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Crosstalk between type I and II interferons in regulation of myeloid cell responses during bacterial infection

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Abstract

Type I and type II interferons (IFN α/β and IFN γ) are cytokines that play indispensable roles in directing myeloid cell activity during inflammatory and immune responses. Each IFN type binds a distinct receptor (IFNAR or IFNGR) to transduce signals that reshape gene expression and function of myeloid and other cell types. In the context of murine models and human bacterial infections, production of IFN γ generally promotes resistance while production of IFN α/β is associated with increased host susceptibility. Here, we review mechanisms of crosstalk between type I and II IFNs in myeloid cells and their impact on myeloid cell activation and anti-microbial function.

Introduction

Cells of the immune system communicate by direct cell-cell interactions and by the release and detection of proteinaceous cytokines and other soluble factors. Interferons (IFNs) are a class of cytokines discovered more than 60 years ago and named for their ability to “interfere” with virus infections [1]. Three distinct IFN types (types I, II, and III) are now recognized based on their ability to bind distinct cognate cell surface receptors [2–5]. The receptor for each IFN type engages signaling pathways involving Janus kinases and signal transducers and activators of transcription (JAK/STAT). However, the details and outcomes of the signaling engaged by each of the receptors differs. This leads to differential effects on inflammatory and immune responses. Variation in expression of the various IFN receptors also shapes how the IFNs impact immune responses. The receptor for type III IFNs (IFNLR) is selectively expressed on epithelial cells, hepatocytes, and a subset of immune cell types while receptors for type I and II IFNs (respectively IFNAR and IFNGR) are constitutively expressed by nearly all nucleated cells [2–5]. Variation in the magnitude of IFN receptor expression occurs in different cell types and in response to stimulation. Specifically, expression of the IFNGR changes in myeloid cells exposed to IFN $\alpha\beta$ or IFN γ [3, 6, 7]. These and other mechanisms for crosstalk between the IFNs have the potential to suppress, promote, or tune myeloid cell activation in the context of inflammatory and immune responses. In this review, we summarize differences in type I and II IFNs and their beneficial or harmful effects on the host response to bacterial infections. We further review known

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mechanisms for crosstalk between these cytokines during bacterial infections and how this influences myeloid cell activity and host resistance, with a focus on the suppressive effects type I IFNs have on myeloid cell accumulation and activation at sites of infection.

Canonical cellular responses to Type I and II IFNs

Type I IFNs comprise at least 13 IFN α subtypes, IFN β , IFN δ , IFN ϵ , IFN κ , IFN τ , and IFN ω , the genes for which are clustered on mouse chromosome 4 or human chromosome 9 [8]. Nearly all hematopoietic and non-hematopoietic cell types secrete type I IFN proteins in response to stimuli such as viral and bacterial nucleic acids, cyclic-dinucleotides, or lipopolysaccharide. When secreted IFNs bind the heterodimeric IFNAR, JAK1 and TYK2 tyrosine (Tyr-) kinases that are constitutively associated with the IFNAR1 and IFNAR2 subunits phosphorylate substrates that include STAT1 and STAT2 [2, 4]. These Tyr-phosphorylated (p)STAT proteins associate with interferon-regulated factor (IRF-) 9 to form the ISGF3 complex, which enters the nucleus to bind IFN-stimulated response elements (ISRE) and induce the transcription of interferon stimulated genes (ISGs) [2, 4, 9]. Many ISGs encode factors that promote antiviral immunity; hence IFN α is clinically useful for treatment of human viral infections [2, 9]. IFN α is also used to treat melanomas and other cancers due to its effects on cellular survival and apoptosis [2, 10]. Type I IFNs further have regulatory effects that are exploited for suppression of neuroinflammatory responses in patients with relapsing-remitting multiple sclerosis [2]. The mechanisms for these regulatory effects remain incompletely-defined.

The type II IFN (IFN γ) is encoded by a single gene on mouse chromosome 10 or human chromosome 12. IFN γ is largely produced by lymphocytes. T lymphocytes secrete IFN γ upon TCR ligation by cognate peptide/MHC complexes, while both T and natural killer (NK) cells can also produce IFN γ in response to inflammatory cytokines such IL-12 and IL-18. The cell surface receptor for IFN γ (IFNGR) comprises IFNGR1 and IFNGR2 subunits [2–4]. Ligation of IFNGR by dimeric IFN γ assembles a tetrameric complex that activates Tyr kinase activity of JAK1 and JAK2 and promotes formation of pSTAT1 homodimers that can enter the nucleus to bind gamma activated sequence (GAS) elements in DNA and induce transcription of gamma-activated genes (GAGs) [2–4]. The ability of pSTAT1 dimers to promote transcription is further modulated by additional post-translational modifications to STAT1, including phosphorylation of a serine 727 in the transactivation domain or protein acetylation [11–13]. Methylation and ubiquitination of STAT1 also impact induction of target gene expression [14–16]. Additionally, responsiveness to both type I and II IFNs is negatively regulated by suppressors of cytokine signaling (SOCS) proteins, phosphatases, and other factors – many of which are induced by the IFNs themselves. These and other positive and negative regulatory mechanisms permit fine-tuning of cellular responses to IFNs, and thus of the inflammatory and immune events they incite.

Type I and II IFNs have divergent effects on resistance to many bacterial infections

Despite similarities in the type I and II IFN systems and their common ability to induce a subset of antiviral host genes, these cytokines have opposing effects on resistance to bacterial infection. Defects in the response to IFN γ heightens susceptibility to

Mycobacteria, *Listeria*, and other bacteria [17, 18]. Mice whose myeloid cells conditionally lack *ifngr1* or express a dominant negative IFNGR rapidly succumb to infection by *Lm* and other intracellular pathogens [19–21], further indicating that these cells are an important target cell of host-protective IFN γ . Mice lacking expression of *ifnar1* or treated with antibodies to block binding of type I IFNs to IFNAR conversely resist infections by *Listeria monocytogenes* (*Lm*), *Mycobacterium tuberculosis* (*Mtb*) and several other pathogens [22, 23], and production of type I IFNs drives increased survival and replication of pathogenic bacteria [24–26]. The susceptibility-enhancing effects of IFN $\alpha\beta$ are not limited to a particular class of bacteria or a particular infection niche; these effects apply broadly to both Gram-positive and Gram-negative pathogens whether they normally survive inside or outside of host cells (Figure 1). Type I IFNs also contribute to chronic infection by certain viral pathogens [27, 28], and crosstalk between type I and II interferons limits tissue inflammation induced by acute Influenza A virus infection [29]. A better understanding of crosstalk between type I and II IFNs and its influence on host resistance may thus be relevant for therapy in a broad-spectrum of infections.

Type I IFNs suppress myeloid cell accumulation at sites of infection

To engulf and kill microbes, myeloid cells must be appropriately recruited to infection foci. IL-1 β and TNF α elicit production of pro-inflammatory chemokines and lipid mediators that can promote such recruitment. Both of these mediators are reportedly elevated in *ifnar1*^{−/−} mice following infection with *Lm* or *Mtb* [30–32], possibly due to reduced expression of *Ch25h* and thus sterol-response inhibitory 25-hydroxycholesterol [33]. A recent study further suggested that type I IFN-mediated suppression of IL-1 β -induced prostaglandin E2 synthesis (PGE2); hence restoration of PGE2 improved outcome in a murine model of *Mtb* infection [34]. Increased production of neutrophil chemoattractants CXCL1 and CXCL2 was also observed in *ifnar1*^{−/−} mice in a model of *influenza*-enhanced streptococcal pneumonia [26]. More recently, IFN $\alpha\beta$ -mediated induction of the Setdb2 methyltransferase was shown to suppress *cxc11* expression to dampen lung inflammation and increase susceptibility in post-influenza *S. pneumoniae* infection [35]. Type I IFNs further suppress monocyte recruitment to spleens during systemic *Lm* infection [30, 36].

Monocyte accumulation in infected tissues reflects the combined effects of cell recruitment and cell death. Type I IFNs have long been known to increase vulnerability of virus-infected cells to apoptosis, which may limit viral spread and increase availability of viral antigens for uptake by uninfected antigen presenting cells [37]. IFN β production indeed upregulates programmed death-ligand 1 (PD-L1) and increases myeloid cell apoptosis during chronic LCMV infection [27, 28, 38]. Mice pre-treated with blocking antibodies against IFNAR exhibit decreased expression of immune-suppressive PD-L1 and an increased clearance of LCMV that relies on IFN γ responsiveness [27, 28]. In bacterial infections, death-sensitizing effect of type I IFNs correlate with induction of the pro-apoptotic genes promyelocytic leukemia (PML), death-associated protein 6 (Daxx) and TNF-related apoptosis-inducing ligand (TRAIL) in *Lm*-infected macrophages from wild type mice [25]. Cultured macrophages from mice deficient for *irf3*, *ifnb*, *ifnar1*, or *stat1* were also shown to resist cell death induced by *Lm*-infection [25, 39]. More recently, induction of type I IFN, IRF7, and IRF9 was reported to drive host-detrimental cell death during *Francisella novicida* infection

[40]. Studies using TUNEL staining further support the argument that apoptosis in the lymphocyte-rich follicles of *Lm*-infected spleens is dependent on IFN $\alpha\beta$ [25, 41]. Together, these studies suggest type I IFNs impair immunity in part through the suppression of myeloid cell recruitment or survival at sites of bacterial infection. However, it should be noted that in some infection models type I IFNs are not associated with suppression of monocyte recruitment, but rather with an increased accumulation of monocytes that show heightened permissiveness to bacterial infection and immune-suppressive function [42–44].

IFN γ promotes anti-microbial activation of myeloid cells

Pioneering work by George Mackaness first demonstrated the existence of lymphocyte-derived factors that “activate” macrophages to a state that resists infection by *Lm* and other pathogenic bacteria [45, 46]. Nathan and colleagues subsequently identified IFN γ as the key factor driving this “M1-type” activation [47]. Stimulation of macrophages with IFN γ induces expression of several hundred genes. Many of these GAGs are uniquely or more potently induced by IFN γ versus type I IFNs. Examples include class II major histocompatibility complex (MHC-II) and certain other factors involved in antigen processing and presentation [48], IFN γ -inducible GTPases [49], enzymes that generate nitric oxide or reactive oxygen species [50], and chemokines such as CXCL9 [51]. Gene deletion or knockdown approaches implicate some GAGs as contributors to the cell-intrinsic resistance to infection that IFN γ induces in macrophages. Nevertheless, the mechanisms by which these and other GAGs promote containment and killing of ingested microbes remain to be fully-defined.

The effects of IFN γ -stimulation on the macrophage are not limited to activation of gene expression. M1-activated macrophages shift metabolism towards glycolysis [52], have altered responses to other cytokines and microbial products [53, 54], and exhibit an altered chromatin landscape [55, 56]. In many cases the mechanisms responsible for these changes are still being defined, as is their impact have on the ability of M1-activated monocytes or macrophages to regulate or mediate anti-microbial resistance.

Another feature of the myeloid cell response to IFN γ that a brief stimulation of cultured macrophages with IFN γ fails to elicit maximal expression of certain GAGs, such as *Mhc2*, and is insufficient to stimulate development of certain effector functions associated with the activated M1 phenotype [48, 57]. How does the prolonged exposure to IFN γ mediate the full induction of macrophage M1-activation? This is associated with multiple cycles of STAT1 phosphorylation, nuclear entry, dephosphorylation, and exit [58]. Some GAGs (e.g. *Irf1*, *C2ta*) encode factors that regulate gene transcription. IFNGR ligation can also induce non-canonical signaling pathways to activate other transcription factors, such as NF κ B [59]. Further, altered chromatin landscape and mRNA translation activity likely influences secondary responses in stimulated macrophages [56]. Such mechanisms might ensure that full M1-activation occurs only in the context of prolonged IFN γ production, but also should result in a partially-or distinctly-activated myeloid cell when there is limited IFN γ signaling. Such cells may lack full microbicidal capacity and perhaps even exhibit distinct functional phenotypes, such as regulatory function observed in monocytes “primed” by an exposure to IFN γ in the bone marrow [60].

Type I IFNs inhibit IFN γ -driven activation of myeloid cells

Exposure to microbial products stimulates dendritic cells and some other myeloid cells to release IL-12 and IL-18, which co-stimulate the production of IFN γ by T and innate lymphoid cells. Release of IL-12 and inflammasome activation necessary for IL-18 release can both be inhibited by type I IFNs, potentially reducing IFN γ production during the response to *Lm*, *Mtb*, and *Staphylococcus aureus* [24, 30, 61]. Though IFN γ still accumulates to stimulatory concentrations in the sera of these infected mice, its reduced production may limit access to some myeloid cells and thus impair their M1-type activation.

Type I IFNs also more directly suppress the ability of murine and human myeloid cells to respond to treatment with IFN γ as measured by upregulation of the prototypical GAG product, MHC class II [62, 63]. This effect is seen not just in cultures, but also during *in vivo* infection by bacteria such as *Lm* [7]. Impaired responsiveness to IFN γ in these contexts correlates with a reduction in myeloid surface expression of IFNGR1 [7]. Myeloid cell IFNAR expression was necessary for these effects and recombinant IFN β sufficed to induce down regulation of IFNGR in cultured mouse or human myeloid cells [7, 64]. Myeloid cells from *Mtb*-infected patients also exhibit significantly reduced IFNGR1 staining compared to healthy controls, which is restored in patients receiving anti-mycobacterial treatment [65]. Recent work showed that B cells were an important source of the type I IFN production during *Mtb* infection and that this correlated with polarization of macrophages away from an M1-phenotype and towards a more regulatory M2-phenotype [42]. During murine infections with *Lm*, *Mtb*, or *F. novicida*, the reduced expression of IFNGR1 further correlates with reduced phosphorylated STAT1 and impaired induction of MHC class II [7, 65, 66]. However, production of IL-10 has also been correlated with type I IFN production in *Mycobacterium leprae* infected individuals [67]. IL-10 production is induced by type I IFNs in an IL-27-independent manner and can block production of IL-12 [67, 68], a key driver of IFN γ production. Thus, it has been difficult to establish the relative importance of IFNGR down regulation versus IL-10 production in the type I IFN-driven dampening of inflammatory myeloid cell recruitment and response to IFN γ .

Abrogating myeloid cell IFNGR1 reductions improves IFN γ -driven activation and host resistance to bacterial infection

Decreases in myeloid cell surface IFNGR1 staining are preceded by reductions in abundance of *ifngr1* transcripts [7, 64]. The reduced *ifngr1* transcripts reflect rapid silencing of *de novo* transcription at this locus. IFNAR ligation recruits a repressive transcriptional complex to the proximal *ifngr1* promoter and promotes histone modifications indicative of transcriptionally inactive chromatin [64]. This transcriptional silencing leads to a rapid reduction in cell surface IFNGR1 protein due to its short (~4 hour) half-life [69]. These features of the IFNGR down regulation process provided an opportunity to specifically investigate the relevance of IFN $\alpha\beta$ -driven myeloid cell IFNGR down regulation using a novel transgenic mouse model. This model uses the well-characterized myeloid cell specific *c-fms* promoter to drive expression of *ifngr1* in a manner that is not subject to down regulation by type I IFNs. Both endogenous and transgenic (flag-epitope tagged) IFNGR1 proteins are observed in the transgenic ("fGR1") mice [70]. Macrophages from the fGR1 mice respond similarly to IFN γ as measured by phosphorylation of STAT1^{Y701} in response

to IFN γ treatment [70]. However, upon IFNAR ligation the loss of myeloid cell surface IFNGR1 expression is abrogated in the fGR1 mice [70]. When infected with a sublethal dose of *Lm*, fGR1 mice exhibited decreased bacterial burdens at 72 and 96 hours post infection (hpi) [70]. Consistent with the preservation of myeloid cell IFNGR1 expression, the increased resistance of fGR1 mice to *Lm* infection was dependent on IFN γ and associated with increased expression of activation markers on monocytes recruited to infected tissues [70]. The expression of fGR1 also improved the ability of monocytes to resist productive *Lm* infection and increased bacterial association with LAMP1 in these cells, suggesting the monocytes had heightened cell-intrinsic resistance against the bacteria. Together, these data argue that crosstalk between type I IFNs and IFN γ as manifest in the suppression of *ifngr1* expression does indeed represent an important mechanism in the attenuation or differential tuning of myeloid cell activation in the context of bacterial infection (Figure 2). Future efforts to refine understanding of the mechanisms contributing to this crosstalk and identify specific IFN γ -induced gene products elevated in fGR1 monocytes could reveal new targets for host-directed therapies that increase host resistance to *Lm* and potentially other intracellular bacteria.

Conclusion

Type I and II IFNs have opposing effects on host resistance to bacterial infection, which correlate with crosstalk between these IFNs. IFNAR ligation suppresses the accumulation of myeloid cells at sites of infection and renders these cells less responsive to IFN γ . Type I IFNs can suppress production of IFN γ by dampening myeloid cell production of IL-12 and act to reduce myeloid cell IFNGR expression. This latter effect renders murine and human myeloid cells less responsive to subsequent stimulation with IFN γ . Evidence that IFNGR down regulation is important comes from recent studies using a transgenic mouse model where this effect is abrogated. Myeloid cell responsiveness to IFN γ and anti-bacterial responses the context of systemic *Lm* infection are improved in the transgenic mice despite infection-induced production of IFN $\alpha\beta$. Future studies may demonstrate a similar impact of abrogating IFNGR down regulation in other infections. Better understanding the mechanisms and consequences of this crosstalk may yield new therapies for infectious and inflammatory diseases.

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Highlights

- Type I and II IFNs have opposing effects in bacterial infections
- Type I IFNs dampen inflammatory myeloid cell responses
- Suppressive effects of type I IFNs correlate with reduced myeloid cell IFNGR
- Abrogating loss of IFNGR improves host resistance to systemic bacterial infection

Figure 1. Type I IFNs increase susceptibility to bacteria that occupy different niches.

Illustrated are the typical compartments infected by a sample of bacteria known to benefit from type I IFN production. *Listeria monocytogenes* and *Francisella tularensis* infect the cytosol of macrophages and other host cell types. *Mycobacterium tuberculosis*, *M. leprae*, *Salmonella typhimurium*, and *Chlamydia muridarum* replicate within membrane-enclosed vacuolar compartments. Susceptibility to bacteria that are generally considered to remain extracellular is also increased, for example *Staphylococcus aureus* and *Streptococcus pneumoniae*. The latter has specifically been observed in models of secondary bacterial infection in mice recovering from *Influenza*.

Figure 2. M1 activation and proposed effects of type I IFNs in IFN γ -exposed macrophages. Resting (M0) monocytes or macrophages demonstrate minimal ability to kill ingested bacteria and thus are readily infected by intracellular pathogens such as *L. monocytogenes*. Lymphocyte-derived IFN γ can activate these myeloid cells into an M1 state that is highly resistant to infection and kills ingested microbes. One feature of this killing is enhanced recruitment of lysosomes to bacteria-containing phagosomes. In the presence of type I (T1) IFNs, responsiveness to IFN γ is dampened or truncated by reductions in IFNGR1. This leads to incomplete or partial M1 activation that is associated with a reduced ability to contain and kill pathogens in phagolysosomes.