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Differential effects of type I and II interferons on myeloid cells and resistance to intracellular bacterial infections

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Abstract

The type I and II interferons (IFNs) play important roles in regulating immune responses during viral and bacterial infections and in the context of autoimmune and neoplastic diseases. These two IFN types bind to distinct cell surface receptors that are expressed by nearly all cells to trigger signal transduction events and elicit diverse cellular responses. In some cases, type I and II IFNs trigger similar cellular responses while in other cases the IFNs have unique or antagonistic effects on host cells. Negative regulators of IFN signaling also modulate cellular responses to the IFNs and play important roles in maintaining immunological homeostasis. In this review article, we provide an overview of how IFNs stimulate cellular responses. We discuss the disparate effects of type I and II IFNs on host resistance to certain intracellular bacterial infections and provide an overview of models that have been proposed to account for these disparate effects. Mechanisms of antagonistic cross talk between type I and II IFNs are also introduced.

Keywords

Interferon; macrophage; bacterial infection; cell signaling; interferon receptor

Introduction

Production of the type II interferon, interferon gamma (IFN γ), and expression of the IFN γ receptor (IFN γ R) play essential roles in host defense against intracellular bacterial pathogens such as *Listeria monocytogenes* (*Lm*), *Francisella tularensis* (*Ft*), *Mycobacteria tuberculosis* (*Mtb*), and *Chlamydia muridarum* (*Cm*) [1–7], which share the ability to replicate within professional phagocytes. Several lines of evidence indicate that myeloid cells such as macrophages and dendritic cells (DCs) are key targets of IFN γ during early immune responses to intracellular bacterial infections. Activated natural killer (NK) and T cells are the sources of IFN γ production. During early stages of infection, production of the cytokines interleukin (IL)-12 and IL-18 drives antigen-nonspecific IFN γ production by these lymphocyte populations [8, 9]. However, contact dependent mechanisms are also important for NK cell activation [10, 11]. Antigen-specific CD4⁺ and CD8⁺ T cells also can produce IFN γ in response to these pathogens [12–15]. The ability of myeloid and other cell types to respond to IFN γ is regulated by a variety of suppressive factors, including suppressor of cytokine signaling (SOCS), protein inhibitor of activated STAT-1 (PIAS), and interleukin 10 (IL-10). The importance of negative regulation is underscored by the fact that mice lacking expression of SOCS1 die from unchecked inflammatory responses soon after birth [16], and

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mice lacking IL-10 are prone to inflammatory bowel diseases in the context of a predisposing microbiota [17].

In contrast to the single type II IFN, there are a large number of individual type I IFNs, including ~20 IFN α proteins and a single IFN β . Each of these type I IFNs signals to host cells by binding the conserved cell surface type I IFN receptor, IFN α R. Ligation of cell surface IFN α R induces expression of numerous antiviral immune stimulated gene (ISG) products and thus protects the host from certain viral infections [18]. Consequently, IFN α treatment has emerged as a common therapy for humans with chronic hepatitis C infection. However, type I IFNs have side-effects and can negatively regulate other inflammatory or anti-microbial immune responses. Indeed, IFN β is a common therapy for individuals with relapsing-remitting multiple sclerosis. Myeloid cell expression of the receptor for type I IFNs is crucial for the therapeutic anti-inflammatory effects of IFN β in a mouse model of the inflammatory disease multiple sclerosis [19], suggesting that at least in this model the target for anti-inflammatory effects of type I IFNs is a myeloid cell. However, mice lacking responsiveness to type I IFNs in all cell types are not known to suffer from spontaneous inflammatory diseases.

Over the past decade it has become clear that responsiveness to type I IFNs also correlates dramatically with increased susceptibility to a number of intracellular bacterial infections [20], including *Lm*, *Mtb*, *Ft*, and *Cm* [21–28]. Infection with these and a variety of other bacterial pathogens induces endogenous production of type I IFNs in response to microbial stimulation of various pattern recognition receptors. Moreover, as mentioned above, type I IFNs are used therapeutically for treatment of certain human diseases. Thus, it is important to better understand how type I IFNs suppress resistance to these intracellular bacteria. Below, we review cellular responses to type I and II IFNs and provide an overview of various models that have arisen to potentially account for the suppressive effects of type I IFNs during intracellular bacterial infections. We also introduce mechanisms of antagonistic cross talk between these two IFN types.

Canonical and non-canonical responses to the type II IFN, IFN γ

IFN γ is secreted as a homodimer and acts on host cells by ligating cell surface receptors. Each IFN γ receptor is a heterodimer comprised of two type I integral membrane subunits, IFN γ R1 and IFN γ R2 [29]. Binding of an IFN γ homodimer to the cell causes the aggregation of two receptor complexes, such that there are two IFN γ R1 subunits and two IFN γ R2 subunits, as well as additional signaling components. While both subunits are required for signal transduction, the actual binding site for IFN γ is located on IFN γ R1 [29]. Fluorescence imaging shows that the IFN γ R subunits exist in a weak association prior to ligand binding [30]. When IFN γ interacts with an IFN γ R1 subunit, it induces a conformational change that permits a closer association of the IFN γ R1 and IFN γ R2 subunits [30]. These rearrangements in the receptor induce auto- and cross-phosphorylation of Janus-associated kinases (JAKs) that are constitutively associated with the receptor [31]. IFN γ R1 contains a binding motif for JAK1, and IFN γ R2 contains a binding motif for JAK2 [31]. Phosphorylation of the JAK proteins stimulates their catalytic activity and they then phosphorylate a tyrosine residue (Y₄₄₀) at the C-terminus of IFN γ R1 [31]. This phosphorylated tyrosine residue provides a docking site for the SH2 domain on the Signal Transducer and Activator of Transcription-1 (STAT-1) protein [29, 32]. Because each receptor complex contains two IFN γ R1 subunits, two STAT-1 proteins are able to bind to the receptor. JAK1 and JAK2 remain receptor-associated and phosphorylate each recruited STAT-1 protein at tyrosine residue 701 (Y₇₀₁) [29, 32]. This phosphorylation allows release of the STAT-1 monomers from the receptor and their formation of homodimers. STAT-1 homodimers translocate to the nucleus and bind Gamma-Activated Sequences (GAS) in the promoter DNA of IFN-stimulated genes

(ISGs), resulting in their increased transcription [33]. IFN γ treatment also silences the transcription of a subset of cellular genes [34, 35]. The transcriptional activity of STAT1 homodimers is also regulated by phosphorylation of serine residue 727 (S727). Multiple kinases, including Pyk2, p38, and Erk2 [36–39], may contribute to S727 phosphorylation in response to different stimuli and/or in different cell types.

Many ISGs encode proteins that function to create a more microbicidal environment within the host. One such gene encodes the inducible Nitric Oxide Synthase, NOS2 (or iNOS) [40]. NOS2 mediates generation of nitric oxide (NO), a small molecule with numerous biological effects, including direct microbicidal effects on bacteria [41]. IFN γ also increases myeloid cell expression of the NADPH oxidase, which generates reactive oxygen species (ROS) that modify the function of diverse signaling proteins and enzymes and have direct microbicidal effects [42]. A key component of NADPH oxidase is gp91^{phox}, encoded by the gene *nox2*. STAT-1 homodimers bind elements in the *nox2* promoter region to increase its transcription [42]. In addition to upregulating genes involved in microbial killing, the canonical JAK-STAT signaling pathway activated by IFN γ drives transcription of genes that enhance antigen presentation by both MHC class I (MHCI) and MHC class II (MHCII) molecules. IFN γ induces expression of genes coding for the MHCI and MHCII molecules themselves, e.g. β 2-microglobulin, H-2K and D, HLA-A,B,C, and MHC II α and β chains, as well as additional molecules that enhance loading of these molecules, such as transporters associated with antigen processing (TAP) and the class II-associated invariant chain peptide (CLIP) [32].

IFN γ stimulation can also lead to activation of less inveterate signaling pathways. Signaling molecules other than JAKs may mediate signaling following receptor ligation by directly interacting with the IFN γ R complex and/or by interaction with soluble JAK or other kinases that are released from the ligated IFN γ R complex. Phosphoinositide 3-Kinase (PI3K) functions at the plasma membrane and becomes activated in response to IFN γ stimulation. Activation of PI3K in cells responding to IFN γ occurs independent of JAK1/2 [43]. Activated PI3K can elicit multiple downstream signaling events, including activation of Protein Kinase C (PKC) isoforms PKC α , PKC δ , and PKC ϵ [44]. PKC phosphorylates the transcription factor, PU.1 [45], and this phosphorylation promotes the STAT-1 dependent induction of Fc γ R1 transcription by IFN γ [44]. Upregulation of Fc γ R1 can augment host resistance to bacterial infection by permitting increased phagocytosis of opsonized bacteria. PKC isoforms can also impact IFN γ signaling independent of STAT-1. Upregulation of the adhesion molecule ICAM1 by macrophages in response to IFN γ is augmented by PKC α activity [46], and PKC ϵ initiates signaling through the MEK1-ERK1/2 cascade [47], but in both cases STAT-1 is not required. In addition to PKC ϵ , the *raf-ras* pathway is activated in response to IFN γ and regulates ERK1/2 signaling. The serine kinase Raf1 interacts with JAK2 following IFN γ stimulation [44]. Phosphorylation of Raf1 and activation of Ras promote ERK signaling [44].

Once activated, ERK proteins target multiple transcription factors that are important for IFN γ -stimulated gene expression, including CCAAT/enhancer binding protein beta (C/EBP β) and Activating Protein-1 (AP-1) family members. MEK1/ERK1/2 activation of c-Jun, an AP-1 family member, participates in the transcription of iNOS and other ISGs [48], presumably modulating the ability of IFN γ to increase host resistance to bacterial infections. A protective role for CEBP β was more clearly established using *cebpb*^{-/-} mice [49]. Mice lacking CEBP β succumb to normally sub-lethal doses of *Lm* or *Salmonella typhimurium* between 4–6 days post-infection. This increased susceptibility correlated with increased intracellular replication of *Lm* in *cebpb*^{-/-} peritoneal macrophages. CEBP β drives transcription of several inflammatory cytokines [50], including Interferon Regulatory Factor-9 (IRF-9) [51] and antimicrobial peptides [52]. However, C/EBP β is also associated

with suppression of *c2ta* transcription in response to IFN γ [53]. Thus, while C/EBP β plays a net protective role during these bacterial infections, it may suppress some IFN γ -regulated gene expression.

The aforementioned signaling events illustrate the complex and intricate nature of cellular responses to IFN γ stimulation. However, there is evidence to suggest that additional signaling events not highlighted above can also impact IFN γ -regulated gene transcription. Ongoing studies should continue to uncover alternative signaling pathways that are activated in cells treated with IFN γ , and play important roles in regulating the diverse transcriptional response of various cell types to this potent cytokine.

Canonical and non-canonical cellular responses to type I IFNs

Multiple subsets of type I IFNs exist. These include numerous IFN α family members, IFN β , IFN δ , IFN ϵ , IFN κ , IFN τ and IFN ω [54, 55]. These IFNs all utilize the same cell surface receptor, IFN α R, which is a heterodimer comprised of IFN α R1 and IFN α R2 proteins [55–60]. Like the subunits of the IFN γ R, each component is constitutively associated with a member of the JAK family; IFN α R1 with TYK2 and IFN α R2 with JAK1. Receptor ligation by different type I IFN proteins elicits overlapping, yet different, cellular responses [61]. The initial response elicited by IFN α R signaling is altered transcription of numerous cellular genes, many encoding proteins with functions in antigen presentation, apoptosis, and growth inhibition. Altered expression of these proteins creates an environment within the host cell that is unfavorable for virus replication and contrary to cancer cell survival and growth [62].

Type I IFNs principally signal through a canonical JAK/STAT pathway with parallels to that activated by IFN γ (Figure 1). Ligand binding to the IFN α R initiates dimerization of the two receptor subunits and trans-phosphorylation of their associated TYK2 and JAK1 kinases [54, 63–65]. The kinases phosphorylate residues in the cytoplasmic tails of IFN α R1 and IFN α R2 to recruit STAT1 and STAT2 proteins via their SH2 domains. Docking of these STAT proteins to the receptor subunits allows their phosphorylation by the activated JAK proteins at Y₇₀₁ on STAT-1 and Y₆₉₀ on STAT-2 [54, 55, 64]. Phosphorylation of the STAT monomers releases them from their docking site, allowing them to dimerize and combine in a homodimeric or heterodimeric form with IRF9 to produce the transcription factor ISG factor 3 (ISGF3). ISGF3 translocates into the nucleus to identify ISGs and induces their transcription. ISGs induced by type I IFN signaling typically contain interferon stimulated response element (ISRE) or a gamma activated sequence (GAS) elements within their promoters, although there is a clear preference for genes containing an ISRE. Some examples of ISGs transcribed as a result of type I IFNs are ISRE containing genes ISG15, IP-10, IRF-7 and PKR [66], and GAS containing genes IRF-1, IRF-2, IRF-8 and IRF-9 [64, 67].

In addition to activating the canonical JAK/STAT pathway described above, stimulation of the IFN α R also stimulates several non-canonical signaling events (Figure 2). Depending on the cell type, type I IFNs can initiate recruitment and phosphorylation of STATs-3-6 [64, 65, 67, 68]. However, the efficiency with which these others STATs are activated varies between different cell types, which may contribute to cell-type specific responses to the type I IFNs. Other non-canonical signaling pathways activated in response to type I IFN include tyrosine phosphorylation (hence activation) of insulin receptor substrates 1 (IRS1) and 2 (IRS2) by activated TYK2 and JAK1 [55, 64]. Tyrosine phosphorylated IRS1, IRS2, and STAT3 bind PI3K and stimulate its kinase activity. This IRS activation in the response to type I IFNs appears to be somewhat redundant, since human THP-1 and mouse 32D myeloid cells are IRS-deficient and respond normally to IFN α in terms of STAT 1–3 activation and antiviral responses [69]. However, the recruitment and activation of PI3K by IRS or other

factors is important for mediating the effects of IFN α on cell proliferation and survival [64]. PI3K activates AKT, which activates mTOR to prevent cell proliferation and the I κ B kinase to initiate NF- κ B activity. NF- κ B promotes cell survival and induces expression of genes involved in antigen processing and presentation activities.

In myeloma and lymphoma cells, activated Tyk2 was shown to interact with the guanine nucleotide exchange factor VAV [70]. VAV is tyrosine phosphorylated in response to IFN α treatment [71], and likely contributes to activation of ras-related C3 botulinum toxin substrate 2 (Rac1) and p38 MAPK by IFN α [72]. Rat sarcoma protein (RAS) and RAC1 activity also regulates activation of c-Jun N-terminal Kinase (JNK) and ERK MAP kinases by type I IFNs [64]. This MAPK activation is thought to explain the ability of type I IFNs to induce apoptosis, growth inhibition, and regulate cell differentiation.

Type I IFN responses can be suppressed by a negative feedback loop, primarily utilizing suppressors of cytokine signaling (SOCS). This loop begins with transcription of TAM receptor Axl by the canonical IFN α R signaling pathway. Following protein synthesis, Axl accumulates at the cell surface, and associates with IFN α R [73]. This association engages TAM receptor signaling and induction of SOCS1 and SOCS3 expression [74]. SOCS molecules repress type I IFN signaling in a number of ways, including, preventing JAK activity, and inducing degradation of IFN α R and its associated proteins via ubiquitination [65].

IFN γ production and activation of antimicrobial immunity

Both natural killer (NK) cells and T cells produce IFN γ during bacterial infection. Within 12–24 h after systemic *Lm* infection, over 50% of the total splenic NK cell population stains positive for intracellular IFN γ , which correlates with a spike in serum IFN γ concentrations [10]. Similarly, NK cells are activated in response to mucosal infections with *Mtb*, *Ft*, and *Chlamydia* spp. [75–78]. The requirements for NK cell production of IFN γ in response to *Lm* infection include IL-18, IL-12, and direct contact with dendritic cells [10, 79]. In addition, a highly secreted *Lm* protein stimulates increased NK cell activity in *Lm* infected mice [10, 79]. In addition to NK cells, non-antigen specific CD8⁺ T cells have been shown to produce IFN γ in response to IL-12 and IL-18 within the first 1–2 days post infection by *Lm*, *Burkholderia*, and *Salmonella* infections [80–82]. In addition, antigen specific T cells produce IFN γ at later times after infection by *Lm*, *Mtb*, *Ft*, and other intracellular bacteria [12, 14, 83].

A key effect of IFN γ during the innate immune response is its ability to drive the differentiation of immature macrophages towards a classical (M1) microbicidal activation state. M1 activated macrophages are thought to be the predominant cell type responsible controlling bacterial expansion during both innate and adaptive phases of the immune response. Depletion of macrophages at early stages of *Lm* or *Cm* infection using antibodies to CR3, liposomes containing clodronate, or by diphtheria toxin (DT) treatment of transgenic mice expressing a DT receptor on CCR2⁺ cells, significantly increased bacterial burdens and lethality [27, 84, 85]. In addition, macrophage-specific expression of a dominant negative form of IFN γ R1 significantly increased susceptibility to systemic *Lm* infection [86, 87]. Evidence suggests that multiple consecutive waves of receptor ligation, internalization, and recycling are required for complete M1 macrophage differentiation [88]. Each wave of signaling may thus permit induction of a subset of the several hundred IFN γ -induced genes associated with differentiation into the M1 activation state.

The mechanisms used by M1 macrophages to kill phagocytosed bacteria remain incompletely defined. M1 activated cells exhibit increased ability to produce reactive

nitrogen (NO) and oxygen (ROS) species that can kill a variety of bacterial species *in vitro*. Reactive nitrogen species arise from NO production by NOS2, whose transcription is upregulated by IFN γ . Transcriptional regulation of NOS2 expression is the primary determinant of NO production, although NOS2 activity is also positively and negatively regulated post-transcriptionally [89]. NOS2 activity increases NO production and may inhibit survival of certain phagosome-encapsulated bacteria [32]. Under appropriate conditions, NO has also been shown to impair escape of the engulfed cytosolic bacterial pathogens *Lm* and *Ft* from phagosomes into the macrophage cytosol [90, 91]. However, the ability of activated macrophages to kill engulfed *Lm in vitro* is independent of NOS2 [92, 93]. Moreover, expression of *nos2* plays only a modest role in host resistance to *Lm* during early stages of *in vivo* infection [92–95], and has a net deleterious impact during *in vivo* infections by the cytosolic intracellular bacterial pathogens *Burkholderia pseudomallei* and *Shigella* [41, 92, 96]. The lack of a clear protective role for NO in some of these settings is likely due to the fact that *Mtb* and other pathogenic bacteria have evolved mechanisms to resist NOS2-mediated immunity [97, 98]. In addition, NO production was recently shown to enhance the ability of bacteria capable of cell-cell spread to infect activated macrophages [99]. Ultimately, mice deficient for iNOS do succumb to normally sublethal infections by *Lm*, *Mtb* and *Ft* [100–102]. These protective effects of NO may be due to the ability of NO to induce the apoptosis of macrophages infected with *Lm* or *Mtb* [103, 104], or due to its ability to regulate cell signaling and other aspects of the immune response [105].

As mentioned above, macrophage activation by IFN γ increases ROS production. The active NADPH complex that produces ROS is composed of multiple subunits that assemble following activation [32]. IFN γ treatment of macrophages induces expression of the gp91^{Phox} (NOX2) subunit. Mice with combined deficiency in both NOS2 and NOX2 have substantially increased susceptibility to bacterial infection, and develop spontaneous bacterial infections [92]. However, mice deficient for NADPH oxidase activity alone demonstrate only a moderate increase in early bacterial burdens in the livers, but not spleens, of mice systemically infected with *Lm* [106]. Similarly, mice given a pulmonary *Mtb* infection exhibited a moderate increase in bacterial load in the absence of ROS production very early during infection [107]. These findings support the notion ROS and NO production induced by IFN γ are important, but redundant during host defense against intracellular bacterial infections.

IFN γ also modulates vesicular trafficking in macrophages. One mechanism by which this occurs is through the induction of GTPases that associate with pathogen-containing vacuoles. Several of these GTPases selectively play crucial roles in defense against specific intracellular bacterial pathogens [108, 109]. IFN γ also promotes autophagy within infected cells. Autophagy has long been recognized as a cellular mechanism that delivers cytoplasmic material to lysosomes for degradation. This is accomplished by formation of a double-membrane phagosome compartment known as the autophagosome [110]. The autophagosome then matures into a degradation vessel following fusion with a lysosome [110]. While traditionally recognized as a process that occurs in response to cellular starvation, more recent studies highlight its importance in bacterial resistance. During *Mtb* infection, stimulation of infected macrophages with IFN γ induces autophagy, facilitating fusion of lysosomes with *Mtb*-containing phagosomes [111]. As a survival strategy, multiple intracellular bacteria express virulence factors that allow them to evade autophagy [110, 112, 113]. Autophagy related genes (Atg's) can also contribute to host resistance independent of autophagosome formation. Deletion of Atg5, specifically in macrophages and neutrophils, resulted in decreased host resistance to *Lm* infection [114].

Another important effect of IFN γ stimulation during bacterial infection is the induction or regulation of inflammatory cytokine and chemokine production. IFN γ treatment can enhance

transcription of genes for multiple inflammatory cytokines, including IL-1 α , IL-1 β and TNF α [115], each of which are important for host resistance to various intracellular bacteria. However, it should be noted that some reports indicate that IFN γ can inhibit production of IL-1 under specific circumstances [115]. IFN γ also augments production of IL-12 in the presence of lipopolysaccharide [115]. Some of the principal inflammatory chemokines produced following IFN γ stimulation include CCL2, CCL4, CXCL4, CXCL9, and CXCL10 [32, 116]. Most of these chemokines attract monocytes and macrophages to the site of infection; however, some also recruit adaptive immune cells, such as T cells [32]. Recruitment of T cells fits with the well-established ability of IFN γ to promote antigen presentation by upregulating antigen processing machinery and surface expression of MHC I and MHC II molecules [32]. A key factor in the upregulation of antigen presentation by IFN γ is the Class II Transactivator (CIITA). CIITA is a limiting component of the transcription complex that drives expression of most MHC II-related genes [117]. IFN γ , but not IFN α/β , increased expression of CIITA to increase expression of and antigen presentation by MHC II molecules [118]. Hence, increased surface expression of MHC II is a token indicator of macrophage activation by IFN γ .

Type I IFN production and increased susceptibility to certain intracellular bacterial pathogens

In contrast to IFN γ , which is primarily produced by lymphocytes during intracellular bacterial infections, type I IFNs can be produced by a wide variety of host cell types. The initial production of type I IFNs occurs by cells that recognize fragments of bacteria via pattern recognition receptors such as toll-like receptors (TLRs) or other intracellular proteins. The recognition receptors responsible for mediating production of type I IFNs during bacterial infections remain incompletely defined. By contrast, recent studies have determined that the bacterial ligands sensed by these receptors are at least in some cases secreted into the host cell by bacterial efflux pumps. During *Mtb* infection, bacterial expression of the ESX-1 secretion system is necessary for production of type I IFNs by infected macrophages [119], whereas during *Lm* infection, efflux pumps that regulate secretion of c-di-AMP (e.g. MdrM) regulate IFN β production by infected host cells [120]. It was recently shown that expression of a host factor termed MPYS or STING governs the ability of bone marrow derived macrophages and DCs to sense c-di-AMP and c-di-GMP [121–123]. Expression of MPYS/STING was also required for type I IFN and IL-6 production by *Lm* or *Ft*-infected bone marrow derived macrophages, although mice deficient for this protein still produced type I IFNs during systemic infection with either pathogen [121].

Over the past decade, it has surprisingly been demonstrated that a number of bacterial infections are actually exacerbated in the presence of endogenously produced type I IFNs. In an early report, Manca *et al.* examined the differences in host resistance to infection with multiple strains of *Mtb* and found that hypervirulence correlated with excessive production of type I IFNs [24]. Neutralization of type I IFNs during infection with a hypervirulent *Mtb* strain correspondingly resulted in significantly improved host survival. Similarly, IFN $\alpha R^{-/-}$ mice experience prolonged survival during *Mtb* and *Cm* infections [24, 25, 27], and IFN $\alpha R^{-/-}$ mice demonstrate an abbreviated *Cm* infection in the lungs and genital tract [25, 27]. In the context of systemic *Lm* infection, IFN $\alpha R^{-/-}$ mice harbor up to 1000-fold fewer bacteria at 72 hours after infection than do type I IFN-responsive controls [21, 22, 26, 28]. This increased resistance of the IFN $\alpha R^{-/-}$ mice is not due to poor initial infection, because the numbers of *Lm* recovered from wild type (wt) and IFN $\alpha R^{-/-}$ mice are similar at 24 and 48 hours post infection [21, 124]. Type I IFNs impose similar effects during *Ft* infection;

with IFN α R^{-/-} mice exhibiting decreased bacterial burdens and prolonged survival following both intradermal and pulmonary infections [23].

Viral infections and treatments that increase type I IFN production even further increase host susceptibility to bacterial infections. For example, influenza infection is a potent inducer of type I IFNs. Influenza also predisposes mouse and human hosts to bacterial pneumonias, which are responsible for up to 25% of human deaths from influenza [125, 126]. In mice, influenza-infected IFN α R^{-/-} mice resist secondary bacterial infections [127]. Type I IFN-responsiveness is also required for increased susceptibility to systemic *Lm* infection following LCM virus infection [128]. Other mouse model systems have shown that treatment with poly I:C, a potent inducer of type I IFNs, exacerbates pulmonary *Mtb* and systemic *Lm* infections, as evidenced by increased bacterial loads and tissue pathology [26, 129]. Likewise, intranasal treatment with recombinant IFN α /β increased pulmonary bacterial loads in mice infected with *Mtb* and decreased host survival [130].

Proposed mechanisms for pro-bacterial effects of type I IFNs

Several models have been proposed to explain the deleterious effects of type I IFN production in the context of various bacterial infections. These models are summarized below and in Figure 3.

Increased immune cell apoptosis

As noted above, type I IFNs can suppress proliferation and survival of tumor cells. In addition, the ability of primary host cells to respond to type I IFNs was found to be required for a dramatic increase in TUNEL staining (presumably indicative of apoptosis) in tissues of mice during early stages of systemic *Lm* infection [22, 26]. The TUNEL staining in these studies correlated with the death of lymphocytes, suggesting that the induction of lymphocyte apoptosis by type I IFNs might cause the suppressed host resistance to *Lm* infection [22, 131]. Consistent with this model, type I IFNs sensitize lymphocytes to the apoptotic effects of the *Listeria* virulence factor LLO hemolysin [22, 124]. In this scenario, uptake of the apoptotic lymphocytes may suppress macrophage activation by inducing production of the anti-inflammatory cytokine IL-10 [131]. However, it is unclear that this model could be generalized to other pathogens that lack LLO or similar proteins, yet still benefit from host type I IFN production.

Type I IFNs can also induce apoptosis in neutrophils and macrophages. IFN α R expression increased apoptosis of granulocytes during LCM virus infection under conditions where resistance to a subsequent *Lm* infection was reduced [128]. Reduced macrophage apoptosis in IFN α R^{-/-} mice also correlates with improved resistance to endogenous *Lm* infection [26], and apoptosis of lung macrophages correlates with increased pulmonary *Cm* infection [27]. Cells from IFN α R^{-/-} mice show reduced upregulation of the pro-apoptotic factor TRAIL [27]. TRAIL^{-/-} mice likewise have increased resistance to systemic *Lm* infection, reduced TUNEL staining in infected tissues, and reduced macrophage and lymphocyte apoptosis during the infection [132]. However, the resistance of TRAIL^{-/-} mice is considerably less pronounced than that of IFN α R^{-/-} mice, thus TRAIL-mediated apoptosis fails to fully explain the pro-bacterial effects of type I IFN production. In addition, it remains unclear whether the observed effects of TRAIL are due to apoptosis induction or other developmental or signaling events.

Suppression of inflammatory responses

The production of several inflammatory cytokines and chemokines with important roles in the innate immune response are also affected by type I IFN. During *Lm* infection, IFN α R^{-/-}

mice have increased production of both IL-12 and TNF α in comparison to wt control mice [21]. Both of these cytokines contribute to anti-*Lm* immune responses. Production of TNF α is also increased in the lungs of IFN α R^{-/-} mice infected with *Mtb* [24]. Type I IFNs can further impair production of IL-1 β by triggering STAT-1 to inhibit the NLRP3 and NLRP1 inflammasomes [133]. Additionally, production of IL-1 β is selectively inhibited by type I IFNs during *Mtb* infection, which appears to contribute to increased host susceptibility during these infections [134, 135]. Type I IFNs also impede production of the chemokines that orchestrate recruitment of inflammatory cells to the site of infection. Specifically, production of chemokines that attract neutrophils and monocytes, including CCL2, CXCL4, and CXCL9 is reduced by type I IFNs [25, 116, 136]. CCL2 recruits inflammatory monocytes to the site of infection via interaction with its receptor CCR2 [137]. Mice lacking CCR2 are deficient in their mobilization of inflammatory monocytes to sites of *Lm* infection and have increased susceptibility [137, 138]. IFN α R^{-/-} mice experience an increased recruitment of inflammatory monocytes [21], which might contribute to the increased resistance of these mice to *Lm*. However, this model again falls short of explaining the increased susceptibility of type I IFN responsive mice in other pathogen models, since type I IFNs increase production of CCL2 during pulmonary *Mtb* infection [129]. A more recent study correlated reduced *Lm* growth in IFN α R^{-/-} mice with increased CXCL4 production and neutrophil recruitment [116], and increased production of CXCL9 in IFN α R^{-/-} mice correlated with improved host resistance in a *Cm* infection model [25]. Similarly, IL-17 production and increased neutrophil recruitment were observed in IFN α R^{-/-} mice following *Ft* and *Lm* infections [23]. However, the effects on neutrophil recruitment were somewhat modest, and a recent paper has questioned whether neutrophils are protective in the context of intracellular bacterial infections [85].

Suppression of myeloid cell responses to IFN γ

Type I IFNs have long been known to diminish myeloid cell responsiveness to IFN γ . This effect of type I IFNs appears to be critical, as IFN α R^{-/-} mice no longer experience increased resistance to *Lm* infection when IFN γ is neutralized [28]. Studies indicate that type I IFNs diminish responsiveness by two primary mechanisms. First, type I IFNs upregulate proteins that suppress JAK-STAT signaling, namely SOCS family members. SOCS proteins suppress IFN γ signaling by binding to the JAK proteins associated with the IFN γ R complex, inhibiting their phosphorylation [31]. Therefore, these repressors can diminish the upregulation of ISGs, particularly through the canonical IFN γ signaling cascade. Intranasal infection of mice with a hypervirulent strain of *Mtb* that induces exorbitant amounts of IFN β potently increased mRNA expression of SOCS 1, 4, and 5, as well as PIAS-1 [24]. *Lm* infection of macrophages also results in upregulation of SOCS1 and 3 [139, 140], and macrophages infected with *Ft* demonstrate a marked increase in SOCS3 expression in conjunction with a decrease in STAT-1 phosphorylation, as well as CXCL10 and iNOS production [141]. Dalpke *et al.* demonstrated that stimulation of macrophage cell lines with a TLR9 antagonist that induces production of type I IFNs results in a significant upregulation of SOCS1 and SOCS3 mRNA and decreased responsiveness to IFN γ [142]. Altogether, these data suggest that induction of SOCS proteins by type I IFNs can blunt responsiveness to IFN γ to impair microbicidal functions of M1 macrophages.

A second mechanism by which type I IFNs suppress IFN γ responsiveness in antigen presenting cell types is by decreasing cell surface expression of the IFN γ R complex [28]. This occurs both in cell culture and in response to type I IFNs produced during *in vivo* infection with *Lm*, *Mtb*, and *Francisella novicida* (*Fn*) [28, 143, 144]. Treatment of bone marrow derived macrophages with recombinant IFN β is sufficient to reduce IFN γ R surface expression, while several other cytokines do not have this effect [28]. Decreased expression of the receptor is accompanied by decreased activation of some of the canonical signaling

molecules and expression of ISGs. Reduced surface expression of IFN γ R1 by a human macrophage cell line infected with *Mtb* correlated with reduced expression of MHCII in response to IFN γ stimulation [143]. During *Lm* infection, down regulation of IFN γ R1 correlated with reduced MHCII expression, STAT-1 tyrosine phosphorylation, and GAS-dependent transcription [28]. Likewise, decreased IFN γ R expression during *Fn* infection reduced MHCII expression and STAT-1 activation [144]. During an *in vivo* infection with *Lm*, down regulation of IFN γ R was seen to occur in macrophages, dendritic cells and B cells, but not T or NK cells [28]. These effects of IFN α/β correlated with diminished IFN γ -dependent cell surface expression of MHCII on macrophages and DCs from wt, as compared to IFN α R^{-/-} mice [28]. Induction of type I IFNs by *in vivo* treatment with poly I:C during pulmonary *Mtb* infection likewise decreased expression of MHCII on infiltrating inflammatory monocytes in wt but not IFN α R^{-/-} mice [129]. Another study also correlated decreased surface expression of IFN γ R1 with decreased expression of MHCII in macrophages infected with *Mtb* [143]. Thus, myeloid cell responsiveness to type I IFNs reduces IFN γ R surface expression and correlates with diminished responsiveness of myeloid cells to IFN γ . Given the correspondence of these observations with increased bacterial burdens, it is likely that IFN γ R down regulation and impaired myeloid cell activation contribute to the ability of type I IFNs to exacerbate intracellular bacterial infections.

Concluding remarks

The cellular responses to type I and II IFNs are complex and dynamic. Although the signaling pathways utilized by these IFN types share many parallels and can in several cases elicit similar changes in gene expression, there are also numerous examples where these two IFN types elicit divergent cellular outcomes. A key example of this is the unique ability of IFN γ to stimulate macrophage differentiation into the activated bactericidal M1 state. Such activation plays a crucial role in the ability of the immune system to combat bacterial infections in both naïve and immune individuals [145]. Type I IFNs fail to drive M1 macrophage differentiation and, in fact, suppress such activation by impairing responsiveness of macrophages and other antigen presenting cell types to IFN γ stimulation. The ability of type I IFNs to suppress myeloid cell responsiveness to IFN γ may be an underlying mechanism to explain how these IFNs act to exacerbate host resistance to intracellular bacterial infections. Many of the cytokines and chemokines shown to be repressed by type I IFN signaling are also induced by IFN γ . By reducing IFN γ R expression, type I IFNs decrease activation of key signaling molecules and expression of ISGs, contributing to both macrophage activation and the recruitment and activation of other inflammatory cells. Hence, the reduction in IFN γ signaling may profoundly impair the ability of the host to check the replication of invading intracellular bacteria. IFN γ signaling can also rescue macrophages infected with low doses of *Mtb* from cell death [146], and stimulates hematopoiesis to repopulate depleted lymphocytes and neutrophils in infected tissues [147]. Thus, suppression of IFN γ signaling by type I IFNs could account for an increased presence of dying cells in tissues of infected mice. The mechanism by which type I IFNs suppress myeloid cells surface expression of the IFN γ R are poorly understood. However, the reduced surface expression correlates with decreased IFN γ R1 transcript abundance [28, 143, 148]. Thus, down regulation of IFN γ R expression is associated with type I IFN-induced silencing of *ifngr1* transcription. Further dissecting the mechanisms by which type I IFNs suppress transcription of *ifngr1* and perhaps other myeloid cell responses may reveal strategies to safely improve macrophage activation in patients undergoing IFN-based therapies or infected with IFN-inducing viruses and bacteria. Such strategies could lead to new therapies for prevention or treatment of severe bacterial infections.

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Figure 1. Canonical JAK/STAT signaling by the type I interferon receptor

Type I interferons such as IFN- β bind to cell surface IFNAR1 & 2 proteins to induce conformational changes that cause the activation of IFNAR1 bound TYK2 and IFNAR2 bound JAK1 via transphosphorylation. Activated TYK2 and JAK1 phosphorylate residues in the cytosolic domains of the IFNAR to permit docking of cytosolic STAT-1 & 2 proteins. Upon docking, STAT-1 is phosphorylated at Y701 and STAT-2 at Y690 by TYK2 & JAK1. The phosphorylation event releases the pSTAT proteins and allows them to homo or heterodimerize. IRF9 is recruited to the pSTAT1/2 complex to create the trimeric ISGF3 complex. ISGF3 moves into the nucleus to bind ISRE elements in the promoters of interferon stimulated genes (ISGs). Type I IFN signaling also results in formation of some pSTAT1 homodimers that can bind GAS elements to regulate ISG expression. See text for additional details and references.

Figure 2. Major non-canonical signaling pathways activated by the type I interferon receptor
Ligand binding to the IFNAR and transphosphorylation of TYK2 & JAK1 can cause recruitment and phosphorylation of STAT proteins other than STAT1 and STAT2 (e.g. STAT-3). In addition, IFNα binding to the IFNαR can trigger phosphorylation of IRS-1 & 2 and VAV. STAT-3 or IRS-1/2 bind and stimulate PI3K upon phosphorylation to activate AKT. Activated AKT block proliferative responses and further signals via the NF-κB pathway. NF-κB activation regulates transcription of genes with pro-survival functions as well as genes that increase antigen processing and presentation. Phosphorylated VAV also activates NF-κB, as well as multiple MAP kinases (MAPK). MAPK activity can induce apoptosis, inhibit growth and prevent differentiation. See text for additional details and references.

Figure 3. Potentially detrimental effects of type I IFNs during intracellular bacterial infections
 In wildtype mice, type I IFNs increase expression of the apoptotic factor TRAIL and SOCS proteins, while decreasing expression of certain inflammatory cytokines and chemokines and silencing transcription of *ifngr1*. These cellular changes increase apoptosis of certain immune cells, decrease recruitment of inflammatory cells, and decrease responsiveness to IFN γ . The absence of one or more of these effects may explain the increased susceptibility of mice that lack expression of the type I IFN receptor (IFN α R^{-/-}) to infections by diverse intracellular bacterial pathogens.