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The Roles of Type I Interferon in Bacterial Infection

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Abstract

Type I interferons (IFNs) are pleiotropic cytokines well recognized for their role in the induction of a potent anti-viral gene program essential for host defense against viruses. They also modulate innate and adaptive immune responses. However, the role of type I IFNs in host defense against bacterial infections is enigmatic. Depending on the bacterium, they exert seemingly opposite and capricious functions. In this review we summarize the effect of type I IFNs on specific bacterial infections and highlight the effector mechanisms regulated by type I IFNs in an attempt to elucidate new avenues to understanding their role.

Introduction

The innate immune system is the first line of defense against invading bacteria. Germ line encoded pattern recognition receptors (PRRs) bind bacterial components and initiate an antibacterial inflammatory gene program that promotes immune cell recruitment and directs antibacterial activities. Engagement of select PRRs also leads to the induction of what is classically considered an antiviral gene program. The role of these antiviral genes in the context of bacterial infections is unclear.

Antiviral gene expression is directed by type I interferons (IFNs), a group of small, inducible cytokines that were discovered to ‘interfere’ with the ability of a virus to successfully replicate (Isaacs and Lindenmann, 1957). Type I IFNs are one of three families of IFNs. They include IFNβ, IFNω, IFNκ, IFNε, IFNζ, IFNδ, IFNτ, and 14 IFNα subtypes. Among them, IFNβ and the IFNαs are the most abundant and well-studied, thus all subsequent reference to type I IFNs herein will mainly refer to these two types. Type II IFN is composed of single IFNγ, while type III IFN includes IFNλ1 (IL-29), IFNλ2 (IL-28A), IFNλ3 (IL-28B), and IFNλ4. Unlike type II and type III IFNs, type I IFNs are broadly expressed. They signal through the heterodimeric, interferon α/β receptor (IFNAR) and induce over 300 interferon stimulated genes (ISGs). These ISGs directly inhibit key steps of the viral life cycle (Yan and Chen, 2012), stimulate host cell death, activate innate immune cells and promote the development of the adaptive immune response (Crouse et al., 2015).

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Although early investigations focused on the antiviral properties of type I IFNs, several groups studying the intracellular bacteria *Chlamydia* observed that type I IFNs were induced by the bacterium (Sueltenfuss and Pollard, 1963) and that, in turn, they restricted bacterial growth (de la Maza et al., 1985). Much later, studies with another intracellular bacteria, *Listeria monocytogenes* (*L. monocytogenes*), substantiated a functional role for type I IFNs in directing the outcome of bacterial infections. Using mice deficient in IFNAR signaling, three groups revealed type I IFNs enhanced the susceptibility of mice to *Listeria* infection. Taken together, these seminal studies illustrated that type I IFN signaling plays a decisive role in *Listeria* infection by: (i) Reducing the efficiency of bacterial clearance; (ii) Decreasing the abundance of proinflammatory myeloid cells; (iii) Promoting the expression of proapoptotic genes; and (iv) Enhancing T cell sensitivity to apoptotic cell death (Auerbuch et al., 2004; Carrero et al., 2004; O'Connell et al., 2004).

These striking results encouraged further investigation into how type I IFNs modulated the outcome of other bacterial infections. Studies conducted for over more than a decade have revealed a paradoxical role for type I IFNs. They play an adverse role in certain bacterial infections, while in others they are critical for host defense. In this review we will focus on how type I IFNs function to direct disparate outcomes in a spectrum of bacterial infections.

Pathways of recognition and response

Expression of type I IFNs is driven by the interferon regulatory factor (IRF) family of transcription factors, namely IRF3 and IRF7. In most cells IRF3 is the dominant transcription factor during early type I IFN expression. Later, IRF7, which is also an ISG, is expressed and it amplifies type I IFN transcription (Honda et al., 2006). In specific cell types, however, other IRFs direct early expression of type I IFNs. For example, in plasmacytoid dendritic cells (pDCs) constitutive expression of IRF7 makes it the preferred IRF (Honda et al., 2006; Prakash et al., 2005). Interestingly, IRF5 appears to play a more dominant role in the induction of type I IFNs in response to bacterial pathogens (Bergstrom et al., 2015; Castiglia et al., 2016; Gratz et al., 2011; Pandey et al., 2009; Parker et al., 2014), and to a lesser extent against viruses (Lazear et al., 2013). Following PRR stimulation, IRFs are activated in a phosphorylation dependent manner. PRR ligation recruits a signaling adapter molecule which further recruits and activates the IRF kinases TBK1, IKKε, IRAK, IKKα. There are five classes of PRRs that detect bacterial components to activate IRFs. Toll like receptors (TLRs) are membrane bound PRRs, while RIG-I like receptors (RLRs), nucleotide-binding and oligomerizing domain (NOD) like receptors (NLRs), DNA sensors, and AIM-like receptors (ALRs) are found in the cytoplasm (Figure 1).

TLRs are a family of 14 transmembrane receptors that are anchored in the cytoplasmic and endosomal membranes. Ligation of TLRs predominately induces proinflammatory and antibacterial genes, however a subset of TLRs also induce the expression of type I IFNs. Initially located at the plasma membrane, TLR4, and to a much lesser extent TLR2, induce type I IFNs following endocytosis, by ligating components derived from the bacterial cell surface (Barbalat et al., 2009; Kagan et al., 2008). In immune cells, such as dendritic cells (DCs), endosomal membrane anchored TLR9 is activated by bacterial DNA, whereas single stranded RNA is sensed by TLR7 (Mancuso et al., 2009), TLR8 (Eigenbrod et al., 2015),

and TLR13 (Castiglia et al., 2016) to activate type I IFN expression. All TLRs, except TLR3, activate the downstream signaling adapter, MyD88. TLR4, however, activates both MyD88 and TRIF, but induces type I IFNs only through TRIF dependent signaling (Kawai and Akira, 2011).

In the cytoplasm, RNA is recognized by the RLRs, RIG-I and MDA-5. Ligand binding promotes association with the mitochondrial signaling adapter MAVS/Cardif/IPS/VISA (Kawai and Akira, 2011). Peptides derived from the bacterial cell wall elicit type I IFNs by engaging the NLRs, NOD1 (Watanabe et al., 2010) and NOD2; which in turn recruit the signaling adapter RIP2 (Pandey et al., 2009). Finally, DNA sensing is primarily carried out by cyclic GMP-AMP synthase (cGAS), an enzyme that has been recognized for its critical role in the catalyzing the formation of cyclic-GMP-AMP (cGAMP) (Sun et al., 2013). Other DNA sensors include the DExD/H box helicase, DDX41 which binds cyclic-di-GMP and cyclic-di-AMP, secondary metabolites unique to bacteria (Parvatiyar et al., 2012), and IFI16 (murine, IFI204), an ALR which binds double stranded DNA (Unterholzner et al., 2010). The adapter for the DNA sensors, as well as for cGAMP, is the Stimulator of Interferon Genes (STING), a transmembrane protein that resides in the endoplasmic reticulum (Ishikawa and Barber, 2008).

Unlike bacteria, viruses parasitize the host translation machinery to replicate and, as a consequence, the major pathways of recognition leading to type I IFNs are initiated by cytosolic PRRs. RLRs are engaged by viral RNAs, while viral DNA relies on STING dependent cGAS (Sun et al., 2013) and IFI16 (Unterholzner et al., 2010). Distinguishing viral and host nucleic acids is predicated on the detection of nucleotide sequence motifs and secondary structure formations unique to viruses (Kell et al., 2015; Sanchez et al., 2008). In the endosome, viral nucleic acids stimulate TLR3, TLR7, TLR8, and TLR9. TLR3 detects viral double stranded RNA, and like TLR4, signals through the TRIF signaling adapter. Lastly, contributing to a lesser extent, TLR2 and TLR4 ligation of viral proteins also triggers type I IFN induction (Kawai and Akira, 2011).

All type I IFNs signal in an autocrine and paracrine fashion through IFNAR, the heterodimeric transmembrane receptor composed of IFNAR1 and IFNAR2. Once crosslinked, the cytoplasmic tails of the IFNAR1/2 heterodimer activate Janus kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2), which in turn phosphorylate members of the STAT family allowing them to dimerize and translocate to the nucleus. Formation of different transcription factor complexes is determined, in part, by the abundance and type of STAT produced by the cell (Miyagi et al., 2007), but also by positive and negative regulators (Ivashkiv and Donlin, 2014). Most cells express STAT1, STAT2 and IRF9, the canonical type I IFN transcription factors. STAT1/2 heterodimers recruit IRF9 to form the interferon stimulated gene factor 3 (ISGF3) complex. This complex binds to IFN-stimulated response elements (ISRE) located in the promoters of antiviral genes. In addition, both type I and type II IFNs can activate STAT1 homodimers, which bind γ-activated sequences that lead to the transcription of genes such as IRF1. STAT independent pathways are also activated by type I IFN and they contribute to the induction and expression of ISGs, reviewed elsewhere (Platanias, 2005) (Figure 2). Taken together, type I IFNs induce a diverse set of ISGs that

extend beyond antiviral genes to include genes involved in modulating cellular activation and death pathways.

Disparate roles of type I IFNs during bacterial infection

How type I IFNs direct the outcome of bacterial infections hinges on many factors including, but not limited to, the bacterial replication strategy and virulence factors, as well as the route and site of the infection. These factors influence which type of host cell is activated, the magnitude of induction, the timing, and the duration of the response. Here we will present a vignette of different bacterial infections that, from the host perspective, are either negatively or positively affected by type I IFNs (also see Table 1).

Type I IFN exacerbates bacterial infections

Widely used to study bacterial pathogenesis, *Listeria*, in humans, causes meningitis and sepsis in immunocompromised individuals and fetal infections in pregnant women. Infection by *Listeria* induces a strong type I IFN response that promotes host susceptibility, as deficiency in either IFNAR1 or IRF3 protects mice from *Listeria* infection (O'Connell et al., 2005). Listeriolysin O (LLO), a cytolysin secreted by *Listeria* to disrupt the integrity of the vacuole, allows the bacteria to escape into the cytoplasm. Escape is critical for bacterial replication, and it also exposes bacterial DNA to detection by cGAS, and to a lesser extent by IFI16 (Hansen et al., 2014) and bacterial RNA to RIG-I (Abdullah et al., 2012). Activation of these cytoplasmic sensors leads to type I IFN dependent induction of the proapoptotic genes such as DAXX (DAP6) and TRAIL, that promote macrophage (O'Connell et al., 2004) and lymphocyte (Carrero et al., 2004) apoptosis; ultimately promoting dissemination and proliferation of the bacteria. Consequently, *Listeria* is cleared more rapidly in the absence of IFNAR signaling (Auerbuch et al., 2004; Carrero et al., 2004; O'Connell et al., 2004). In addition, type I IFNs have been observed to attenuate expression of the IFNγ receptor (IFNRG1) (Rayamajhi et al., 2010), likely through the recruitment of gene silencing proteins by the early growth response transcription factor 3 (Erg3) in complex with NGFI-A binding protein 1 (Nab1), culminating in decreased IFNRG1 transcription (Kearney et al., 2013). Finally, type I IFNs inhibit the expression of IL-17A by γδ T cells, a type of innate immune lymphocyte, to suppress neutrophil recruitment (Henry et al., 2010).

Francisella tularensis, is responsible for tularemia, a highly contagious and life-threatening respiratory disease. Expression of genes in the *Francisella* pathogenicity island trigger the escape of the bacteria from the phagosome to the cytoplasm, and once in the cytoplasm the bacteria induce type I IFN through a cGAS- and IFI204-STING-IRF3 dependent pathways (Henry et al., 2007; Storek et al., 2015). Type I IFNs suppress the innate antibacterial response by inhibiting expression of IL-17A by γδ T cells. As in *Listeria* infections, elevated expression of IL-17A in IFNAR1 deficient mice enhances splenic neutrophil recruitment and is correlated with both improved bacterial clearance and survival (Henry et al., 2010). Interestingly, though deficiency in cGAS, STING, IFNAR1 or IRF3 renders mice resistant to infection by *Francisella* (Henry et al., 2007; Storek et al., 2015), deletion of AIM2, an ALR induced by type I IFNs, is detrimental to host defense (Jones et al., 2010; Rathinam et al., 2010). Yet, while type I IFNs potentiate AIM2 expression and indirectly its

antibacterial activity, simultaneously AIM2 suppresses induction of type I IFNs by negatively regulating the cGAS-STING-IRF3 pathway (Corrales et al., 2016).

The Gram negative, intracellular bacterium, *Salmonella enterica* serovar Typhimurium causes acute gastroenteritis in humans, and, if uncontrolled, may disseminate and cause a more life-threatening disease. RIGI detection of *Salmonella* mRNA induces type I IFNs in non-phagocytic cells, whereas recognition of *Salmonella* LPS by TLR4 drives type I IFN induction in phagocytic cells (Schmolke et al., 2014). During systemic infection, IFNAR1 deficient mice accumulate less bacteria in the spleen and liver, and have markedly survival compared to wild type (WT) mice. Enhanced survival and defense noted in IFNAR1 and IFNβ deficient mice is associated with increased antibacterial proinflammatory responses (Perkins et al., 2015). Moreover, induction of type I IFNs during *Salmonella* infection promotes macrophage death by necroptosis (Henry et al., 2007; Robinson et al., 2012). Necroptosis is a type programmed cell death, that unlike TRAIL mediated apoptosis, proceeds in a caspase independent manner. Here IFNβ, not IFNα, promotes necroptosis (Robinson et al., 2012); illustrating an exclusive effector function for IFNβ.

Infections caused by the Gram positive, extracellular bacterium *Staphylococcus aureus* (*S. aureus*) are also exacerbated by type I IFNs. *S. aureus* is a common etiological agent of local skin infections, but it is also a primary cause of severe lung pneumonia and bloodstream infections. Type I IFNs are induced by protein A, a virulence factor, (Martin et al., 2009) and via TLR9-IRF1 or NOD2-IRF5 (Parker et al., 2014). In vivo, IFNAR1 deficiency confers resistance to lethal pneumonia. Survival is associated with increased $CD11c^+$ DCs in the lungs and reduced TNFα in the bronchoalveolar lavage fluid (Martin et al., 2009). Interestingly, while IFNβ expression is inducible in cultured lung epithelial cells (Martin et al., 2009; Parker et al., 2014), transcript for IFNα is not detected (Martin et al., 2009). This suggests strain specific effects, as well as host specific capacities as differences between hematopoietic and non-hematopoietic cells are also noted (Parker et al., 2014).

Type I IFNs protect against bacterial infections

Legionella pneumophilia is responsible for Legionnaires' disease, a severe lung pneumonia. Its type IV secretion system, Dot/Icm, is required for entry into and replication within the macrophage cytosol (Lippmann et al., 2011). It has been reported that the host detects *Legionella* in the cytosol by a STING dependent pathway (Lippmann et al., 2011), leading to IRF3 dependent type I IFN expression (Plumlee et al., 2009). While in a mouse model of pulmonary *Legionella* infection, IFNAR2 deficient mice did not reveal a role for type I IFNs (Ang et al., 2010), proliferation of *Legionella* in macrophages is inhibited by type I IFNs (Lippmann et al., 2011; Plumlee et al., 2009). Moreover, type I IFN, along with type II IFN, promote host defense likely through induction of cell intrinsic ISGs such as immune-responsive gene 1 (IRG1) (Naujoks et al., 2016).

Type I IFNs also fortify the host against infections caused by Gram positive Streptococci. *Streptococcus pyogenes*, the group A streptococcus, causes superficial and deep tissue infections that can develop into necrotizing fasciitis. Both group A streptococci and group B streptococci (*Streptococcus agalactiae*) activate the STING-TBK1-IRF3 pathway in macrophages (Gratz et al., 2011); while in cDCs, TLR7-Myd88-IRF5 and to a lesser extent

IRF1, both play a role (Castiglia et al., 2016; Gratz et al., 2011; Mancuso et al., 2009). In a mouse model of *S. pyogenes* cellulitis, survival of WT mice is significantly greater than IFNAR1 deficient mice (Gratz et al., 2011). Enhanced survival is linked to the anti-inflammatory properties conferred by type I IFN signaling (Castiglia et al., 2016). Likewise, systemic infection of adult or neonatal mice with group B streptococci also requires IFNAR signaling to protect the host; and while IFNα4 was induced in WT group B streptococci infected mice, IFNβ plays a dominant role in conferring protection as IFNβ KO mice are more susceptible than WT mice (Mancuso et al., 2007).

Streptococcus pneumoniae causes life-threatening pneumonia. Host detection of *S. pneumoniae* is facilitated by the expression of autolysin and pneumolysin, two virulence factors that cooperate to introduce bacterial DNA into the cytosol. In epithelial cells, bacterial DNA activates STING to induce IFNβ (Parker et al., 2011). In two independent studies it was observed that in the absence of IFNAR1, even though immune cell recruitment was enhanced, more bacteria were found in the lungs (Parker et al., 2011) or escaping from the lungs into the bloodstream (LeMessurier et al., 2013). Exogenous IFNβ decreases transmigration into the bloodstream by promoting the expression of genes encoding tight junction proteins and, simultaneously, downregulating the expression of platelet activating receptor, the receptor by which the bacteria enter the cell (LeMessurier et al., 2013). Moreover, treatment of mice with an IFNα expressing adenoviral vector, led to decreased immunopathology and enhanced antibacterial activity in macrophages, resulting in an overall increase in survival (Damjanovic et al., 2014).

The Gram negative bacterium, *Helicobacter pylori* is the etiological agent of acute gastric infections, as well as chronic gastric ulcers and cancer. In non-hematopoietic cells, NOD1 sensing of a peptide derived from *H. pylori* peptidoglycan induces type I IFN expression in an IRF7 dependent manner. IFNAR1 or NOD1 deficient mice fail to restrict *H. pylori* proliferation. Concurrently, a significant reduction in expression of the chemotactic ISG, Cxcl10, suggests type I IFN induced Cxcl10 is critical for the control of *H. pylori* proliferation (Watanabe et al., 2010); and it is further supported by elevated Cxcl10 levels observed in vaccinated mice (Flach et al., 2012) and patients that are asymptomatic carriers (Jafarzadeh et al., 2013).

Type I IFN induced Cxcl10 also promotes host resistance during polymicrobial sepsis. Using a model of cecal ligation and puncture (CLP) in mice, investigators found the absence of IFNAR signaling led to increased mortality. Although the chemokine Cxcl1 was elevated in IFNAR1 deficient mice, decreased levels Cxcl10, were also noted. Administration of Cxcl10 to IFNAR1 deficient mice, restored hematopoietic cell recruitment and antibacterial activity which led to enhanced bacterial clearance and host resistance to polymicrobial sepsis (Kelly-Scumpia et al., 2010).

Type I IFNs are detrimental to secondary bacterial infections

High mortality rates associated with seasonal and pandemic influenza are driven by the development of secondary bacterial pneumonia caused by *S. pneumoniae* or *S. aureus*, and, at a lower incidence, other bacteria (McCullers, 2014). This enhanced susceptibility is transient, limited by the initiation and the duration of type I IFN expression. As discussed,

type I IFNs promote host defense against *S. pneumoniae* infection, yet preceding expression of type I IFNs has detrimental effects. First, prior induction of type I IFNs attenuates the expression of neutrophil chemokines (Shahangian et al., 2009). Neutrophil recruitment is restored by deletion of either IFNAR1 (Shahangian et al., 2009) or the type I IFN responsive methyltransferase, Setdb2, which culminates in bacterial clearance (Schliehe et al., 2015; Shahangian et al., 2009). Second, prior expression of type I IFNs suppresses production of IL-17 by T cells (Cao et al., 2014; Kudva et al., 2011). In the absence of IL-17, diminished secretion of antibacterial peptides lipocalin 2 and BPIFA1 is associated with increased bacterial growth (Lee et al., 2015). Lastly, the duration of type I IFN expression dictates sensitivity to secondary bacterial infection, as superinfection do not develop if initiated 14 days after influenza infection (Lee et al., 2015).

Type I IFN promotes chronic bacterial infections

Mycobacteria comprises a group of highly contagious pathogens that establish chronic infections of the lungs (*M. tuberculosis*) or skin (*M. leprae*). The host relies on cGAS sensing of bacterial DNA (Collins et al., 2015; Wassermann et al., 2015; Watson et al., 2015), as well as NOD2 sensing of cell wall associated muramyl dipeptides (Pandey et al., 2009) to detect *M. tuberculosis*. Virulent strains provoke higher IFNα expression in the lungs compared to less virulent strains. IFNAR signaling suppresses IL-12 and IFNγ, thereby arresting the development of the antibacterial adaptive T cell (Th1) response and reducing host survival (Manca et al., 2001; Mayer-Barber et al., 2014). Similar results have been reported in human patients. Examination of the gene expression pattern of whole blood revealed a distinct gene expression signature defined by type I IFN and downstream ISGs in patients with active tuberculosis, that was not present in patients with latent tuberculosis (Berry et al., 2010). Likewise, ex vivo studies with *M. leprae*, demonstrate IFNβ induced anti-inflammatory cytokines drive the progression to chronic leprosy by inhibiting the development of Th1 immunity (Teles et al., 2013, 2015).

Disparate effector mechanisms of type I IFNs

Given their pleotropic nature, type I IFNs have the capacity to influence multiple host defense mechanisms. Productive host response to acute bacterial infection requires secretion of proinflammatory cytokines and chemokines that recruit and activate innate immune cells. Herein, we will explore the effect of type I IFN on key antibacterial mechanisms.

Suppression of Type II IFN responses by type I IFN

Like type I IFN, type II IFN is expressed during microbial infections and it exerts antiviral and immunomodulatory activities. Type II IFN, solely consisting of IFNγ, is induced by IL-12 and IL-18, with natural killer (NK) and T cells being the dominant producers. Type I and type II IFNs activate distinct and overlapping gene programs by signaling through their respective canonical JAK-STAT pathways. IFNγ preferentially induces phosphorylation and dimerization of STAT1 to promote expression of the γ-activated sequence-dependent genes. Type I IFNs favor the assembly of the ISGF3 transcription factor complex which drives ISRE controlled genes, but also activate STAT1 dimerization. (Manca et al., 2001). Intriguingly, NK cells express high basal levels of STAT4, which enables rapid induction of

IFNγ following type I IFN stimulation. However, in the absence of IL-12 signaling, IFNγ expression is transient as STAT4 is displaced by STAT1, thus negatively regulating the production of type II IFN (Mack et al., 2011; Miyagi et al., 2007). IFNγ is critical for defense against many bacterial pathogens (Harty and Bevan, 1995; Lippmann et al., 2011; Teles et al., 2013). Despite numerous studies, it is still not clear how type I and type II IFN play opposite roles in host defense against certain bacteria and which downstream effector genes are responsible for such differences. In addition to regulating downstream effector genes, type I IFNs also suppress IFNγ expression by attenuating the transcription of its inducer, IL-12 (Berry et al., 2010; Carrero et al., 2004; Manca et al., 2001) and its receptor, IFNRG1 (Kearney et al., 2013; Rayamajhi et al., 2010) (Figure 3). Insufficient IFNγ expression can have drastic consequences. *M. leprae* infections that manifest as "self-healing" leprosy provoke an IFNγ driven Th1 response, while a type I IFN signature dominates during chronic, disseminated infections (Liu et al., 2012; Teles et al., 2013). Further, hypervirulent strains of *M. tuberculosis* promote the expression of type I IFNs, and concurrently attenuate IL-12 and IFNγ (Manca et al., 2001), further reinforcing that induction of type I IFNs is favorable for bacterial pathogenesis.

Anti-inflammatory responses by type I IFN

Productive host antibacterial response relies on the coordination and balance of proinflammatory molecules, to clear bacteria, and anti-inflammatory molecules to limit tissue damage. Type I IFNs propagate the anti-inflammatory response by upregulating the expression of IL-10 and IL-27. IL-10 is a type I IFN inducible immunosuppressive and anti-inflammatory cytokine. Induction of IL-10 has been described to occur through both IL-27-dependent (Iyer et al., 2010) and -independent mechanisms (McNab et al., 2014). IL-10 inhibits the acute phase cytokines, TNFα and IL-1 (Bogdans et al., 1992), thereby attenuating expression of adhesion molecules and chemokines required for leukocyte recruitment (Yarilina et al., 2008). Downregulation of the proinflammatory response is essential to protect against tissue damage induced mortality as observed during *Escherichia coli* sepsis (Sewnath et al., 2001), but it is detrimental to the clearance of other bacterial infections (Auerbuch et al., 2004; Di Paolo et al., 2015; Mayer-Barber et al., 2014; McNab et al., 2014). Similarly, IL-27 protects against tissue damage during acute influenza infection (Liu et al., 2014), but compromises the host response to both secondary (Cao et al., 2014; Robinson et al., 2015) and chronic bacterial infections (Teles et al., 2015). The delicate balance between proinflammatory and anti-inflammatory responses is further illustrated by chemokine recruitment. Type I IFN mediated suppression of proinflammatory chemokines, Cxcl1 and Cxcl2, reduces myeloid recruitment and may protect against excessive tissue damage (Ellis et al., 2015), but may also compromise myeloid mediated bacterial clearance (Perkins et al., 2015; Schliehe et al., 2015; Shahangian et al., 2009) (Figure 3).

Inhibition of antimicrobial peptides by type I IFN

One consequence of the anti-inflammatory action mediated by type I IFNs is the suppression of several antimicrobial peptides (Figure 3). Antimicrobial peptides exert non-enzymatic activities that inhibit microbial functions by directly inhibiting the pathogen or host specific targets. Cathelicidin (CAMP) and beta-defensin 2 (DEFB4) are two antimicrobial peptides induced by IL-1β and cytochrome P450 family 27 subfamily B member 1 (CYP27B1), an

enzyme in the vitamin D pathway. They are indirectly downregulated by IFNβ-IL-10 (Teles et al., 2013), through the induction of miR-21, an ISG that inhibits the translation of IL1B and CYP27B1 transcripts (Liu et al., 2012). Type I IFNs also negatively regulate the expression antimicrobial peptides induced by IL-22, such as lipocalin 2 and BPIFA1 (Lee et al., 2015). Downregulation of these antimicrobial peptides also occurs indirectly, as type I IFNs target IL-23, the cytokine that induces IL-22 (Kudva et al., 2011).

Regulation of metabolic pathways by type I IFN

There is a growing appreciation for the role of cellular metabolism in the coordination of immune response. TLR signaling and microbial infections have been observed to redirect the metabolic strategy of macrophage and dendritic cells. Type I IFNs downregulate sterol biosynthesis triggering a shift away from de novo cholesterol synthesis (Blanc et al., 2011) and towards cholesterol import. This shift, by an unknown mechanism, drives spontaneous STING-IRF3 dependent IFNβ expression (York et al., 2015). Type I IFNs also promote key antiviral responses such as upregulation of cholesterol-25 hydroxylase (Ch25h), an ISG that inhibits viral entry (Liu et al., 2013). During *Listeria* infection, however, Ch25h expression increases the susceptibility of mice to bacterial infection by negatively regulating capase-1 and IL-1β maturation (Reboldi et al., 2014). Other metabolic pathways are also influenced by type I IFNs. Prostaglandin E2 (PGE2), an arachidonic acid derived lipid mediator that promotes host defense against *Mycobacterium*, is negatively regulated by type I IFN suppression of IL-1β, but, at the same time, negatively regulates type I IFN expression (Mayer-Barber et al., 2014). Conversely, type I IFNs induce IRG1, an ISG that generates, itaconic acid, an antimicrobial metabolite that effectively restricts the growth of intracellular bacteria (Naujoks et al., 2016) (Figure 3).

Regulation of tissue integrity by type I IFN

Tissue integrity is maintained by the expression of tight junction proteins such as cadherins, claudins, and the peripheral scaffolding proteins such as occludins. The arrangement and density of these proteins determines the permeability of the epithelial barrier and act to confine local tissue infections (LeMessurier et al., 2013; Long et al., 2014). Type I IFNs, augmented by RNase-L, an ISG that mediates induction of type I IFNS, promote the expression of tight junction proteins (LeMessurier et al., 2013). RNase-L deficiency reduces IFNβ expression and, subsequently, diminishes tissue integrity (Long et al., 2013). This promotes host susceptibility to opportunistic (Long et al., 2013) and acquired bacterial infections (Li et al., 2008). In addition, group 2 innate lymphoid cells (ILC2s) have recently emerged as the key tissue resident cell type orchestrating tissue repair (Monticelli et al., 2011). ILC2s foster tissue integrity by upregulating expression of amphiregulin, an epithelial growth factor that promotes sustained signaling. Type I IFNs attenuate the expression of amphiregulin and stunt ILC2 proliferation (Monticelli et al., 2011) (Figure 3). This has been observed to confer long lasting deficiencies to the integrity of the mesenteric adipose tissue and the mesenteric lymph nodes (Fonseca et al., 2015).

Conclusion and Future Outlook

Type I IFNs direct a potent antiviral response through the induction a diverse set of ISGs. Some ISGs have evolved to exert broad antiviral activities, while others act to specifically target different classes of viruses. Over the past few decades, numerous studies have uncovered a pivotal role for type I IFNs in dictating host response to bacterial infections. Unlike their role in viral infections, type I IFNs play an unpredictable role in bacterial infections. Their pleiotropic nature leads not only to the induction of antiviral genes, but also to genes that modulate innate and adaptive immune responses. While some of the immunomodulatory genes are beneficial to host defense against bacterial infections, many are detrimental to the formation of an antibacterial inflammatory response.

Given the disparate role of type I IFNs among different bacterial infections, it is clear that the field will benefit from more comprehensive analyses of the type I IFN response. Crucially, the current state of our knowledge does not allow us to determine whether type I IFNs will be beneficial or detrimental based on the biology of the pathogen. Studies of the role of type I IFNs during viral infections have shown that a short, strong type I IFN response is generally beneficial to clearing the infection. However, sustained expression seems to be detrimental to the clearance of persistent viral infections (Wilson et al., 2013). Recently, it has been demonstrated that IFNβ and IFNα exert discreet functions during chronic viral infection; in early stages IFNβ promotes disorganization of the spleen, whereas IFNα limits viral dissemination (Ng et al., 2015). Thus, it is becoming increasingly apparent that type I IFNs are not redundant, but that they have overlapping and distinct functions.

Furthermore, functional differences may result not only from preferential expression of IFNα or IFNβ by different cell types (Honda et al., 2006; Prakash et al., 2005) or from their difference in affinity for IFNAR (Weerd et al., 2013), but also from the route of infection. *Listeria* administered by oral gavage enhances host resistance, whereas infection initiated by intraperitoneal injection leads to host susceptibility (Kernbauer et al., 2013). Both routes elicit type I IFN expression by inflammatory myeloid cells, however differences in hepatic colonization appear to shape the response (Kernbauer et al., 2013; Stockinger et al., 2009). Few have undertaken comprehensive studies of route even though it has been shown to play a role in both host response and pathogen biology (Fitzgeorge et al., 1983; Kernbauer et al., 2013; Martins et al., 2013).

Extending these observations to the role of type I IFNs on the outcome of bacterial infections, we suggest that more detailed examinations of the composition, magnitude, and duration of type I IFN expression will complement mechanistic investigations into the effector functions of specific type I IFNs and lead to more precise management of infections.

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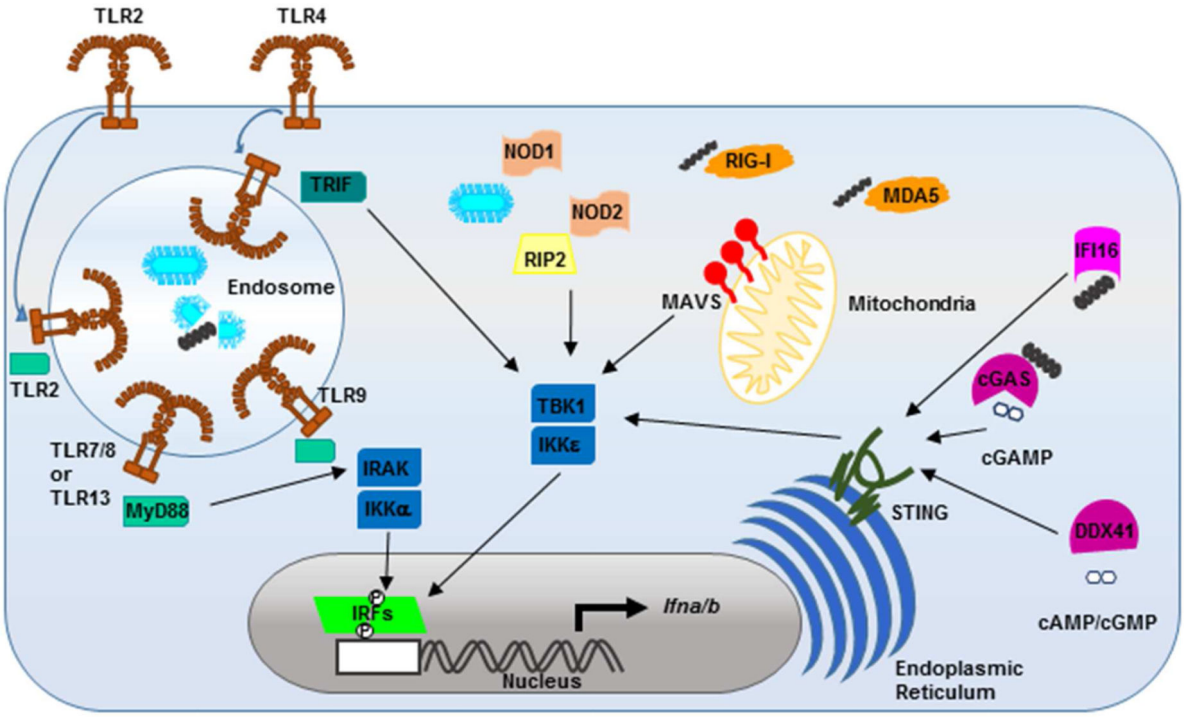

Figure 1. Signaling pathways leading to the induction of type I IFNs

Recognition of components derived from bacteria occurs at the membrane and in the cytosol. Ligand binding of TLRs recruits the signaling adapter molecule MyD88 to TLR2/7/8/9/13 leading to activation of IRF kinases IRAK and IKKα. TLR4 recruits the adaptor TRIF and together they activate the IRF kinases TBK1 and IKKε. Engagement of cytosolic sensors leads to the recruitment of the signaling adapter molecule MAVS to the RLRs (RIG-I and MDA-5), STING to the DNA sensors (cGAS, DDX41 and IFI16), and RIP2 to the NLRs (NOD1 and NOD2). Like TRIF, cytosolic signaling adapters all activate TBK1 and IKKε. IRF kinases activate IRFs by phosphorylation dependent dimerization, allowing them to translocate into nucleus and drive type I FN expression.

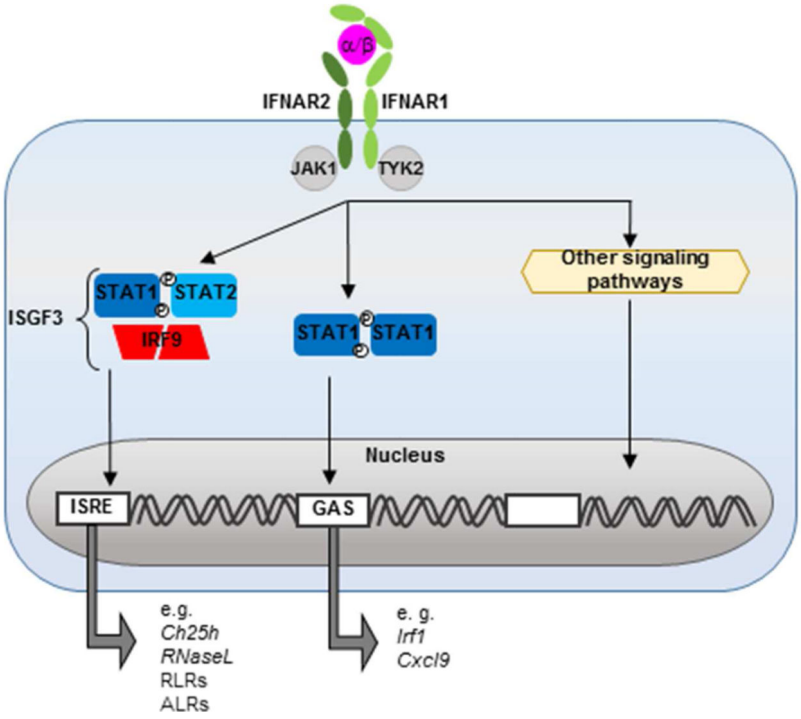

Figure 2. Type I IFNs induce ISGs expression through JAK/STAT signaling

Binding of type I IFNs to the IFNAR1-IFNAR2 heterodimer activates Janus kinases, JAK1 and TYK2, to phosphorylate STAT transcription factors. Dimerization of activated STAT1 and STAT2 further recruits IRF9 and forms the ISGF3 complex, that promotes expression of genes containing an ISRE sequence in their promoter. Homodimerization of activated STAT1, drives the expression of genes containing a γ-activated sequence (GAS) in their promoter.

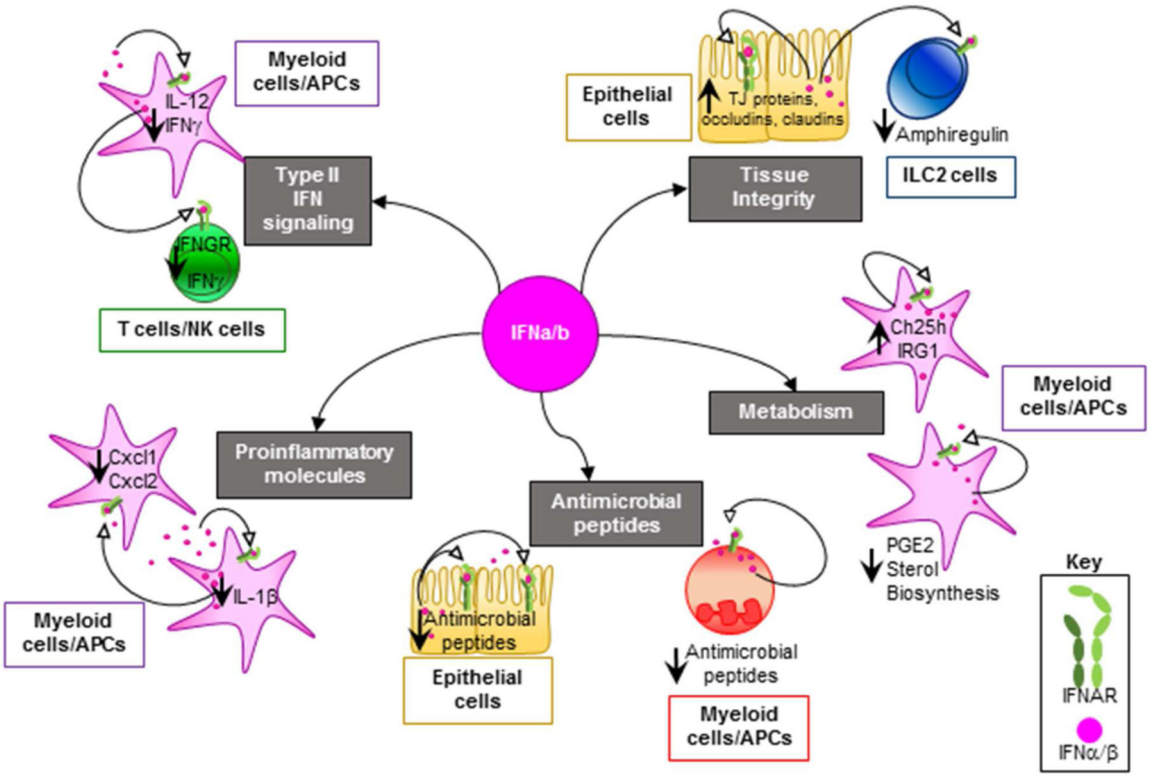

Figure 3. Effector mechanisms mediated by type I IFNs during bacterial infection

Autocrine and paracrine signaling of type I IFNs suppress type II IFN signaling, proinflammatory responses and production of antimicrobial peptides to contribute to overall detrimental host outcomes. Modulation of metabolism by type I IFNs also exerts negative effects by either suppressing sterol biosynthesis and PGE2 or by upregulating CH25H, but may also promote host defense by inducing expression of IRG1. Tissue integrity is strengthened by type I IFNs through the induction of tight junction (TJs) proteins, claudins and occludins, yet suppressive effects on ILC2s and amphiregulin are also observed. See text for details.

Table 1

Role of type I IFNs in different bacterial infections

Pathogen	Gram reaction	Location	IFNα/β signaling	Key Mechanisms	Citations
Listeria monocytogenes	(+)	Intracellular	Detrimental	Promotion of apoptosis. Suppression of type II IFN and IL-17	(Auerbuch et al., 2004; Carrero et al., 2004; Henry et al., 2010; O'Connell et al., 2004; Rayamajhi et al., 2010)
Francisella tularensis	(−)	Intracellular	Detrimental	Suppression of IL-17A	(Henry et al., 2007, 2010; Jones et al., 2010; Storek et al., 2015)
Salmonella enterica serovar Typhimurium	(−)	Intracellular	Detrimental	Promotion of necroptosis Suppression of innate cell recruitment and proinflammatory response.	(Perkins et al., 2015; Robinson et al., 2012; Schmolke et al., 2014)
Staphylococcus aureus	(+)	Extracellular	Detrimental	Suppression of innate cell recruitment and proinflammatory response.	(Martin et al., 2009; Parker et al., 2014)
Legionella pneumophilia	(−)	Intracellular	Protective	Promotion of IRG1 (itaconic acid)	(Lippmann et al., 2011; Naujoks et al., 2016; Plumlee et al., 2009)
Streptococcus pyogenes	(+)	Extracellular	Protective	Suppression of excessive proinflammatory response.	(Castiglia et al., 2016; Gratz et al., 2011; Mancuso et al., 2007, 2009)
Streptococcus pneumoniae	(+)	Extracellular	Protective	Promotion tissue integrity.	(Damjanovic et al., 2014; LeMessurier et al., 2013; Parker et al., 2011)
Helicobacter pylori	(+)	Extracellular	Protective	Promotion of Cxcl10 mediated cell recruitment.	(Flach et al., 2012; Watanabe et al., 2010)
Polymicrobial sepsis	(+) and (−)	Extracellular	Protective	Promotion of Cxcl10 mediated cell recruitment.	(Kelly-Scumpia et al., 2010)
Post influenza bacterial pneumonia	(+) or (−)	Extracellular	Detrimental	Suppression of proinflammatory response.	(Lee et al., 2015; Shahangian et al., 2009)
Mycobacterium tuberculosis	(+)	Intracellular	Detrimental	Promotion of IL-10 anti-inflammatory response.	(Berry et al., 2010; Manca et al., 2001; Mayer-Barber et al., 2014)
Mycobacterium leprae	(+)	Intracellular	Detrimental	Promotion of IL-10, IL-27 anti-inflammatory response.	(Liu et al., 2012; Teles et al., 2013, 2015)