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Impact of type I interferons on susceptibility to bacterial pathogens

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Abstract

Interferons (IFNs) are a broad class of cytokines that have multifaceted roles. Type I IFNs have variable effects when it comes to host susceptibility to bacterial infections, that is, the resulting outcomes can either be protective or deleterious. The mechanisms identified to-date have been wide and varied between pathogens. In this review, we discuss recent literature that provides new insights into the mechanisms of how type I IFN signaling exerts its effects on the outcome to infection from the host's point of view.

Keywords

bacteria; infection; type I IFN; type I interferons; interferon; IFN

Introduction

Interferons (IFNs) are a broad class of pleiotropic cytokines elicited upon encounter of the innate immune system with pathogens. These innate immune mediators owe their name to the initial observation that they could "interfere" with viral replication [1]. Although they were originally identified for their antiviral properties, it is now recognized that they also play a multitude of roles in cancer, autoimmunity and can modulate infection with a range of other microorganisms including parasites, fungi and bacteria [2–7]. This review will focus on the role of type I IFNs in bacterial infection, with a focus on recent studies that have defined their impact on infection resolution.

There are three classes of interferons type I, type II and type III. In humans, the type I interferon (IFN) family includes IFN-α (13 subtypes), IFN-β, IFN-ε, IFN-κ and IFN-ω subtypes. In mice, 14 IFN-α subtypes have been identified along with individual IFN-β, IFN-ε, IFN-κ and IFN-ζ subtypes [8]. IFN-α and IFN-β are the best characterized and most broadly expressed genes of this family. All type I IFNs interact with a single heterodimeric receptor composed of two subunits, IFNAR1 and IFNAR2. This receptor is ubiquitously

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expressed and binding of its ligand signals through the JAK-STAT pathway and interferon regulatory factors (IRFs) that induces expression of hundreds of interferon stimulated genes (ISGs), as well as autocrine and paracrine signaling [9] (Figure 1).

Type I IFNs are induced through extracellular and intracellular pattern recognition receptors (PRR) of the innate immune system. These PRR mediate the recognition of specific motifs found on pathogens, called pathogen-associated molecular patterns (PAMPs). PAMPs are comprised of structural components of the bacterial cell wall such as lipopolysaccharides (LPS), lipoproteins, peptidoglycan fragments and flagellin subunits. Other microbial components such as nucleic acids (DNA and RNA) can also be sensed by these receptors [10]. Several families of PRR have been identified in mammals. They include Toll-like receptors (TLRs) which are the primary sensors of extracellular bacteria, nucleotide binding leucine rich repeat (NLRs) proteins that detect cytosolic bacteria, RIG-I like receptors (RLR) that detect short RNA sequences in the cytosol and the DNA sensors also found in this subcellular compartment [10]. Although activation of most of these PRR leads to the expression of proinflammatory and antibacterial genes, only a subset of them have been linked with type I IFN production during bacterial infection. In the TLR family, TLR2, TLR4, TLR7/8, TLR9 and TLR13 have been shown to stimulate a type I IFN response after binding of their respective ligands [11–16]. TLR3 has been shown to stimulate the production of IFN-β after sensing of commensal bacteria, but not in the context of bacterial infections [17]. In the NLR family, recognition of bacterial peptides by the nucleotide-binding and oligomerizing domain (NOD) like receptors, NOD1 and NOD2 also elicits type I IFN production [18, 19]. cGAS-dependent and independent stimulation of STING has also been linked with type I IFN induction via sensing of intracellular DNA [12, 20–22]. Finally, the cytosolic sensor RIG-I has been linked to the induction of type I IFN production via sensing of bacterial RNA [23, 24]. The transcription factors IRFs, in particular IRF1, IRF3, IRF5 and IRF7, together with NF-κB are subsequently activated and lead to expression of type I IFNs [14, 19, 25].

The roles of type I IFNs in bacterial infections

Because of the multifaceted roles of these cytokines, the effect of type I IFN signaling on host susceptibility to bacterial infections are diverse. Many factors can influence this response and the infection outcome. These can be intrinsic to the bacterium and its capacity to activate different PRR, its replication programs, virulence factor expression and immune evasion strategies. The types of cells that encounter the pathogen, the target organs, and its cellular lifestyle all can influence this response. In many cases (Table. 1) a differential effect is seen based on the route of infection. As there are several reviews on the ability of bacteria to activate type I IFN signaling [26, 27], here, we summarize existing data (Table. 1) and discuss below, recent literature that provides new insights into the mechanisms of how type I IFN signaling exerts its effects on the outcome to infection from the host point of view (Figure. 2).

1- Protective effects of type I IFNs

Any aspect of the immune system is typically viewed as serving a critical role against invading organisms. However, sometimes this activation disrupts the balance of controlling infection and maintaining a harmonious state. Until recently, most studies exploring the mechanism of type I IFN-mediated protection have largely converged on neutrophils and the ability of type I IFN to positively regulate their antimicrobial production, such as reactive nitrogen species [20, 28–31] [32, 33]. In recent studies, two unique mechanisms whereby type I IFN can be beneficial to the host are discussed.

In a pulmonary infection model of *Acinetobacter baumannii* infection, *Ifnar*$^{-/-}$ and *Irf3*$^{-/-}$ / *Irf7*$^{-/-}$ mice, in which IFN-β signaling and production is impaired, exhibited significantly higher bacterial burdens in their lung and spleen compared to WT mice [34]. Type I IFN signaling also initiated cell death, via activation of apoptosis, necroptosis and pyroptosis. This was evident by activation of the NLRP3 inflammasome and caspase-11. *A. baumanni*-induced type I IFN was shown to generate epigenetic modifications (H3K27ac marks) at the promoters of these key programmed cell death mediators. While it was recently shown that interferon exposure can induce an immunological innate memory [35], this study is the first to implicate bacteria in inducing a type I IFN mediated epigenetic change to influence host outcome.

Two recent studies were able to demonstrate that bacterial proteins can directly suppress the type I IFN response to reduce the beneficial effects afforded to the host. Group A *Streptococcus* (GAS) produces a DNase, Sda1, involved in protection against neutrophil extracellular traps, which can also impair TLR9-mediated type I IFN production. Mice infected with a GAS sda1 mutant, produced higher type I IFN levels, which reduced bacterial numbers and lesion sizes [36]. While a phenotype was not observed in IFNAR knockout mice, this is presumably due to the active suppression mediated by Sda1.
The obligate cytosolic human pathogen *Rickettsia parkeri* is also sensitive to type-I IFN-mediated killing. Increased mortality and bacterial burdens are observed when both type I and II interferon receptors are inactivated. While a specific factor is yet to be identified, it has been demonstrated to reduce type I IFN production in macrophages by antagonizing the inflammasome [31].

2- Detrimental effects of type I IFN on the host

There have been several examples in the literature whereby type I IFNs sensitize cells to apoptosis and recently this was shown to be evident with *Francisella novicida* [37]. Inactivation of either component of the IFNAR receptor led to increased survival after infection with *F. novicida* infection. Likewise, inactivation of the downstream IRF, *Irf3* (as well *Irf3*/*Irf7* double knockout mice) also had a protective phenotype. While previous reports have suggested that type I IFN can regulate the AIM2 inflammasome [38], which helps in infection protection, it was still functional in the mice lacking IFNAR. Type I IFN was shown to exert its negative effects through enhancing apoptosis, as shown in liver tissue with increased active caspases 3, 7 and 8. The TNF-related apoptosis inducing ligand (TRAIL) is upregulated by type I IFNs [37] and binding to its receptor, DR5, triggers

apoptosis [39]. This was shown to be the likely mechanism in this case, as neutralization of TRAIL aided in mouse survival [37].

One of the first bacterial pathogens to be identified as activating a detrimental type I IFN host immune response was *Listeria monocytogenes* [40, 41]. Several different mechanisms have been documented to explain this including: suppression of the Th17 response, sensitizing cells to apoptosis, T cell death, enhanced IL-10 production, decreased neutrophil recruitment and promotion of actin-based motility (Table. 1). Most of these studies have been conducted in systemic models of infection. The exception to this rule to-date has been a study investigating oral infection (intragastric inoculation) as a model for foodborne contamination with *L. monocytogenes* that didn't see a change in outcome in WT versus *Ifnar*$^{-/-}$ mice [42]. Focusing back on sepsis, recent studies have been able to elucidate molecular mechanisms behind this response as well as bacterial products to manipulate this response to their advantage.

Two different bacterial products of *L. monocytogenes* have been shown to help facilitate infection by activating type I IFN signaling. Frantz *et al* [24] identified several small RNAs (sRNAs) that could induce type I IFNs. One of these sRNAs that induced the highest levels of IFN-β was rli32. It induced IFN-β via RIG-I and indicative of this strong type I IFN response, was able to inhibit influenza virus replication. rli32 was shown to promote intracellular survival of *L. monocytogenes* in a type-I IFN-dependent manner and aided in resistance to hydrogen peroxide [24]. A second *L. monocytogenes* product, this time the RNA binding protein, Zea, also leads to enhanced type I IFN signaling, mediated through RIG-I. Zea is able to bind to several RNAs that accumulate in the extracellular medium, potentiating type I IFN production. Inactivation of Zea attenuates virulence [23].

Ubiquitin-specific peptidase 18 (USP18) was identified as an interferon stimulated gene (ISG) increased in macrophages and dendritic cells after *L. monocytogenes* stimulation. USP18 was primarily responsible for the deleterious effects of type IFN signaling during mice infection with *L. monocytogenes* [43]. Likewise, in the context of superinfection with acute lymphocytic choriomeningitis virus (LCMV), LCMV enhanced *L. monocytogenes* persistence in a type I IFN- dependent manner via CD11c^{+} cells. CD11c^{+} cells were identified as the cause, as inactivation of *Ifnar* or *Usp18* in CD11c^{+} cells lead to reduced bacterial titers in multiple organs as well as increased survival rates. USP18 is known to prevent TNF-α signaling by targeting TAK1 and NEMO for deubiquitination [44]. This proved to be the mechanism behind the phenotype with USP18, by inhibiting TNF-α production it promoted bacterial replication. This observation did not prove to be unique to *L. monocytogenes*. Respiratory infection with *Staphylococcus aureus*, yielded similar observations that were dependent upon signaling through CD11c^{+} cells and USP18 [43].

S. aureus also benefits from the activation of type I IFN signaling [14, 45, 46]. This detrimental impact of type I IFN on the host is further exacerbated with antecedent viral infection. Influenza decreases IL-17, IL-22 and IL-23, which are important for *S. aureus* clearance [47]. It was also observed that mice lacking STAT2 (downstream of IFNAR) exhibited increased susceptibility to influenza infection but decreased lethality and improved bacterial clearance upon super-infection with methicillin resistant *S. aureus* [48]. This

mechanism could be explained by a compensatory effect of type II IFN driving the induction of M1-polarized macrophages. In the study mentioned above for *L. monocytogenes* [43], it was also shown that $CD11c^+$ DCs appear to be integral mediators in the negative response to *S. aureus*, as inactivation of *Ifnar* in these cells confers an improved outcome. Specific deletion of the ISG USP18, which can regulate type I IFN signaling, in $CD11c^+$ dendritic cells also led to significant reductions in bacteria. It remains to be determined how this protein negatively impacts bacterial clearance. Several studies have shown in the context pneumonia that type I IFN signaling benefits *S. aureus* infection [14, 43, 45, 46]. As an example that mice can vary their phenotype between suppliers, facilities and housing conditions, a recent study using a neutralizing antibody observed a protective role for type I IFN with *S. aureus* [33]. In this case, type I IFN was observed to enhance granzyme production in neutrophils and thus facilitate bacterial killing. This study would concur with Kaplan *et al* [49], which observed direct antibacterial killing by IFN-β. However, this study also saw direct killing against *L. monocytogenes* that, as described above, benefits from type I IFN signaling. The discrepancy between these studies maybe true when examining differences between *in vitro* and *in vivo* but could be due to the specific strains studied as well.

We were able to recently demonstrate significant diversity within *S. aureus* in its ability to activate the production of type I IFNs. It had been assumed that within a given species activation was somewhat conserved. We identified two strains with divergent activation [14, 46] before screening dozens of *S. aureus* isolates. We identified a broad range of IFN-β activation potential with vancomycin intermediate strains generating reduced amounts of IFN-β. These low levels of type I IFN induction correlated with increased resistance to autolysis and lysostaphin *in vitro*. This is probably as a result of the thickened cell wall seen in vancomycin intermediate strains [50], protecting the bacterial cells from endosomal processing and release of PAMPS to receptors to signal. In an *in vivo* model of acute pneumonia, we observed that an *S. aureus* strain with reduced type I IFN induction ability to be more readily cleared than a strain with higher IFN-β induction propensity, however whether this was solely due to their differences in type I IFN induction needs to be further investigated [51].

In the context of mycobacterial infections, type I IFN response has been associated with pathogenesis [52, 53]. The detrimental phenotype of type I IFN to *Mycobacterium* does not necessarily hold true *in vitro*. Type I IFN signaling enhanced the intrinsic capability of macrophages to effectively clear the *M. tuberculosis* and *M. abscessus* by inducing nitric oxide production [11, 54]. *M. tuberculosis* was also shown to inhibit autocrine type I IFN signaling (by 50–60%) via reduced phosphorylation of the IFNAR-associated protein kinases JAK1 and TYK2, leading to reduced phosphorylation of STAT1 and STAT2 [54]. Suggesting that the type I IFN response could be detrimental to the pathogen but a good example of how *in vitro* does not always correlate to *in vivo*. Murine models with the bovine turbercule bacilli, *Mycobacterium bovis* are protected against infection when IFNAR is neutralized [55]. Both cellular and immune signaling differences were noted. A reduction in neutrophil recruitment was observed *in vivo* along with reduced IL-10, IL-6 and increased in IFN-γ and IL-1β. *In vitro*, macrophages treated with αIFNAR1 induced decreased levels of M2 markers such as *Arg1*, *Ym1* and *Mrc1* and increased expression of M1 markers such

as *Nos2*, and *Ifng* suggesting that type I IFN signaling mediates macrophage polarization toward an anti-inflammatory profile during *M. bovis* infection [55]. Another study found that macrophages deficient in either IFNAR or STAT exhibited increased viability compared to WT cells after infection with *M.tuberculosis* [56]. The authors also observed that IFNAR antibody blockade increased the protective effects of rifampin, a first-line tuberculosis drug.

Type I IFN-mediated effects on macrophage function were also observed with nontypeable *Haemophilus influenzae* (NTHi). WT macrophages pre-treated with IFN-β showed impaired phagocytosis and bacterial killing, while *Ifnar*$^{-/-}$ macrophages had increased phagocytic and killing abilities compared to WT cells. *In vivo* infection corroborated these results, *Ifnar*$^{-/-}$ mice showing reduced susceptibility to NTHi infection and reduced weight loss. Likewise, in a COPD model, animals treated with IFN-β and NTHi fared worse compared to controls. Type I IFNs also induced enhanced proinflammatory signaling through MAP kinase activation [57].

3- Dual effects of type I IFN signaling on infection outcomes

We have summarized (Table. 1) and discussed so far, several examples where contrary phenotypes exist. This tends to occur when different routes of infection are studied, further highlighting what is beneficial for one organ can be detrimental to another. A good example of this binary phenotype is *Streptococcus pneumoniae*. Type I IFN signaling has been shown to be important for protection against pneumococcal infection however, with preceding influenza infection, this creates a more susceptible environment that is propagated by type I IFN signaling [29, 43, 58–68] (Table. 1). Where mechanisms are known, this further the illuminates the pleiotropic effects type I IFN signaling can exert on the host. In the context of respiratory tract infection with *Coxiella burnetii*, the dual effect of type I IFN signaling has also been documented [69]. Inactivating IFNAR led to reduced bacterial burdens and better weight retention. When WT mice received an injection of recombinant IFN-α, disease-induced weight loss was exacerbated, suggesting that type I IFN signaling is deleterious. However, when mice received recombinant IFN- α intratracheally, bacterial replication was decreased in all tissues. A reduction in IL-1β expression was observed in the lung of mice that received recombinant IFN-α intraperitoneally, thus inflammatory cytokine dampening could be responsible for this, tissue specific, dual phenotype [69].

A reduction in cell death improved the outcome in *Ifnar*$^{-/-}$ mice infected with *Salmonella enterica* Serovar Typhimurium [70, 71] and recent work showed that the absence of STAT2- dependent type I IFN signaling led to decreased reactive oxygen species (ROS) production by neutrophils and disruption of hypoxia in the intestinal epithelium, resulting in respiration inhibition of *S.* Typhimurium and impaired luminal expansion [72]. Suggesting that type I IFN signaling is beneficial for the bacterium, in this context. However, a unique study recently examined the influence of pregnancy on the outcome to infection with *L. monocytogenes* and *S.* Typhimurium in the presence and absence of type I IFN. While pregnancy did not influence the detrimental outcome conferred by type I IFNs in *L. monocytogenes* infection, the protection afforded in *Ifnar*$^{-/-}$ mice to *S.* Typhimurium infection was lost in pregnant mice. The compromised outcome in pregnant mice to

Salmonella was attributed to decreased production of several cytokines including IFN-γ, TNF, MCP-1 and IL-12 [70].

A further recent example in which type I IFN signaling appears to have dual effects was with *Pseudomonas aeruginosa*. In a murine two-hit infection model to reproduce sepsis-related acute respiratory distress syndrome (ARDS) consisting of cecal ligation and puncture (CLP)- mediated peritoneal sepsis followed by respiratory tract infection with *Pseudomonas aeruginosa,* IFN-β production was beneficial to the host [73]. IFN-β administration reversed the suppressive effects of prior sepsis on the functions of alveolar macrophages, improving their phagocytosis and increasing CXCL1-mediated neutrophil recruitment. Lung bacterial burdens were reduced, mouse survival was improved and sepsis-related ARDS reduced [73]. IFN-β administration after CLP but before pneumonia also reduced mortality, lung bacterial burden and lung injury score [73]. This contrasts to a mono-infection acute lung injury model of *P. aeruginosa* infection. In this model, type I IFN led to activation of neutrophils which mediated tissue damage and also supported biofilm formation and tissue persistence by *P. aeruginosa* [74]. Mouse knockouts in both *Ifnar1* and *Ifnb1* exhibited lower lung colonization of *P. aeruginosa* and reduced tissue damage compared to WT controls. Type I IFN-deficient neutrophils were found to be impaired in their ability to produce and release long neutrophil extracellular traps (NETs) and ROS. Upon infection with *P. aeruginosa*, NETs were found to support bacterial biofilm formation and thereby to promote persistence of the pathogen in the lung by protecting it from the immune system. The direct effect of IFN-β on NETosis and biofilm formation was also demonstrated [74]. These examples of dual effects highlight how the model and infection site as well as immune status can alter the outcome, while antimicrobial products, such as reactive oxygen species can both support and repress bacterial clearance depending upon the pathogen.

Concluding remarks

The studies summarized here illustrate the complex interactions of type I IFN signaling with the immune system in the context of bacterial infections. These cytokines can have drastically different effects on the host, ranging from deleterious to beneficial. The specific reasons behind these phenotypes are still poorly understood (see Outstanding Questions). The type of bacterial pathogen and their mode of infection can account for some of these differences. However, other examples show that the context of infection (different tissues, cell types and many other host factors such as pregnancy and prior exposure to heterologous pathogens) can be as crucial as the bacterial species in determining the outcome of infection. Some progress has been made with the discovery of specific bacterial factors (noncoding RNA and RNA-binding proteins) that can directly modulate IFN expression. The identification of ISGs that contribute to the deleterious effects of type I IFN signaling in bacterial infections is a further step towards characterizing these responses, but many questions remain (see Outstanding Questions). Furthermore, the entirety of the studies discussed in this review focused on the effect of IFN-α and β on host response to bacterial infections. With the exception of one publication demonstrating the protective role of IFN-ε against *Chlamydia muridarum*-induced sexually transmitted infection [75], very little is known about the effects of other type I IFNs on bacterial infection outcomes. Future

research that aims to define the conditions in which type I IFN signaling leads to enhanced susceptibility or protection to bacterial infections would be most informative.

Due to the diverse roles of type I interferons in bacterial infections, we are left without any unifying theme that could, based on niche, infection site, genus or species, predict pathogen susceptibility to type I IFN. This is exemplified by the observations that even with the same pathogen, there are examples of dual effects of type I IFN on the outcome to infection. We have observed that within the same species, a diversity of induction can occur strain-to-strain. The level of induction evoked by each specific strain, the duration of this induction and the location of infection may all dictate the outcome to infection. This leaves us with the question of what the true role of type I IFN is. It might have evolved as an antiviral pathway and has adapted additional innate sensors to respond to bacterial products; however, its role is truly variable from pathogen-to-pathogen. Based on the data to-date, it would be presumptive to assume any given species or strain would behave the same way as a standard laboratory strain analyzed. It is very clear that there are significant differences in the ability to induce type I IFN and the infection outcome between different species, strains and sites of infection. Likewise, the ability to activate this pathway is not a one size fits all system that again varies considerably between species and within species. It is unlikely in the short term that we will come to a unified conclusion on what specific factors and events lead to a positive or negative outcome in regards to type I IFN activation. It will not be until we have a significant body of work that investigates a single infection site with different species that might activate type I IFN through the same receptors we will get closer to this point. But given the complexity already observed amongst different pathogens and strains, this would require some very large labor intensive experiments. What is clear, is that type I IFN signaling can have a major impact on the outcome to bacterial infections, the outcome of which can be both positive and detrimental to the host.

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Outstanding Questions Box

- Why can type I IFN activation in the same site be beneficial to one microbe but detrimental to another?
- How does the route of infection impact type I IFN induction and infection outcome?
- How does the magnitude and duration of type I IFN induction impact infection outcome?
- What controls the magnitude of type I IFN induction between strains?
- How similar is the signaling for type I IFN to the related type III IFN pathway?
- Identification of bacterial factors that can manipulate this pathway.
- Identification of specific ISGs that influence bacterial clearance.
- What are the cells influenced by type I IFN from species-to-species?
- What specific factors determine the protective and detrimental effects of type I IFN signaling on the host during bacterial infections?
- What impact does epigenetics play in the type I IFN response and does it impact subsequent infections?

Highlights box

- Type I IFN signaling can be detrimental or beneficial to the host during bacterial infections and this varies between species and by infection site
- Bacterial factors can directly modulate type I IFN signaling and its downstream effects
- Significant diversity is seen between strains of the same species to activate this response
- Type I IFN can cause epigenetic changes that aid in cell death for bacterial clearance but can also sensitize cells to apoptosis
- Expression of USP18 in $CD11c^{+}$ cells suppresses antibacterial production of TNF
- Type I IFNs can manipulate neutrophil recruitment for the benefit and detriment of the host, while their products can aid in bacterial persistence

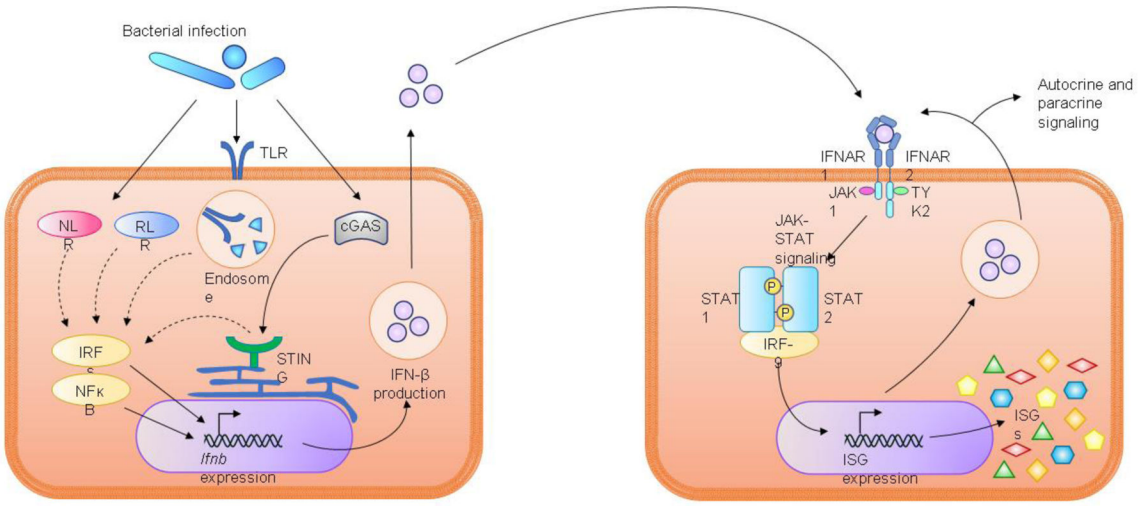

Figure 1: Type I IFN signaling in the context of bacterial infection.

Type I IFNs are induced when bacteria are recognized by PRR, including nucleotide binding leucine rich repeat proteins such as NOD-1 and NOD-2 (NLR), RIG-I like receptors (RLR) and toll-like receptors (TLR) and cyclic GMP-AMP Synthase (cGAS). PRR sensing activates the transcription factors of the interferon regulatory factors (IRF) family, which, with NF-κB, stimulate the expression of type I IFNs, depicted here with IFN-β. IFN-β is then secreted and binds to the IFNAR receptor which signals through the JAK-STAT pathway. The phosphorylated forms of STAT-1 and STAT-2 and the interferon regulatory factors form a transcription factor complex that translocates to the nucleus where it induces the expression of hundreds of interferon stimulated genes (ISGs). IFN-β is also produced, allowing a positive feedback loop and paracrine signaling.

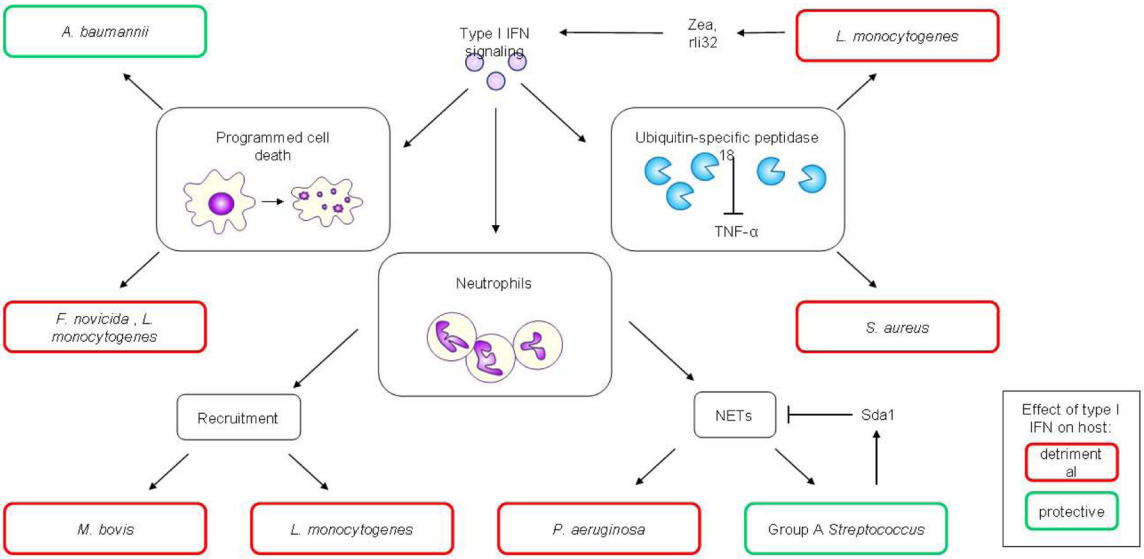

Figure 2: Recently described effects of type I IFN signaling on clearance during bacterial infections.

Type I IFN signaling induces different cell death programs, which in the context of *A.baumannii* infection is beneficial for the host as it aided bacterial clearance. However, in the context of *F. novicida* and *L. monocytogenes* infections, type I IFN-mediated cell death is detrimental to the host. Type I IFN signaling exerts different effects on neutrophils: in the context of *M. bovis* infection, increased neutrophil recruitment is observed and is detrimental to the host. In the context of *L.monocytogenes* infection, neutrophil recruitment is increased and is detrimental to the host, while during *P .aeruginosa* infection, type I IFN-mediated production of neutrophil extracellular traps (NETs) facilitiates biofilm production and bacterial persistence, making this process detrimental to the host. However, in the context of Group A *Streptococcus* (GAS) infection, type I IFN-mediated NET production aids in bacterial clearance, making type I IFN a protective host factor. GAS produces the bacterial DNase, SdaI that degrades NETs, allowing the bacteria to evade this immune response. Finally, type I IFN signaling induces the production of USP18, an ISG able to inhibit the antibacterial effects of TNF-α. This contributes to the detrimental effects of infections with *S. aureus* and *L. monocytogenes*. The latter is also able to produces factors such as small noncoding RNAs and RNA binding proteins that stimulate type I IFN production, reinforcing its detrimental effects.

Table 1:

Impact of type I IFN signaling on the outcome of bacterial infections

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
Acinetobacter baumannii	TRIF	• Downstream IFNAR signaling leads to H3K27ac mark deposition at promoters of key programmed cell death mediators : *Zbp1, Mlkl, Casp-11* and *Gsdmd*	• Increased inflammation, apoptosis, necroptosis and pyroptosis • Increased bacterial clearance in WT mice compared to *Ifnar*$^{-/-}$ mice	Host protection	[34]
Brucella abortus	cGAS, STING, IRF5	• IFN suppression of NO and induction of apoptosis	• Increased bacterial burden in *Sting*$^{-/-}$ mice compared to WT mice • Uncontrolled bacterial replication in *Ifnar*$^{-/-}$ macrophages compared to WT macrophages • Reduced bacteria in *Ifnar*$^{-/-}$, sepsis model	Differential effects between studies	[21, 32]
Chlamydia muridarum	STING, IRF3	• KO mice have increased *C. muridarum* T cells and enhanced T cell recruitment • IFN enhances apoptosis of macrophages	• Reduction in shedding and duration of infection in *Ifnar*$^{-/-}$ mice, genital model • Decreased bacteria in pneumonia model	Detrimental	[76–78]
Coxiella burnetii	-		• Infected *Ifnar*$^{-/-}$ show reduced weight loss and decreased bacterial burden in the spleen 6 days post infection, intratracheal inoculation • Contrasting KO mice, intratracheal treatment of WT mice with recombinant IFN-α decreased bacterial burdens • Intraperitoneal treatment of WT mice with recombinant IFN-α increased weight loss	Differential effects	[69]
Escherichia coli	-		• IFNAR mice exhibited decreased survival after intravenous infection compared to WT mice	Host protection	[30]
Escherichia coli- viral		• type I IFN-associated suppression of type 17 immunity	• Increased bacterial burden in the lung of WT mice with prior exposure to influenza	Detrimental effect	[79]

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
			• reduced pulmonary bacterial burden in *Ifnar*$^{-/-}$ mice with flu antecedent compared to WT mice		
Francisella novicida	cGAS, STING, IRF3/7	• Suppression of apoptotic caspases and cell death	• *Ifnar*$^{-/-}$ mice exhibited increased survival	Detrimental	[37]
Francisella tularensis	IRF3	• IFN negatively regulate γδ T cell IL-17 production and neutrophil expansion	• Increased survival and decreased bacteria in *Ifnar*$^{-/-}$ mice	Detrimental	[80]
Haemophilus influenza (nontypeable)	cGAS, STING, TBK1		• WT macrophages pre-treated with IFN-β showed impairment in phagocytosis and bacterial killing • *Ifnar*$^{-/-}$ macrophages displayed significantly increased phagocytic and killing abilities compared to WT cells • *Ifnar*$^{-/-}$ mice showed reduced susceptibility to NTHi infection	Detrimental	[57, 81]
Helicobacter pylori	NOD1, IRF7		• Increased bacterial burden in *Ifnar*$^{-/-}$ mice	Host protection	[18]
Legionella pneumophila	STING, IRF3		• Type I IFN-stimulated macrophages resist intracellular replication • *Ifnar*$^{-/-}$ *Ufngr*$^{-/-}$ increased bacteria burden	Host protection	[82, 83]
Listeria monocytogenes	RIG-I, STING, TLR2, TRIF	• Bacteria secrete sRNAs (rli32) that induce type I IFN induction in a RIG-I dependent manner • Zea, a small RBP modulates type I IFN via RIG-I signaling • USP18 contributes to deleterious effects of type I IFN signaling by inhibiting antibacterial effect of TNF-α • IFN-activated integrated stress response and not protein folded response	• *Ifnar*$^{-/-}$ mice control the infection better, systemic • rli32 overproduction promotes intracellular growth, resistance to H_2O_2 and changes in cell envelop • Mice lacking *USP18* in CD11c cells exhibited significantly reduced mortality and bacterial burdens in multiple organs (liver, spleen, kidney and lung) compared to littermate controls • Intragastric model, type I IFN beneficial, increased bacteria and	Dual effects	[23, 24, 40–43, 70, 80, 84–89]

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
		• Promote ActA polarization and motility • Type I IFN suppress IL-17 from γδ T cells • Type I sensitizes cells to apoptosis • Decreased neutrophil recruitment to spleen	mortality in *Ifnar*$^{-/-}$ mice.		
Mycobacterium abscessus	TLR2, TLR4, MyD88, TRIF, IRF3	• Induces nitric oxide production	• *Ifnar1*$^{-/-}$ cells exhibited higher intracellular bacterial counts than WT cells	*In vitro*: Host protection	[11]
Mycobacterium bovis	-	• Type I IFN signaling mediates macrophage polarization toward an anti-inflammatory profile during *M. bovis* infection	• IFNAR-1 blocking antibody decreased mortality and bacterial numbers • Changes in cytokine expression (increased IL-1β, IFN-γ/decreased IL- 10 and IL-6 in treated mice) • reduced neutrophil recruitment and increased macrophage activation in αIFNAR mice	Detrimental	[55]
Mycobacterium smegmatis	cGAS, STING, TBK1, IRF3/7		• Improved survival in absence of IFNAR	Detrimental	[20]
Mycobacterium tuberculosis	Early phase: cGAS, STING, TBK1, IRF3 Late phase: RIG-I, MAVS, TBK1, IRF7	• *In vitro,* IFN-β had anti-microbial activity via induction of nitric oxide production • Bacteria inhibit autocrine type I IFN signaling via reduced phosphorylation of JAK1 and TYK2, and subsequently STAT1 and STAT2 • Inhibition of IL-1β, important for clearance • Differential activation of strains, partially dependent on mitochondrial stress • IFN gene signature in active human infection	• *Ifnar*$^{-/-}$ and *Mavs*$^{-/-}$ mice have increased survival and decreased bacterial burdens • Autocrine type I IFN signaling was reduced by 50–60% in cells infected with *M. tuberculosis* compared to uninfected control • Type I IFN production was significantly reduced in cells infected with virulent mycobacterial species compared to non-virulent species	*In vivo*: Detrimental *In vitro:* Host protection	[53, 54, 90–93]

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
Neisseria gonorrhoeae	cGAS, STING, TLR4, TRIF, IRF3		• Macrophages cannot kill in absence of TLR4 or cGAS • IFN-β increased macrophage killing	*In vitro:* detrimental	[12]
Pseudomonas aeruginosa	TLR4, TRIF, MD2, TBK1	• Post-sepsis ARDS, IFN-β induced neutrophil recruitment and alveolar macrophage cytokine production • Increase mature dendritic cells • Type I IFN signaling increases NET release and ROS production by neutrophils and promotes tissue damage, biofilm formation and bacterial persistence	• IFN-β treated, postseptic ARDS mice, exhibited significantly reduced mortality rates, lung bacterial burdens and lung injury scores. • *Ifnar1*$^{-/-}$ and *Ifnb1*$^{-/-}$ mice showed lower bacterial burden and reduced tissue damage • polyI:C treated mice had enhanced clearance in the lung	Dual effects	[73, 74, 94]
Pseudomonas aeruginosa-viral		• Th17 and antimicrobial peptide suppression	• Neutropenia and loss of lysozyme expression	Detrimental	[64, 79]
Rickettsia parkeri	cGAS, IRF5	• *In vitro,* bacteria are sensitive to type I IFN-mediated killing and evade this signal via inflammasome mediated-antagonism of type I IFN • Induced iNOS	• *Ifnar*$^{-/-}$ *mice* display similar survival rates compared to WT • *Ifnar*$^{-/-}$/*Ifngr*$^{-/-}$ animals exhibited increased mortality rates and bacterial burdens in spleen and liver	Host protection	[31]
Salmonella enterica serovar Typhimurium	TLR3, TLR4, TRIF	• Reduced splenic monocyte numbers • Macrophages without *Ifnar* are highly resistant to necroptosis	• *Ifnar*$^{-/-}$ pregnant mice were more susceptible to systemic infection • Opposite effects seen in the oral model • *Ifnar*$^{-/-}$ improved survival in systemic model	Dual effects	[70, 71, 95, 96]
Salmonella Typhimurium-viral		• Gut microbiota dysbiosis • Inhibition of antimicrobial peptides • Decreased IL-6, CXCL2	• Increased bacterial burden	Detrimental	[97]
Staphylococcus aureus	TLR9, NOD2, MyD88, IRF1,	• USP18 in CD11c cells contributes to deleterious effects of type I IFN signaling	• *Ifnar*$^{-/-}$ mice have decreased bacteria and reduced mortality in pneumonia model	Dual effects	[14, 33, 43, 45, 46, 51, 98]

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
	IRF5, cGAS, STING	by inhibiting antibacterial effect of TNF-α • Observed correlation between IFN-β induction by bacterial strains and resistance to autolysis and lysostaphin degradation *in vitro* • IFN-β induces granzyme B production in neutrophils	• Mice that received anti-IFNAR1 antibody exhibited increased bacterial burden in lung • *Sting*$^{-/-}$ mice improved clearance in cutaneous model		
Staphylococcus aureus-viral		• Th17 suppression	• Increased bacterial burden	Detrimental	[47, 79]
Streptococcus agalactiae	cGAS, STING	• Produces CdnP that hydrolyzes cyclic-di-AMP	• Increased bacteremia and mortality • Reduced macrophage IFN-γ, NO, TNF • Increased killing with strain inactivated for *cdnP*	Host protection	[30, 99]
Streptococcus pneumoniae	STING, TBK1, IRF3	• Increased junction proteins in airway, downregulation of pneumococcal uptake receptor • Prevention of alveolar epithelial cell death • Increased neutrophil and macrophage ROS and NOS	• *Ifnar*$^{-/-}$ mice have increased nasal colonization • Increased dissemination from lung in *Ifnar*$^{-/-}$ mice	Host protection	[29, 58–60]
S. pneumoniae-viral		• Influenza inhibits CXCL1 and CXCL2 • IL27-mediated suppression of Th17 • CCL2 inhibition • IL-1β inhibition and GM-CSF release	• Reduced neutrophil recruitment and function • Impaired macrophage recruitment • Increased bacteria	Detrimental	[43, 61–68]
Streptococcus pyogenes	STING, TBK1, MyD88, IRF3, IRF5	• The bacterial DNAse Sda1 blunts TLR-9-mediated type I IFN signaling.	• Increased mortality in *Ifnar*$^{-/-}$ mice and exacerbated levels of IL-1β increasing tissue damage • Suppressed excessive neutrophil recruitment • Mice infected with Δ*sda* mutant exhibited higher type I IFN levels, reduced	Host protection	[15, 28, 36]

Bacterium	Known IFN signaling receptors	Mechanism	Outcome	Impact of type I IFN signaling[1]	Reference
			bacterial numbers and skin lesions		
Yersinia enterocolitica	TLR4, TRIF	• Sequential activation of macrophage induced IFN-β and NK-induced IFN-γ leading to enhanced bactericidal activity of macrophages	• *Trif*$^{-/-}$ impaired macrophage phagocytosis, increased bacterial dissemination and mortality	Host protection	[100]
Yersinia pestis	TLR7		• *Ifnar*$^{-/-}$ and *Tlr7*$^{-/-}$ mice have less bacteria and more neutrophils, systemic infection • *Tlr7*$^{-/-}$ mice, impaired bacterial clearance, pneumonia model	Dual effects	[101, 102]

Abbreviations: ARDS: acute respiratory distress syndrome, c-di-GMP: cyclic dimeric guanosine monophosphate, STING: stimulator of interferon genes, NTHi: nontypeable *Hemophilus influenzae*, sRNAs: noncoding small RNAs. RIG-I: retinoic acid inducible gene I, RBP: RNA-Binding protein, ROS: reactive oxygen species, iNOS-inducible nitric oxide species

[1]Impact is based on *in vivo* data unless otherwise stated