICAM).^{16–19} TLR7 and TLR9 form a subgroup within the TLR family due to their exclusive intracellular localization in endoplasmic reticulum (ER) and recognition of MAMPs (ssRNA and CpG DNA respectively) in endosomal/lysosomal compartments.^{20, 21} Unlike TLR3/TLR4, TLR7 and TLR9 mediate induction of type I IFNs in a MyD88-dependent manner,^{20, 22–24} which is a common adaptor molecule²⁵ through which all TLRs signal (except TLR3) to activate the MAP kinase/NF κ B pathway. This unique ability of TLR7 and TLR9 to induce type I IFN in a MyD88-dependent manner separated from their ability to induce inflammatory cytokines is due to their ability to migrate to a specialized lysosome-related organelle by forming a complex with adaptor protein-3.²⁶ In addition to these TLRs, TLR2 has also been reported to induce IFN β in Ly6C high inflammatory monocytes in response to viral, but not bacterial ligands.²⁷

2. The NLR and RLR pathway—In addition to the TLRs, innate immune cells possess a parallel set of PRRs that reside in the cytoplasm. Cytosolic PRRs that induce type I IFN include the Rig-like receptors (RLRs) and NOD-like receptors (NLRs), which recognize double-stranded viral RNA²⁸ and bacterial cell wall components,²⁹ respectively. Many of

the MAMPs are identical or analogous to the structures recognized by TLRs, suggesting that RLRs and NLRs might have emerged during evolution to complement the surveillance of TLRs for sensing MAMPs where TLRs cannot access. It has also been proposed that NLR signaling may be needed for redundancy when TLRs become refractory to their ligands after initial MAMP exposure, as in the case of TLR4 desensitization.³⁰

RLRs consist of the RNA helicases RIG-I and MDA5. RIG-I and MDA5 consist of a caspase activation recruitment domain (CARD), a helicase domain and a RNA binding/repressor domain [reviewed in³¹]. Viral RNA binds to the RNA-binding domain to induce a conformational change in the presence of ATP. The conformational change exposes the CARD domain, which is masked by helicase and repressor domain, and allows its interaction with downstream adaptor molecule. RIG-I and MDA5 have some overlapping specificity with both being able to respond to double stranded RNA,³² yet also have distinct roles in sensing viruses.³³ RIG-I is essential for the production of interferons in response to RNA viruses including paramyxoviruses, influenza virus, and Japanese encephalitis virus, whereas MDA5 is critical for picornavirus detection. Uncapped single stranded RNA can also be sensed by RIG-I,³⁴ suggesting that this protein might be involved in sensing bacterial RNA in addition to viral RNA. Similar to TLRs, RLRs exhibit signaling convergence by using the adaptor protein mitochondrial anti-viral signaling protein (MAVS),³⁵ also known as IPS-1,³⁶ and Cardif,³⁷ linked via homotypic caspase recruitment domain (CARD) interactions. Recognition of viral DNA by RIG-I activates MAVS, by forming large prion-like aggregates of MAVS on mitochondrial membrane.³⁸ Aggregated MAVS associates with TRAF3, leading to potent activation of Interferon response factors (IRF) transcription factors and IFN β expression.³⁹ In addition to TRAF3, an ER-associated host protein called stimulator of interferon genes (STING) functions downstream of the MAVS signaling cascade and is essential for RIG-I/MDA5-mediated IFN β induction.⁴⁰ The NLR and RLR pathway inducing IFN β are summarized in Figure 1.

The NOD-like receptor (NLR) family is very large (>20 proteins), comprised of proteins with a LRR domain, a nucleotide-oligomerization domain, and CARD domain, with diverse function. Among the NOD family of proteins, NOD1 and NOD2, have been implicated in IFN β induction. The NOD proteins were originally thought to sense only the bacterial cell wall components γ -D-glutamyl-meso-diaminopimelic acid (iE-DAP)²⁹ and muramyl dipeptide (MDP),⁴¹ respectively. Unexpectedly however, it has been determined that NOD2 can also recognize structurally unrelated viral single stranded RNA.⁴² Upon recognition of ssRNA, NOD2 can signal via MAVS to induce IFN β similar to RLRs. Conversely, when recognizing bacterial ligands, NOD1 and NOD2 can only utilize the adaptor protein Rip2 to activate NF- κ B and MAPK⁴³ via TRAF2 and TRAF5.⁴⁴ This contributes to the NF κ B activation, which is required for optimal IFN β induction.⁴⁵ The explanation for the disparate use of MAVS in one circumstance and not the other remains unknown. The vast majority of the other characterized NLRs are known to be involved in activation of caspase-1 [reviewed in⁴⁶]. Unlike the viral RNA sensors, the role for NOD in IRF3 activation appears not to be critical, but NOD1/2 contributes to NF κ B activation, which is required for optimal IFN β induction.

3. The DNA-sensors—More recently a number of DNA sensors that induce type I IFN have been discovered. These sensors likely evolved to detect DNA viruses or intracellular bacterial infection. The DNA sensors discovered to date do not classify into a single family, as each have unique structure. DNA-dependent activator of IFN-regulatory factors (DAI/ZBP-1), the cytosolic DNA sensor was the first to be discovered.⁴⁷ DAI can sense dsDNA and initiate association with IRF transcription factors to induce IFN β . Recently it has been demonstrated that DAI played a specific role in inducing IFN β during human cytomegalovirus (HCMV) infection in fibroblast cells.⁴⁸ RNA polymerase III is another

surprising sensor that detects cytosolic B-form DNA such as poly dA-dT and Epstein Barr virus DNA and converts them to 5'-ppp RNA to induce IFN β through the RIG-I-MAVS pathway.^{47, 49} Recently, IFI16 a novel pyrin-domain containing protein, has been shown to detect ds DNA of longer lengths (70 bp).⁵⁰ IFI16 with AIM2⁵¹ forms a unique group of DNA sensors containing a PYRIN domain. These newly discovered DNA sensors seem to directly bind to the cytosolic DNA such as Vaccinia virus or HSV-1 ds DNA, and recruits STING resulting in IFN β expression. IFI16 functions universally in mouse and human cells and directly recruits STING, with no involvement of MAVS. Recently, another DNA sensor, LRRFIP1, has been shown to bind DNA during VSV infection and *Listeria monocytogenes* infection to induce a IFN β response via the β -catenin pathway.⁵² In addition to the above-mentioned specific DNA sensors, the HMG-B group of proteins is also involved in the IFN β response.⁵³ The function of HMG-B is upstream to activation by TLR3, TLR7 and TLR9 pathways suggesting that selective activation is downstream to promiscuous sensing by HMG-Bs.

4. Other receptors—The ambiguity present regarding a huge number of sensors that sense viral/bacterial products in the cytosol, underscores the point that the field of cytosolic receptors is in its relative infancy with new pathways still being delineated. For example, delivery of the bacterial regulators cyclic di-GMP⁵⁴ or cyclic-di-AMP⁵⁵ into the cytosol triggers PRR pathways leading to IFN- β expression. The specific host receptors recognizing these bacterial second messengers are not yet known. A specific pathogen triggering the cyclic di-GMP recognizing pathway has not yet been identified, but intracellular infection with *Listeria monocytogenes* has been shown to induce a IFN β response through the release of cyclic di-AMP.⁵⁵ Similarly, bacterial substrates such as gluconates can induce type I IFN response, as in the case of *L. monocytogenes* infection,^{56, 57} through an unknown cytosolic surveillance pathway. However, the observation that STING is involved downstream of dsDNA sensors [IFI16^{50, 55, 58} and DAI⁵⁹], RNA sensors [RIG-I/MDA5/MAVS⁵⁸] and cyclic di-nucleotide sensors⁶⁰ suggests that STING serves as a major adaptor protein to many cytosolic pathways, analogous to the role of MyD88 for the TLRs.

B. Kinases and transcription factors regulating type I IFN induction

Induction of type I IFNs is regulated at the level of transcription by IRF and NF κ B.⁶¹ The IRF family of transcription factors consists of nine members (reviewed in⁶²). Three of these transcription factors, namely IRF3, ISGF3, and IRF7, have been characterized as crucial elements in the regulation of type I IFNs. IRF3 is constitutively expressed in most cell types; as discussed, specific binding of MAMP to PRRs results in IRF3 phosphorylation by the kinases TBK or IKK ϵ , and nuclear translocation.⁶³ Nuclear IRF3 plays an important role in initiation of IFN β transcription in conjunction with AP-1 and NF- κ B.^{64–66} The other 2 transcription factors (IRF7 and ISGF3) contribute after autocrine or paracrine signaling of IFN- β via the IFNAR through activation of the JAK/STAT signal transduction pathways.⁶⁷ IRF7 is expressed at low levels inside most cell types but can be induced several fold following initial IFN- β signaling. Unlike IRF3, which does not upregulate IFN- α genes, IRF7 has been termed as a master regulator because of its ability to regulate both IFN- β and also IFN- α genes.⁶⁸ IRF7 translocates to the nucleus and binds synergistically with IRF3, c-jun, and NF κ B to the IFN β promoter, acting as a positive feedback loop.⁶⁹ ISGF3 (a trimeric complex composed of STAT1, STAT2, and IRF9)⁷⁰ and IRF7 are able to bind to promoters with interferon-sensitive response elements (ISRE),⁷¹ leading to the induction of ISGs and enhanced expression of IFN- β .⁷² The common convergence point for all receptor-ligand cross-linking pathways of type I IFN induction is the activation of TBK/IKK ϵ kinases⁷³ and the nuclear translocation of IRF3/IRF7.

2. MECHANISM OF TYPE I IFN INDUCTION DURING INFECTION

The field of PRRs involved in IFN β induction is largely advanced by the study of virally-induced IFN β . A recent review has described RNA viruses and cytosolic sensors involved in IFN β induction in great detail.⁷⁴ The DNA viruses and their receptors have also been discussed in the previous section along with the nucleic acid sensors. Hence, this section is focused mainly on the less well-characterized mechanism of type I IFN induction during bacterial infection.

It is well known that number of bacterial pathogens can induce a potent type I IFN response. [(reviewed in^{75, 76})] However, the PRRs used by different bacteria vary significantly depending on their intracellular niche. Gram-negative bacteria, especially commensals and pathogens such as *Salmonella* spp. and *Yersinia* spp., produce LPS with hexacylated lipid A that are well-recognized by TLR4 on the cell surface to induce a potent IFN β response via the TRIF pathway.⁷⁷ Purified *E. coli* LPS is a potent stimulator for this pathway and routinely used as a positive control for TLR4 activation.⁷⁸ However, a number of gram-negative bacteria including *Chlamydia* spp., *Legionella* spp., and *Francisella* spp. produce weak stimulatory LPS, which is poorly detected by TLR4 and in some cases detected by TLR2.⁷⁹ In addition to LPS, other bacterial ligands can stimulate TLR4, as in the case of purified hsp60 from *Chlamydia* spp.⁸⁰ However, during chlamydial infection, there is no role for TLR4 in IFN β induction.⁸¹ Therefore, studying the PRR used during specific bacterial infection should be ideally determined in the context of whole bacteria and/or its mutant lacking specific MAMP, rather than purified bacterial MAMPs. Interestingly, for a number of gram-negative pathogens that induce a type I IFN response, such as *Chlamydia* spp., *S. typhimurium*, *S. flexneri*, and *E. coli*, cell invasion and in certain cases intracellular growth is a prerequisite for this response. This prerequisite would suggest that intracellular receptors would be preferred over membrane-expressed TLR4 during infection. Intracellular TLRs have been suggested to be involved in bacterial-induced IFN β in a few instances. During infection of conventional DC with group B streptococcus, a phagosomal bacteria, IFN β response occurs through the TLR7-MyD88 dependent pathway.⁸² In another instance, intracellular TLR3 signaling during *Chlamydia muridarum* infection induces IFN β in a specific oviduct epithelial cell line.⁸³ This data contradicts a previous finding that showed TLR-independent STING involvement for IFN β induction in the same cell line,⁴⁵ suggesting activation of multiple pathways during infection. These are clearly exceptions; as for a number of pathogens the route to IFN β induction appears to be TLR-independent.

Chlamydia muridarum induces IFN β independent of TLR2 and TLR4, and some contribution from MyD88 pathway was suggested.⁸¹ However, when the authors used macrophages deficient for both TLR4 and MyD88, the contribution from MyD88 disappeared suggesting a role for intracellular receptors.⁴⁵ Subsequently, the downstream adaptor STING was demonstrated to be necessary for chlamydial-induced IFN β induction in both HeLa cell line and mouse oviduct epithelial cells. IFN β induction was also MAVS independent ruling out the viral RNA sensing mechanism but the specific sensor upstream of STING has not been identified. However, *Chlamydia pneumoniae* in HUVEC cells required MAVS for IFN β induction, unlike *C. trachomatis* infection. Once again these data suggest that multiple pathways are used for IFN β induction depending on the specific species or cell type used. *Chlamydia* spp. possesses type III secretion (T3S) apparatus, which appears to be essential for IFN β induction, based on studies using T3S inhibitors.⁸⁴ However, in the absence of chlamydial T3S mutants, and the fact that the inhibitors also block induction of other cytokines such as IL-6, it is not clear if the inhibitors block delivery of ligands or change inclusion membrane permeability to prevent leakage of bacterial products. The specific chlamydial product that is sensed to induce IFN β is unknown, although one could speculate that it is nucleic acids.

Induction of type I IFN by another gram-negative pathogen, *Legionella*, has been well described. Induction of type I IFN by *L. pneumophila* requires a type IV secretion system but not the TLRs,⁸⁵ and the MAMP was suggested to be DNA. However, the evidence for direct bacterial DNA translocation was not conclusive. A recent report clearly rules out the role for DNA but suggests that viral sensors RIG-I and MDA5 mediate type I IFN response during *Legionella* infection and, it is specifically mediated by bacterial RNA and not DNA.⁸⁶ However, the question whether *Legionella* spp. DNA or RNA is translocated through type IV secretion system is still open. Gram-negative *Fransicella tularamia* follows a similar trend of not requiring TLRs but unlike *Legionella* spp. does not require RIG-I/MDA5 pathway for IFN β induction.⁸⁷ There is a requirement for a type VI secretion system, and it is suggested that nucleic acids escaping into the cytosol from disruption of phagosome induce an IRF3 dependent IFN β response. This in turn is critical for activation of DNA sensing AIM2-inflammasome pathway.⁸⁸

Amongst the gram-positive bacteria, *Mycobacterium tuberculosis* also shows a TLR-independent source for type I IFN requiring NOD2-RIP pathway.^{89, 90} *M. tuberculosis* also requires type VII secretion system for IFN β induction.⁹⁰ In several of these cases, such as *Yersinia* spp.,⁹¹ and *M. tuberculosis* that show a requirement of secretion system for IFN β induction, direct delivery of bacterial components through the secretion system has not been demonstrated. *Listeria monocytogenes* is probably the most well studied gram-positive pathogen with respect to the mechanisms of type I IFN induction. Earlier it was suggested that a “cytosolic surveillance” mechanism was responsible for *L. monocytogenes* - induced type I IFN. These studies used Listeriolysin O-deficient mutant that fails to exit into the cytoplasm and also fails to induce type I IFN response.^{92, 93} Subsequently, it was shown by other investigators that IFN β induction during *L. monocytogenes* infection is independent of TLR4, TLR2, RIP2, and NOD-2 activation pathways and MAVS.^{94, 95} Further studies showed the requirement of the downstream adaptor molecule STING for *L. monocytogenes* - induced IFN β induction.⁹⁶ Using genetic screening methods, a multi-drug transporter (MDR) mutant of *L. monocytogenes*, was shown to be defective for IFN β production,⁵⁶ suggesting transport of small molecules through these transporters could induce IFN β induction. Using mutants that overexpressed MDR, Woodward et al. showed that secreted cyclic-di-AMP made by *L. monocytogenes* is a major player in inducing IFN β .⁵⁵ The specific sensor for this cyclic dinucleotide has not yet been identified although this pathway does function through downstream adaptor molecule STING. A more recent study demonstrated a role for novel cytosolic nucleic acid-sensor LRRFIP1 that induced type I IFN in a β -catenin-dependent pathway during *L. monocytogenes* infection.⁵² It was not demonstrated if STING is required for activation of this pathway. Overall during *L. monocytogenes* infection, multiple sensors are involved in the induction of IFN β , but there is no role for the TLR pathway and the adaptor MAVS.

3. ROLE OF TYPE I IFN DURING INFECTION

A. A protective role in viral infection but conflicting role in bacterial infection

Type I IFNs are deleterious to viruses in a number of ways that prevent viral replication. The specific role of type I IFNs during viral infection has been well reviewed⁵⁻⁷ and includes direct killing, activation of antigen presenting DC, clonal expansion of virus-specific T cells and antibody producing B cells. Overall, the role of type I IFN during viral infection is protective.

In the case of non-viral pathogens, type I IFNs have been reported to have a highly variable role. During *Pneumonitis murina* fungal infection, which can cause life-threatening pneumonia in HIV-infected patients, type I IFNs have been shown to be beneficial.⁹⁷ IFNAR $^{-/-}$ mice exhibit delayed fungal clearance and increased inflammation. Likewise,

during bacterial infection the role of type I IFNs is compounded by number of factors, including infecting bacterial strain and infected tissue site. As a consequence, it has not been possible to assign a global beneficial or detrimental role for type I IFNs during bacterial infections. Few examples of beneficial role for type I IFNs include a slightly enhanced replication of *M. tuberculosis* in the lungs of IFN α/β receptor-deficient mice compared with WT controls.⁹⁸ Studies in mice treated with purified IFN preparation or IFN neutralizing antibodies indicated increased resistance against *Streptococcus pneumoniae* infection,⁹⁹ suggesting that type I IFN plays a critical role directly or indirectly in controlling *S. pneumoniae* infection. Likewise during Group B streptococcus, pneumococci and *E. coli* infection, type I IFN is protective as IFNAR $^{-/-}$ mice show decreased survival and increased bacterial load.¹⁰⁰ A marked reduction in IFN γ , (Nitric oxide) NO, and tumor necrosis factor α (TNF α) was observed in infected IFNAR $^{-/-}$ macrophages, suggesting that IFN α/β boosted macrophage function and improved host resistance. Another instance of protective function with type I IFNs was observed with *Francisella novicida* infection, where IFNAR signaling was required for caspase-1 activation, inflammasome-mediated cell death, and IL-1 β /IL-18 release.⁸⁷ There are also a couple of instances where type I IFN signaling affects in vitro cell function but has a minimal role in vivo due to compensation from other pathways. For instance, during *L. pneumophila* infection, type I IFN has a restrictive role in vitro¹⁰¹ but no role in vivo.⁸⁶ Similarly, no difference in bacterial load between WT and IFNAR $^{-/-}$ mice was observed in *C. pneumoniae* lung infection.¹⁰²

In most other bacterial infections, particularly during intracellular bacterial infections, type I IFN is detrimental to the host. During systemic *L. monocytogenes* infection using IFNAR $^{-/-}$ mice and IRF3 $^{-/-}$ mice, it was found that IFNAR $^{-/-}$ mice were 1000-fold more resistant to *L. monocytogenes* infection^{103, 104}. This resistance to infection was correlated to elevated levels of IL-12 p70 and increased numbers of CD11b macrophages, owing to a block in macrophage apoptosis in the IFNAR $^{-/-}$ strains.^{103, 104} Likewise, mice lacking IFNAR are significantly protected against a lethal *Staphylococcus aureus* strain in comparison to WT mice,¹⁰⁵ providing another example of detrimental role of type I IFNs. In an independent study, intra-nasal administration of IFN α/β in mice infected with a clinical isolate of *Mycobacterium tuberculosis* displayed increased bacterial load and reduced survival,¹⁰⁶ which was associated with the dampening of antigen-specific Th1 response. With respect to *Chlamydia muridarum* infection, both in the lungs and genital tract, type I IFN was shown to be detrimental. In the lung infection model,¹⁰⁷ IFNAR $^{-/-}$ mice showed less bacterial burden, weight loss and less pathology. The protection was attributed to lower macrophage apoptosis in the IFNAR $^{-/-}$ mice. In the genital infection, there was a slightly enhanced clearance of infection in the IFNAR $^{-/-}$ and significantly reduced oviduct pathology.¹⁰⁸ The mechanism for improved bacterial clearance in IFNAR $^{-/-}$ mice was attributed to improved antigen specific T cell response. A similar outcome of enhanced infection clearance and reduced pathology was observed in genital chlamydial infection during IFN β neutralization in wild-type mice, confirming the detrimental role for IFN β .¹⁰⁹ A surprising role for type I IFNs was also discovered in development of Lyme arthritis during *Borrelia burgdorferi* infection in mice, wherein type I IFN receptor blocking by antibodies dramatically reduced arthritis.¹¹⁰ Furthermore, during *Leishmania amazonensis* infection, type I IFN regulates neutrophil infection and regulates innate immunity.¹¹¹ As a consequence, IFNAR $^{-/-}$ mice develop fewer lesions and lower tissue burden of parasites due to enhanced neutrophil/monocyte recruitment. Overall, the role of type I IFN during bacterial infection appears highly diverse.

B. Immune function of IFN β during infection

To understand the mechanism behind the conflicting role of type I IFN, the pleiotropic immune functions of this cytokine needs further understanding. Type I IFNs are a potent

regulator of adaptive immunity, affecting multiple cell types, including macrophages, lymphocytes, and DCs. IFN α/β induces the expression of interferon response genes (IRG): IP-10 (Interferon inducible protein 10), MCP-5 (monocyte chemoattractant protein-5), RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted), iNOS (inducible nitrous oxide synthase), and GARG-16 (glucocorticoid attenuated response gene). The IRGs are important for Th1 maturation.¹¹² Type I IFNs have also been implicated in the generation of cytotoxic T cells and promotion of in vivo T cell proliferation,¹¹³ and T cell survival.¹¹⁴ Besides its immuno-stimulatory role, type I IFNs are also known to inhibit IFN γ induced MHC class II expression,^{115–117} a function that contradicts its TH1 stimulatory role. Type I IFNs have also been shown to inhibit maturation and activation of mouse Langerhans cells.¹¹⁸ IFN β has been reported to augment¹¹⁹ or downregulate IL-12 and CD40 expression in DC.¹²⁰ Further, therapeutic administration of IFN β in multiple sclerosis patients led to inhibition of IL-12 and augmentation of IL-10 production.¹²¹ These paradoxical effects of IFN β on the expression of Th1-type immune responses partly depends on the timing of DC exposure (during maturation vs. mature) to IFN β , with a positive role if exposed during DC maturation and a negative role if exposed after maturation.¹¹² Importantly, type I IFNs are also pro-apoptotic and induce the expression of a number of proapoptotic genes, which play a major role in pathological outcomes in number of infection modes. The proapoptotic function of type I IFNs can also have a direct role in the immune modulation, resulting in conflicting functions. In summary, type I IFNs are either favorable or detrimental to the host during bacterial infection depending on their effect on, i) pathogen killing ii) enhancing or inhibiting the Th1-type response depending on tissue site or kinetics of immune response, and/or iii) inducing an apoptotic response. Overall, the type I IFN-dependent immune response and outcome is largely pathogen- and tissue-dependent.

4. FUTURE DIRECTIONS AND PERSPECTIVES

The most fascinating feature of IFN β inducing pathways are the resources used by the cell to detect a wide variety of pathogens and generate this important cytokine. During evolution of the immune system, viral infections are the major players in driving this arm of innate immunity to the complex form to which it presently exists. Several examples of viral inhibition of these pathways are known. For instance during HIV-1 infection, HIV-1 protease targets cytosolic RIG-I to lysosome, inhibiting IFN β induction.⁸ Influenza virus polymerase also inhibits IFN β induction by directly binding to MAVS (IPS-1).⁹ A number of viruses directly inhibit activation of IRF3. For instance, *Varicella zoster* immediate early protein 62 blocks IRF3 phosphorylation at 3 different serine residues.¹⁰ The structural protein NS5 of some members of flavivirus family function as the major antagonist for IFN-dependent STAT-1 phosphorylation as in the case of West Nile virus.¹²² Overall in this race between the host and the viruses, the pathogen is evolving to evade the host immune system to ultimately be less pathogenic and survive. The host on the other hand is evolving relatively slower to eradicate the pathogens as they target the host's antiviral signaling pathways. There are no winners here until commensalism is reached. Until then the host and the pathogens drive each other's evolutionary variations in a complementary fashion. In the case of bacterial infection, no such direct inhibition of host factors engaged in IFN β induction has been reported. However, in instances where IFN β is detrimental, one can speculate that the intracellular bacterial infection likely exploits this antiviral pathway to its advantage. This could be particularly relevant during bacterial-viral co-infection. For instance during co-infection of *Chlamydia trachomatis* with human papilloma virus, type I IFN response resulting from the viral infection is likely to benefit *C. trachomatis* infection. Whether this results in persistent infection for either or both pathogens is not clear, although there is some evidence for *C. trachomatis* infection to be a risk factor for persistent HPV infection.¹²³

A lot has been learnt about type I IFN induction in the past few years. However, still many unknowns exist. These include the cytosolic PRRs that function upstream to STING during several bacterial infections, the interaction between the sensors and the adaptor molecules and the cell-type specificities of these interactions. Over the following decades, we expect to see discovery of more sensors, which could be used as potential therapeutic targets during infection and autoimmunity.

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Abbreviations

CARD	Caspase recruitment domain
IFNAR	IFN α/β receptor
IRF3	Interferon response factor 3
LRR	Leucine rich repeats
LPS	Lipopolysaccharide
MAMPs	Microbe-associated molecular patterns
MAPK	Mitogen activated protein kinase
NOD	Nucleotide oligomerization domain
NLR	NOD-like receptor
PGN	Peptidoglycan
PRR	Pathogen recognition receptors
RLR	Rig-like receptors
STING	Stimulator of IFN signaling
TBK	Tank-binding kinase
TLR	Toll-like receptors
T3S	Type III secretion apparatus
TRIF	Toll-IL-1 receptor domain-containing adaptor inducing IFN- β
WT	wild-type

References

1. Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc Roy Soc London Set B. 1957; 147:258–73.
2. Young HA, Bream JH. IFN-gamma: recent advances in understanding regulation of expression, biological functions, and clinical applications. Curr Top Microbiol Immunol. 2007; 316:97–117. [PubMed: 17969445]
3. Donnelly RP, Kotenko SV. Interferon-lambda: a new addition to an old family. J Interferon Cytokine Res. 2010 Aug.30:555–64. [PubMed: 20712453]
4. Santini SM, Di Pucchio T, Lapenta C, Parlato S, Logozzi M, Belardelli F. The natural alliance between type I interferon and dendritic cells and its role in linking innate and adaptive immunity. Journal of Interferon and Cytokine Research. 2002 Nov.22:1071–80. [PubMed: 12513906]

5. Stanton GJ, Weigent DA, Fleischmann WR Jr, Dianzani F, Baron S. Interferon review. *Invest Radiol.* 1987 Mar;22:259–73. [PubMed: 2435674]
6. Katze MG, He Y, Gale M Jr. Viruses and interferon: a fight for supremacy. *Nat Rev Immunol.* 2002 Sep;2:675–87. [PubMed: 12209136]
7. Seo YJ, Hahm B. Type I interferon modulates the battle of host immune system against viruses. *Adv Appl Microbiol.* 2010; 73:83–101. [PubMed: 20800760]
8. Solis M, Nakhaei P, Jalalirad M, Lacoste J, Douville R, Arguello M, Zhao T, Laughrea M, Wainberg MA, Hiscott J. RIG-I Mediated Antiviral Signalling is Inhibited in HIV-1 Infection by a Protease-Mediated Sequestration of RIG-I. *J Virol.* 2010 Nov 17.
9. Iwai A, Shiozaki T, Kawai T, Akira S, Kawaoka Y, Takada A, Kida H, Miyazaki T. Influenza A virus polymerase inhibits type I interferon induction by binding to interferon beta promoter stimulator 1. *J Biol Chem.* 2010 Oct 15;285:32064–74. [PubMed: 20699220]
10. Sen N, Sommer M, Che X, White K, Ruyechan WT, Arvin AM. Varicella-zoster virus immediate-early protein 62 blocks interferon regulatory factor 3 (IRF3) phosphorylation at key serine residues: a novel mechanism of IRF3 inhibition among herpesviruses. *J Virol.* 2010 Sep;84:9240–53. [PubMed: 20631144]
11. Martin MU, Wesche H. Summary and comparison of the signaling mechanisms of the Toll/interleukin-1 receptor family. *Biochimica et Biophysica Acta.* 2002 Nov 11;1592:265–80. [PubMed: 12421671]
12. Jin MS, Lee J-O. Structures of the Toll-like Receptor Family and Its Ligand Complexes. *Immunity.* 2008; 29:182–91. [PubMed: 18701082]
13. Takeda K, Kaisho T, Akira S. Toll-like receptors. *Annual Review of Immunology.* 2003; 21:335–76.
14. Horng T, Barton GM, Medzhitov R. TIRAP: an adapter molecule in the Toll signaling pathway. *Nature Immunology.* 2001 Sep;2:835–41. [PubMed: 11526399]
15. Matsumoto M, Funami K, Tanabe M, Oshiumi H, Shingai M, Seto Y, Yamamoto A, Seya T. Subcellular localization of Toll-like receptor 3 in human dendritic cells. *Journal of Immunology.* 2003 Sep 15;171:3154–62.
16. Toshchakov V, Jones BW, Perera PY, Thomas K, Cody MJ, Zhang S, Williams BR, Major J, Hamilton TA, Fenton MJ, Vogel SN. TLR4, but not TLR2, mediates IFN-beta-induced STAT1alpha/beta-dependent gene expression in macrophages. *Nat Immunol.* 2002 Apr;3:392–8. [PubMed: 11896392]
17. Tabeta K, Georgel P, Janssen E, Du X, Hoebe K, Crozat K, Mudd S, Shamel L, Sovath S, Goode J, Alexopoulou L, Flavell RA, Beutler B. Toll-like receptors 9 and 3 as essential components of innate immune defense against mouse cytomegalovirus infection. *Proceedings of the National Academy of Sciences of the United States of America.* 2004 Mar 9;101:3516–21. [PubMed: 14993594]
18. Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, Takeuchi O, Sugiyama M, Okabe M, Takeda K, Akira S. Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science.* 2003 Aug 1;301:640–3. [PubMed: 12855817]
19. Hoebe K, Du X, Georgel P, Janssen E, Tabeta K, Kim SO, Goode J, Lin P, Mann N, Mudd S, Crozat K, Sovath S, Han J, Beutler B. Identification of Lps2 as a key transducer of MyD88-independent TIR signalling. *Nature.* 2003 Aug 14;424:743–8. [PubMed: 12872135]
20. Heil F, Ahmad-Nejad P, Hemmi H, Hochrein H, Ampenberger F, Gellert T, Dietrich H, Lipford G, Takeda K, Akira S, Wagner H, Bauer S. The Toll-like receptor 7 (TLR7)-specific stimulus loxoribine uncovers a strong relationship within the TLR7, 8 and 9 subfamily. *European Journal of Immunology.* 2003 Nov;33:2987–97. [PubMed: 14579267]
21. Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, Lien E, Nilsen NJ, Espevik T, Golenbock DT. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat Immunol.* 2004 Feb;5:190–8. [PubMed: 14716310]
22. Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science.* 2004 Mar 5;303:1529–31. [PubMed: 14976261]

23. Kawai T, Sato S, Ishii KJ, Coban C, Hemmi H, Yamamoto M, Terai K, Matsuda M, Inoue J, Uematsu S, Takeuchi O, Akira S. Interferon- α induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. *Nature Immunology*. 2004 Oct.5:1061–8. [PubMed: 15361868]
24. Honda K, Mizutani T, Taniguchi T. Negative regulation of IFN- α /beta signaling by IFN regulatory factor 2 for homeostatic development of dendritic cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2004 Feb 24.101:2416–21. [PubMed: 14983024]
25. Takeuchi O, Akira S. MyD88 as a bottle neck in Toll/IL-1 signaling. *Current Topics in Microbiology and Immunology*. 2002; 270:155–67. [PubMed: 12467250]
26. Sasai M, Linehan MM, Iwasaki A. Bifurcation of Toll-Like Receptor 9 Signaling by Adaptor Protein 3. *Science*. September 17.2010 329:1530–4. [PubMed: 20847273]
27. Barbalat R, Lau L, Locksley RM, Barton GM. Toll-like receptor 2 on inflammatory monocytes induces type I interferon in response to viral but not bacterial ligands. *Nat Immunol*. 2009 Nov. 10:1200–7. [PubMed: 19801985]
28. Kato H, Sato S, Yoneyama M, Yamamoto M, Uematsu S, Matsui K, Tsujimura T, Takeda K, Fujita T, Takeuchi O, Akira S. Cell type-specific involvement of RIG-I in antiviral response. *Immunity*. 2005 Jul.23:19–28. [PubMed: 16039576]
29. Chamaillard M, Hashimoto M, Horie Y, Masumoto J, Qiu S, Saab L, Ogura Y, Kawasaki A, Fukase K, Kusumoto S, Valvano MA, Foster SJ, Mak TW, Nunez G, Inohara N. An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. *Nat Immunol*. 2003 Jul.4:702–7. [PubMed: 12796777]
30. Kim YG, Park JH, Shaw MH, Franchi L, Inohara N, Nunez G. The cytosolic sensors Nod1 and Nod2 are critical for bacterial recognition and host defense after exposure to Toll-like receptor ligands. *Immunity*. 2008 Feb.28:246–57. [PubMed: 18261938]
31. Yoneyama M, Fujita T. Structural Mechanism of RNA Recognition by the RIG-I-like Receptors. *Immunity*. 2008; 29:178–81. [PubMed: 18701081]
32. Kato H, Takeuchi O, Mikamo-Sato E, Hirai R, Kawai T, Matsushita K, Hiiragi A, Dermody TS, Fujita T, Akira S. Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. *J Exp Med*. 2008 Jul 7.205:1601–10. [PubMed: 18591409]
33. Kato H, Takeuchi O, Sato S, Yoneyama M, Yamamoto M, Matsui K, Uematsu S, Jung A, Kawai T, Ishii KJ, Yamaguchi O, Otsu K, Tsujimura T, Koh CS, Reis e Sousa C, Matsuura Y, Fujita T, Akira S. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature*. 2006 May 4.441:101–5. [PubMed: 16625202]
34. Hornung V, Ellegast J, Kim S, Brzozka K, Jung A, Kato H, Poeck H, Akira S, Conzelmann KK, Schlee M, Endres S, Hartmann G. 5'-Triphosphate RNA is the ligand for RIG-I. *Science*. 2006 Nov 10.314:994–7. [PubMed: 17038590]
35. Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF- κ B and IRF 3. *Cell*. 2005 Sep 9.122:669–82. [PubMed: 16125763]
36. Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, Ishii KJ, Takeuchi O, Akira S. IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. *Nat Immunol*. 2005 Oct.6:981–8. [PubMed: 16127453]
37. Meylan E, Curran J, Hofmann K, Moradpour D, Binder M, Bartenschlager R, Tschopp J. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. *Nature*. 2005 Oct 20.437:1167–72. [PubMed: 16177806]
38. Hou F, Sun L, Zheng H, Skaug B, Jiang QX, Chen ZJ. MAVS Forms Functional Prion-like Aggregates to Activate and Propagate Antiviral Innate Immune Response. *Cell*. 2011 Aug 5.146:448–61. [PubMed: 21782231]
39. Saha SK, Pietras EM, He JQ, Kang JR, Liu SY, Oganessian G, Shahangian A, Zarnegar B, Shiba TL, Wang Y, Cheng G. Regulation of antiviral responses by a direct and specific interaction between TRAF3 and Cardif. *Embo J*. 2006 Jul 26.25:3257–63. [PubMed: 16858409]

40. Zhong B, Yang Y, Li S, Wang YY, Li Y, Diao F, Lei C, He X, Zhang L, Tien P, Shu HB. The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation. *Immunity*. 2008 Oct.29:538–50. [PubMed: 18818105]
41. Girardin SE, Boneca IG, Viala J, Chamaillard M, Labigne A, Thomas G, Philpott DJ, Sansonetti PJ. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. *J Biol Chem*. 2003 Mar 14.278:8869–72. [PubMed: 12527755]
42. Sabbah A, Chang TH, Harnack R, Frohlich V, Tominaga K, Dube PH, Xiang Y, Bose S. Activation of innate immune antiviral responses by Nod2. *Nat Immunol*. 2009 Oct.10:1073–80. [PubMed: 19701189]
43. Chin AI, Dempsey PW, Bruhn K, Miller JF, Xu Y, Cheng G. Involvement of receptor-interacting protein 2 in innate and adaptive immune responses. *Nature*. 2002 Mar 14.416:190–4. [PubMed: 11894097]
44. Hasegawa M, Fujimoto Y, Lucas PC, Nakano H, Fukase K, Nunez G, Inohara N. A critical role of RICK/RIP2 polyubiquitination in Nod-induced NF-kappaB activation. *Embo J*. 2008 Jan 23.27:373–83. [PubMed: 18079694]
45. Prantner D, Darville T, Nagarajan UM. Stimulator of IFN gene is critical for induction of IFN-beta during Chlamydia muridarum infection. *J Immunol*. 2010 Mar 1.184:2551–60. [PubMed: 20107183]
46. Ting JPY, Willingham SB, Bergstralh DT. NLRs at the intersection of cell death and immunity. *Nat Rev Immunol*. 2008; 8:372–9. [PubMed: 18362948]
47. Takaoka A, Wang Z, Choi MK, Yanai H, Negishi H, Ban T, Lu Y, Miyagishi M, Kodama T, Honda K, Ohba Y, Taniguchi T. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. *Nature*. 2007 Jul 26.448:501–5. [PubMed: 17618271]
48. DeFilippis VR, Sali T, Alvarado D, White L, Bresnahan W, Fruh KJ. Activation of the interferon response by human cytomegalovirus occurs via cytoplasmic double-stranded DNA but not glycoprotein B. *J Virol*. 2010 Sep.84:8913–25. [PubMed: 20573816]
49. Ablasser A, Bauernfeind F, Hartmann G, Latz E, Fitzgerald KA, Hornung V. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. *Nat Immunol*. 2009 Oct.10:1065–72. [PubMed: 19609254]
50. Unterholzner L, Keating SE, Baran M, Horan KA, Jensen SB, Sharma S, Sirois CM, Jin T, Latz E, Xiao TS, Fitzgerald KA, Paludan SR, Bowie AG. IFI16 is an innate immune sensor for intracellular DNA. *Nat Immunol*. 2010 Nov.11:997–1004. [PubMed: 20890285]
51. Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E, Fitzgerald KA. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature*. 2009 Mar 26.458:514–8. [PubMed: 19158675]
52. Yang P, An H, Liu X, Wen M, Zheng Y, Rui Y, Cao X. The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway. *Nat Immunol*. 2010 Jun.11:487–94. [PubMed: 20453844]
53. Yanai H, Ban T, Wang Z, Choi MK, Kawamura T, Negishi H, Nakasato M, Lu Y, Hangai S, Koshiba R, Savitsky D, Ronfani L, Akira S, Bianchi ME, Honda K, Tamura T, Kodama T, Taniguchi T. HMGB proteins function as universal sentinels for nucleic-acid-mediated innate immune responses. *Nature*. 2009 Nov 5.462:99–103. [PubMed: 19890330]
54. McWhirter SM, Barbalat R, Monroe KM, Fontana MF, Hyodo M, Joncker NT, Ishii KJ, Akira S, Colonna M, Chen ZJ, Fitzgerald KA, Hayakawa Y, Vance RE. A host type I interferon response is induced by cytosolic sensing of the bacterial second messenger cyclic-di-GMP. *J Exp Med*. 2009 Aug 31.206:1899–911. [PubMed: 19652017]
55. Woodward JJ, Iavarone AT, Portnoy DA. c-di-AMP secreted by intracellular *Listeria monocytogenes* activates a host type I interferon response. *Science*. 2010 Jun 25.328:1703–5. [PubMed: 20508090]
56. Crimmins GT, Herskovits AA, Rehder K, Sivick KE, Lauer P, Dubensky TW Jr, Portnoy DA. *Listeria monocytogenes* multidrug resistance transporters activate a cytosolic surveillance pathway of innate immunity. *Proc Natl Acad Sci U S A*. 2008 Jul 22.105:10191–6. [PubMed: 18632558]
57. Crimmins GT, Schelle MW, Herskovits AA, Ni PP, Kline BC, Meyer-Morse N, Iavarone AT, Portnoy DA. *Listeria monocytogenes* 6-Phosphogluconolactonase mutants induce increased

- activation of a host cytosolic surveillance pathway. *Infect Immun*. 2009 Jul.77:3014–22. [PubMed: 19398547]
58. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. *Nature*. 2008 Oct 2.455:674–8. [PubMed: 18724357]
 59. DeFilippis VR, Alvarado D, Sali T, Rothenburg S, Fruh K. Human cytomegalovirus induces the interferon response via the DNA sensor ZBP1. *J Virol*. 2010 Jan.84:585–98. [PubMed: 19846511]
 60. Sauer JD, Sotelo-Troha K, von Moltke J, Monroe KM, Rae CS, Brubaker SW, Hyodo M, Hayakawa Y, Woodward JJ, Portnoy DA, Vance RE. The ENU-induced Goldenticket (Gt) mouse mutant reveals an essential function of Sting (Tmem173, Mita, Mpys, Eris) in the in vivo interferon response to *Listeria monocytogenes* and cyclic-di-nucleotides. *Infect Immun*. 2010 Nov 22.79:688–94. [PubMed: 21098106]
 61. Barnes B, Lubyova B, Pitha PM. On the role of IRF in host defense. *Journal of Interferon and Cytokine Research*. 2002 Jan.22:59–71. [PubMed: 11846976]
 62. Savitsky D, Tamura T, Yanai H, Taniguchi T. Regulation of immunity and oncogenesis by the IRF transcription factor family. *Cancer Immunol Immunother*. 2010 Apr.59:489–510. [PubMed: 20049431]
 63. Fitzgerald KA, McWhirter SM, Faia KL, Rowe DC, Latz E, Golenbock DT, Coyle AJ, Liao SM, Maniatis T. IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol*. 2003 May.4:491–6. [PubMed: 12692549]
 64. Wathlet MG, Lin CH, Parekh BS, Ronco LV, Howley PM, Maniatis T. Virus infection induces the assembly of coordinately activated transcription factors on the IFN-beta enhancer in vivo. *Mol Cell*. 1998 Mar.1:507–18. [PubMed: 9660935]
 65. Du W, Maniatis T. An ATF/CREB binding site is required for virus induction of the human interferon beta gene [corrected]. *Proc Natl Acad Sci U S A*. 1992 Mar 15.89:2150–4. [PubMed: 1532252]
 66. Lenardo MJ, Fan CM, Maniatis T, Baltimore D. The involvement of NF-kappa B in beta-interferon gene regulation reveals its role as widely inducible mediator of signal transduction. *Cell*. 1989 Apr 21.57:287–94. [PubMed: 2495183]
 67. Silvennoinen O, Ihle JN, Schlessinger J, Levy DE. Interferon-induced nuclear signalling by Jak protein tyrosine kinases. *Nature*. 1993 Dec 9.366:583–5. [PubMed: 7504785]
 68. Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N, Taniguchi T. IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature*. 2005 Apr 7.434:772–7. [PubMed: 15800576]
 69. Yang H, Lin CH, Ma G, Baffi MO, Wathlet MG. Interferon regulatory factor-7 synergizes with other transcription factors through multiple interactions with p300/CBP coactivators. *Journal of Biological Chemistry*. 2003 May 2.278:15495–504. [PubMed: 12604599]
 70. Fu XY, Kessler DS, Veals SA, Levy DE, Darnell JE Jr. ISGF3, the transcriptional activator induced by interferon alpha, consists of multiple interacting polypeptide chains. *Proc Natl Acad Sci U S A*. 1990 Nov.87:8555–9. [PubMed: 2236065]
 71. Kessler DS, Levy DE, Darnell JE Jr. Two interferon-induced nuclear factors bind a single promoter element in interferon-stimulated genes. *Proc Natl Acad Sci U S A*. 1988 Nov.85:8521–5. [PubMed: 2460869]
 72. Sato M, Hata N, Asagiri M, Nakaya T, Taniguchi T, Tanaka N. Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7. *FEBS Lett*. 1998 Dec 11.441:106–10. [PubMed: 9877175]
 73. Perry AK, Chow EK, Goodnough JB, Yeh WC, Cheng G. Differential requirement for TANK-binding kinase-1 in type I interferon responses to toll-like receptor activation and viral infection. *Journal of Experimental Medicine*. 2004 Jun 21.199:1651–8. [PubMed: 15210743]
 74. Baum A, Garcia-Sastre A. Induction of type I interferon by RNA viruses: cellular receptors and their substrates. *Amino Acids*. 2010 May.38:1283–99. [PubMed: 19882216]
 75. Decker T, Muller M, Stockinger S. The yin and yang of type I interferon activity in bacterial infection. *Nat Rev Immunol*. 2005 Sep.5:675–87. [PubMed: 16110316]
 76. Monroe KM, McWhirter SM, Vance RE. Induction of type I interferons by bacteria. *Cell Microbiol*. 2010 Jul.12:881–90. [PubMed: 20482555]

77. Frendéus B, Wachtler C, Hedlund M, Fischer H, Samuelsson P, Svensson M, Svanborg C. *Escherichia coli* P fimbriae utilize the Toll-like receptor 4 pathway for cell activation. *Molecular Microbiology*. 2001; 40:37–51. [PubMed: 11298274]
78. Tapping RI, Akashi S, Miyake K, Godowski PJ, Tobias PS. Toll-like receptor 4, but not toll-like receptor 2, is a signaling receptor for *Escherichia* and *Salmonella* lipopolysaccharides. *J Immunol*. 2000 Nov 15;165:5780–7. [PubMed: 11067937]
79. Erridge C, Pridmore A, Eley A, Stewart J, Poxton IR. Lipopolysaccharides of *Bacteroides fragilis*, *Chlamydia trachomatis* and *Pseudomonas aeruginosa* signal via toll-like receptor 2. *J Med Microbiol*. 2004 Aug;53:735–40. [PubMed: 15272059]
80. Bulut Y, Faure E, Thomas L, Karahashi H, Michelsen KS, Equils O, Morrison SG, Morrison RP, Arditi M. Chlamydial heat shock protein 60 activates macrophages and endothelial cells through Toll-like receptor 4 and MD2 in a MyD88-dependent pathway. *J Immunol*. 2002 Feb 1;168:1435–40. [PubMed: 11801686]
81. Nagarajan UM, Ojcius DM, Stahl L, Rank RG, Darville T. *Chlamydia trachomatis* induces expression of IFN-gamma-inducible protein 10 and IFN-beta independent of TLR2 and TLR4, but largely dependent on MyD88. *J Immunol*. 2005 Jul 1;175:450–60. [PubMed: 15972679]
82. Mancuso G, Gambuzza M, Midiri A, Biondo C, Papasergi S, Akira S, Teti G, Beninati C. Bacterial recognition by TLR7 in the lysosomes of conventional dendritic cells. *Nat Immunol*. 2009 Jun. 10:587–94. [PubMed: 19430477]
83. Taylor T, Kim YJ, Ou X, Derbigny W, Broxmeyer HE. Toll-like receptor 2 mediates proliferation, survival, NF-kappaB translocation, and cytokine mRNA expression in LIF-maintained mouse embryonic stem cells. *Stem Cells Dev*. 2010 Sep;19:1333–41. [PubMed: 20132051]
84. Prantner D, Nagarajan UM. Role for the chlamydial type III secretion apparatus in host cytokine expression. *Infect Immun*. 2009 Jan;77:76–84. [PubMed: 18852236]
85. Stetson DB, Medzhitov R. Recognition of cytosolic DNA activates an IRF3-dependent innate immune response. *Immunity*. 2006 Jan;24:93–103. [PubMed: 16413926]
86. Monroe KM, McWhirter SM, Vance RE. Identification of host cytosolic sensors and bacterial factors regulating the type I interferon response to *Legionella pneumophila*. *PLoS Pathog*. 2009 Nov;5:e1000665. [PubMed: 19936053]
87. Henry T, Brotcke A, Weiss DS, Thompson LJ, Monack DM. Type I interferon signaling is required for activation of the inflammasome during *Francisella* infection. *J Exp Med*. 2007 May 14;204:987–94. [PubMed: 17452523]
88. Rathinam VA, Jiang Z, Waggoner SN, Sharma S, Cole LE, Waggoner L, Vanaja SK, Monks BG, Ganesan S, Latz E, Hornung V, Vogel SN, Szomolanyi-Tsuda E, Fitzgerald KA. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. *Nat Immunol*. 2010 May;11:395–402. [PubMed: 20351692]
89. Pandey AK, Yang Y, Jiang Z, Fortune SM, Coulombe F, Behr MA, Fitzgerald KA, Sassetti CM, Kelliher MA. NOD2, RIP2 and IRF5 play a critical role in the type I interferon response to *Mycobacterium tuberculosis*. *PLoS Pathog*. 2009 Jul;5:e1000500. [PubMed: 19578435]
90. Stanley SA, Johndrow JE, Manzanillo P, Cox JS. The Type I IFN response to infection with *Mycobacterium tuberculosis* requires ESX-1-mediated secretion and contributes to pathogenesis. *J Immunol*. 2007 Mar 1;178:3143–52. [PubMed: 17312162]
91. Auerbuch V, Golenbock DT, Isberg RR. Innate immune recognition of *Yersinia pseudotuberculosis* type III secretion. *PLoS Pathog*. 2009 Dec;5:e1000686. [PubMed: 19997504]
92. O’Riordan M, Yi CH, Gonzales R, Lee KD, Portnoy DA. Innate recognition of bacteria by a macrophage cytosolic surveillance pathway. *Proceedings of the National Academy of Sciences of the United States of America*. 2002 Oct 15;99:13861–6. [PubMed: 12359878]
93. Leber JH, Crimmins GT, Raghavan S, Meyer-Morse NP, Cox JS, Portnoy DA. Distinct TLR- and NLR-mediated transcriptional responses to an intracellular pathogen. *PLoS Pathog*. 2008 Jan;4:e6. [PubMed: 18193943]
94. Soulat D, Bauch A, Stockinger S, Superti-Furga G, Decker T. Cytoplasmic *Listeria monocytogenes* stimulates IFN-beta synthesis without requiring the adapter protein MAVS. *FEBS Lett*. 2006 Apr 17;580:2341–6. [PubMed: 16616525]

95. Stockinger S, Reutterer B, Schaljo B, Schellack C, Brunner S, Materna T, Yamamoto M, Akira S, Taniguchi T, Murray PJ, Muller M, Decker T. IFN regulatory factor 3-dependent induction of type I IFNs by intracellular bacteria is mediated by a TLR- and Nod2-independent mechanism. *J Immunol*. 2004 Dec 15;173:7416–25. [PubMed: 15585867]
96. Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. *Nature*. 2009 Oct 8;461:788–92. [PubMed: 19776740]
97. Meissner NN, Swain S, Tighe M, Harmsen A. Role of type I IFNs in pulmonary complications of *Pneumocystis murina* infection. *J Immunol*. 2005 May 1;174:5462–71. [PubMed: 15843544]
98. Cooper AM, Pearl JE, Brooks JV, Ehlers S, Orme IM. Expression of the nitric oxide synthase 2 gene is not essential for early control of *Mycobacterium tuberculosis* in the murine lung. *Infection and Immunity*. 2000 Dec;68:6879–82. [PubMed: 11083808]
99. Weigent DA, Huff TL, Peterson JW, Stanton GJ, Baron S. Role of interferon in streptococcal infection in the mouse. *Microbial Pathogenesis*. 1986 Aug;1:399–407. [PubMed: 2469934]
100. Mancuso G, Midiri A, Biondo C, Beninati C, Zummo S, Galbo R, Tomasello F, Gambuzza M, Macri G, Ruggeri A, Leanderson T, Teti G. Type I IFN signaling is crucial for host resistance against different species of pathogenic bacteria. *J Immunol*. 2007 Mar 1;178:3126–33. [PubMed: 17312160]
101. Coers J, Vance RE, Fontana MF, Dietrich WF. Restriction of *Legionella pneumophila* growth in macrophages requires the concerted action of cytokine and Naip5/Ipaf signalling pathways. *Cell Microbiol*. 2007 Oct;9:2344–57. [PubMed: 17506816]
102. Rothfuchs AG, Trumstedt C, Mattei F, Schiavoni G, Hidmark A, Wigzell H, Rottenberg ME. STAT1 regulates IFN- α - and IFN- γ -dependent control of infection with *Chlamydia pneumoniae* by nonhemopoietic cells. *J Immunol*. 2006 Jun 1;176:6982–90. [PubMed: 16709859]
103. Auerbuch V, Brockstedt DG, Meyer-Morse N, O’Riordan M, Portnoy DA. Mice lacking the type I interferon receptor are resistant to *Listeria monocytogenes*. *J Exp Med*. 2004 Aug 16;200:527–33. [PubMed: 15302899]
104. O’Connell RM, Saha SK, Vaidya SA, Bruhn KW, Miranda GA, Zarnegar B, Perry AK, Nguyen BO, Lane TF, Taniguchi T, Miller JF, Cheng G. Type I interferon production enhances susceptibility to *Listeria monocytogenes* infection. *Journal of Experimental Medicine*. 2004 Aug 16;200:437–45. [PubMed: 15302901]
105. Martin FJ, Gomez MI, Wetzel DM, Memmi G, O’Seaghdha M, Soong G, Schindler C, Prince A. *Staphylococcus aureus* activates type I IFN signaling in mice and humans through the Xr repeated sequences of protein A. *J Clin Invest*. 2009 Jul;119:1931–9. [PubMed: 19603548]
106. Manca C, Tsenova L, Bergtold A, Freeman S, Tovey M, Musser JM, Barry CE 3rd, Freedman VH, Kaplan G. Virulence of a *Mycobacterium tuberculosis* clinical isolate in mice is determined by failure to induce Th1 type immunity and is associated with induction of IFN- α /beta. *Proceedings of the National Academy of Sciences of the United States of America*. 2001 May 8;98:5752–7. [PubMed: 11320211]
107. Qiu H, Fan Y, Joyee AG, Wang S, Han X, Bai H, Jiao L, Van Rooijen N, Yang X. Type I IFNs enhance susceptibility to *Chlamydia muridarum* lung infection by enhancing apoptosis of local macrophages. *J Immunol*. 2008 Aug 1;181:2092–102. [PubMed: 18641348]
108. Nagarajan UM, Prantner D, Sikes JD, Andrews CW Jr, Goodwin AM, Nagarajan S, Darville T. Type I interferon signaling exacerbates *Chlamydia muridarum* genital infection in a murine model. *Infect Immun*. 2008 Oct;76:4642–8. [PubMed: 18663004]
109. Prantner D, Sikes JD, Hennings L, Savenka AV, Basnakian AG, Nagarajan UM. IRF3 protects from uterine horn pathology during *Chlamydia muridarum* genital infection in mice. *Infect Immun*. 2011 Jul 25.
110. Miller JC, Ma Y, Bian J, Sheehan KC, Zachary JF, Weis JH, Schreiber RD, Weis JJ. A critical role for type I IFN in arthritis development following *Borrelia burgdorferi* infection of mice. *J Immunol*. 2008 Dec 15;181:8492–503. [PubMed: 19050267]
111. Xin L, Vargas-Inchaustegui DA, Raimer SS, Kelly BC, Hu J, Zhu L, Sun J, Soong L. Type I IFN receptor regulates neutrophil functions and innate immunity to *Leishmania* parasites. *J Immunol*. 2010 Jun 15;184:7047–56. [PubMed: 20483775]

112. Nagai T, Devergne O, Mueller TF, Perkins DL, van Seventer JM, van Seventer GA. Timing of IFN-beta exposure during human dendritic cell maturation and naive Th cell stimulation has contrasting effects on Th1 subset generation: a role for IFN-beta-mediated regulation of IL-12 family cytokines and IL-18 in naive Th cell differentiation. *Journal of Immunology*. 2003 Nov 15;171:5233–43.
113. Tough DF, Borrow P, Sprent J. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. *Science*. 1996 Jun 28;272:1947–50. [PubMed: 8658169]
114. Belardelli F, Ferrantini M, Proietti E, Kirkwood JM. Interferon-alpha in tumor immunity and immunotherapy. *Cytokine and Growth Factor Reviews*. 2002 Apr;13:119–34. [PubMed: 11900988]
115. Heise MT, Pollock JL, O'Guin A, Barkon ML, Bormley S, Virgin HW. Murine cytomegalovirus infection inhibits IFN gamma-induced MHC class II expression on macrophages: the role of type I interferon. *Virology*. 1998 Feb 15;241:331–44. [PubMed: 9499808]
116. Lu HT, Riley JL, Babcock GT, Huston M, Stark GR, Boss JM, Ransohoff RM. Interferon (IFN) beta acts downstream of IFN-gamma-induced class II transactivator messenger RNA accumulation to block major histocompatibility complex class II gene expression and requires the 48-kD DNA-binding protein, ISGF3-gamma. *Journal of Experimental Medicine*. 1995 Nov 1;182:1517–25. [PubMed: 7595221]
117. Devajyothi C, Kalvakolanu I, Babcock GT, Vasavada HA, Howe PH, Ransohoff RM. Inhibition of interferon-gamma-induced major histocompatibility complex class II gene transcription by interferon-beta and type beta 1 transforming growth factor in human astrocytoma cells. Definition of cis-element. *Journal of Biological Chemistry*. 1993 Sep 5;268:18794–800. [PubMed: 8103050]
118. Fujita H, Asahina A, Tada Y, Fujiwara H, Tamaki K. Type I interferons inhibit maturation and activation of mouse Langerhans cells. *J Invest Dermatol*. 2005 Jul;125:126–33. [PubMed: 15982312]
119. Gautier G, Humbert M, Deauvieu F, Scuiller M, Hiscott J, Bates EE, Trinchieri G, Caux C, Garrone P. A type I interferon autocrine-paracrine loop is involved in Toll-like receptor-induced interleukin-12p70 secretion by dendritic cells. *Journal of Experimental Medicine*. 2005 May 2;201:1435–46. [PubMed: 15851485]
120. McRae BL, Beilfuss BA, Seventer GAV. IFN- β Differentially Regulates CD40-Induced Cytokine Secretion by Human Dendritic Cells. *Journal of Immunology*. January 1;2000 164:23–8.
121. Byrnes AA, McArthur JC, Karp CL. Interferon-beta therapy for multiple sclerosis induces reciprocal changes in interleukin-12 and interleukin-10 production. *Annals of Neurology*. 2002 Feb;51:165–74. [PubMed: 11835372]
122. Laurent-Rolle M, Boer EF, Lubick KJ, Wolfenbarger JB, Carmody AB, Rockx B, Liu W, Ashour J, Shupert WL, Holbrook MR, Barrett AD, Mason PW, Bloom ME, Garcia-Sastre A, Khromykh AA, Best SM. The NS5 protein of the virulent West Nile virus NY99 strain is a potent antagonist of type I interferon-mediated JAK-STAT signaling. *J Virol*. 2010 Apr;84:3503–15. [PubMed: 20106931]
123. Silins I, Ryd W, Strand A, Wadell G, Tornberg S, Hansson BG, Wang X, Arnheim L, Dahl V, Bremell D, Persson K, Dillner J, Rylander E. Chlamydia trachomatis infection and persistence of human papillomavirus. *Int J Cancer*. 2005 Aug 10;116:110–5. [PubMed: 15756673]

Figure 1. Major pathways and sensors for IFN β induction

A. TLRs: TLR4 and TLR3 can sense bacterial LPS and ds RNA respectively, and recruit the adaptor molecule TRIF. This leads to activation of NF κ B and IRF3, mediated by the respective kinases. TLR7 and TLR9 recognize ssRNA and CpG DNA respectively in the lysosomal compartments and recruit adaptor molecule MyD88, leading to activation of NF κ B and IRF7 activation. **B. RLR/NLR:** Recognition of viral dsRNA by MDA5 and RIG-I or ssRNA by NOD2, results in recruitment and activation of MAVS, and STING, leading to IRF3 phosphorylation. **C. DNA Sensors:** This group is comprised of structurally unrelated proteins that recognize different forms of DNA. RNA polymerase III binds to polydAdT, and transcribes it to RNA, which in turn is recognized by RIG-I. IFI16 is major DNA sensor for longer DNA (>70 bp), and functions independent of MAVS. Bacterial metabolites di-cyc-AMP and di-cyc-GMP are recognized by unknown sensors. All DNA sensors require the adaptor molecule STING for downstream activation. LRRFIP1 recognize cytosolic dsRNA and DNA, and activates β -catenin. All pathways converge to binding of phosphorylated nuclear IRF3 and p65 to the IFN β promoter resulting in IFN β gene transcription.