International Immunology, Vol. 25, No. 12, pp. 663–669
doi:10.1093/intimm/dxt050
Advance Access publication 24 October 2013

Confounding roles for type I interferons during bacterial and viral pathogenesis

Javier Antonio Carrero

Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO 63110, USA

Correspondence to: J. A. Carrero, Washington University School of Medicine, 660 S Euclid Avenue, Box 8118, St Louis, MO 63110, USA; E-mail: jacarrer@wustl.edu

Received 15 July 2013, *accepted* 9 September 2013

REVIEW

Abstract

Although type I interferons (IFN-I) were initially defined as potent antiviral agents, they can also cause decreased host resistance to some bacterial and viral infections. The many antiviral functions of the IFN-I include direct suppression of viral replication and activation of the immune response against viruses. In addition to their antiviral effects, IFN-I are also protective against several extracellular bacterial infections, in part, by promoting the induction of TNF-α and nitric oxide. In contrast, there is a negative effect of IFN-I on host resistance during chronic infection with lymphocytic choriomeningitis virus (LCMV) and acute infections with intracellular bacteria. In the case of LCMV, chronic IFN-I signaling induces adaptive immune system suppression. Blockade of IFN-I signaling removes the suppression and allows CD4 T-cell- and IFN-γ-mediated resolution of the infection. During acute intracellular bacterial infection, IFN-I suppress innate immunity by at least two defined mechanisms. During *Francisella* infection, IFN-I prevent IL-17 upregulation on γδ T cells and neutrophil recruitment. Following *Listeria* infection, IFN-I promote the cell death of macrophages and lymphocytes, which leads to innate immune suppression. These divergent findings for the role of IFN-I on pathogen control emphasize the complexity of the interferons system and force more mechanistic evaluation of its role in pathogenesis. This review evaluates IFN-I during infection with an emphasis on work carried out IFN-I-receptor-deficient mice.

Keywords: cytokine, infection, LCMV, *Listeria monocytogenes*, mouse

Introduction

The type I interferons (IFN-I) are an extensive family of pleiotropic cytokines that all signal through the ubiquitously expressed IFN-I receptor, termed the 'IFN-α receptor' (IFNAR) (1). The activity of these cytokines was discovered in the 1950s because of their ability to 'interfere' with viral infection (2). Molecular cloning techniques and genome sequencing have led to the identification of an extensive number of members of the IFN-I family. In mice, the two best analyzed members of this family are the cluster of 13 IFN-α subtypes and 1 IFN-β molecule. Genetic ablation of IFNAR ($IFNAR^{-/-}$) in the mouse is sufficient to prevent signaling by all members of the IFN-I family and is the biologically defining activity that groups the IFN-I molecules into one family (1).

IFNAR is composed of two chains (IFNAR1 and IFNAR2) that coordinately activate the kinases Jak1 and Tyk2 (tyrosine kinase 2) upon IFN-I binding. Jak1 (Janus Kinase 1) and Tyk2 phosphorylate Stat1 and Stat2 that, together with interferon regulatory factor 9 (IRF9), form the interferon-stimulated gene factor 3 (ISGF3) complex (3). ISGF3 binds to interferon-stimulated response elements to cause upregulation of over 300 genes. The type II interferon receptor, IFNGR1–IFNGR2, which binds IFN-γ, the only type II interferon, activates Jak1 and Jak2, leading to Stat1 phosphorylation and homodimerization (4). Because of the similarities in signaling, many of the genes that are upregulated by IFN-I are also upregulated by IFN-γ, providing some degree of redundancy between the IFN-I and IFN-γ signaling pathways (5). However, there are a large number of genes unique to IFN-I. Although many of the IFN-I-specific genes have defined antiviral functions, the role of many remains unresolved.

The antiviral activity of IFN-I was initially defined with conditioned supernatant inhibition of viral growth and then with purified cytokines. However, it was the generation of mice deficient in IFNAR signaling that permitted examination of infections under more physiological conditions (6). This review will focus on the role of IFN-I during murine infection with viral and bacterial pathogens. There is also extensive work on the role IFN-I in the pathogenesis of autoimmunity and cancer, and more recently, in fungal and protozoan infections (7–9). Although this work has contributed to our

understanding of the biological activities of IFN-I, it is beyond the scope of this review.

Because of the extent of the IFN-I literature, this review will mostly limit itself to experiments that have examined viral and bacterial pathogenesis in IFNAR$^{-/-}$ mice with a particular emphasis on work that has examined lethality and pathogen burden. Four major themes will be covered: First, there is a broad summary of the (generally) protective role of IFN-I in mice infected with viruses. Second is the recent finding that IFN-I promote the suppression of adaptive immunity seen during chronic infection with lymphocytic choriomeningitis virus (LCMV). Third, there is an examination of the divergent results that have been obtained using different bacterial pathogens. Finally, there is a detailed examination of the role of IFN-I during *Listeria monocytogenes* infection.

IFN-I promote beneficial outcomes to most viral infections

The consensus in the field is that IFNAR signaling is protective against most types of viral infection. Table 1 summarizes some of the results obtained after infecting wild-type and IFNAR$^{-/-}$ mice with multiple species and strains of viruses. In most cases, the absence of systemic IFNAR signaling by the mouse led to an increase in viral titer, lethality, or both compared with controls. IFN-I is important in handling all major genetic classes of viruses including single-stranded RNA (ssRNA; +/– stranded), double-stranded RNA and double-stranded DNA viruses, and acute retroviruses (ssRNA-RT). The two exceptions to the strict requirement for IFNAR are influenza and dengue virus infections. In the case of influenza and potentially other respiratory viruses, the type III interferon system (which comprises IFN-λ subtypes and signals using IL-10R2–IFNLR1) plays a dominant role in restricting acute epithelial cell infection, thereby limiting the requirement of IFN-I signaling (10, 11). In dengue, IFN-γ-mediated protection is dominant over IFN-I, although the combined IFNAR$^{-/-}$ × IFNGR$^{-/-}$ mice are more susceptible than the IFNGR$^{-/-}$ mice (12).

The effects of IFN-I that limit viral infection are extensive, but several aspects are important to consider. IFN-I signaling enhances the susceptibility of virally infected cells to undergo programmed cell death, thereby limiting viral replication (4, 23). Dendritic cells (DCs) exposed to IFN-I become activated and secrete proinflammatory cytokines that lead to activation of the adaptive immune response (1). NK cells become potent killers of virally infected cells after exposure to IFN-I (24, 25). IFN-I has direct effects on adaptive αβ T cells and sensitizes them to activation via the TCR (26, 27). IFN-I production by plasmacytoid DCs promotes B-cell activation and production of antiviral antibody (28, 29). In general, these effects of IFN-I signaling are beneficial to the host, as they lead to control of viral replication and spread. The importance of host IFN-I signaling is further reinforced by viral evolution. Viruses have evolved extensive immune-evasion strategies many of which center around inhibition of the host IFN-I response (30, 31). However, the biological responses to IFN-I do not always lead to beneficial outcomes to the host.

IFN-I promote suppression of adaptive immunity during LCMV infection

In the case of viral infections, the best studied example of the negative role of IFN-I are chronic viral infections, in particular infection with LCMV. A long-standing finding in the LCMV field is that small genetic changes can convert an acutely infective strain of LCMV (Armstrong 53b) into a chronically infective strain (Armstrong 53b Clone 13; CL13) (32).

Several hallmarks of the negative effects of chronic viral infection have been discovered using this system. Mice become chronically infected with LCMV because of T-cell 'exhaustion' that prevents normal clearance (33). Several factors have been implicated in the suppression of T-cell-mediated clearance of chronic LCMV; most salient among

Table 1. Phenotype of IFNAR$^{-/-}$ mice infected with different viruses

Virus	Route	Titer	Lethality	References
Dengue	i.v.	Same	N.D.	(12)
Ectromelia	s.c.	+	+	(13)
Friend	i.v.	+	N.D.	(14)
γHV68	i.n.	+	+	(15)
Influenza A/PR/8	i.n.	Same	N.D.	(16)
Influenza A/WSN/33	i.n.	+	N.D.	(17)
LCMV Armstrong	i.v.	+	N.D.	(18)
LCMV Clone 13	i.v.	+	N.D.	(18)
LCMV Docile	i.v.	+	N.D.	(18)
LCMV WE	i.v.	+	N.D.	(18)
LCMV WE	s.c.	+	N.D.	(6)
Mouse hepatitis	i.c.	+	+	(19)
Reovirus T1L	p.o.	+	+	(20)
Semliki Forest	i.v.	N.D.	+	(6)
Theiler's	i.c.	+	N.D.	(21)
Vaccinia	i.v.	+	N.D.	(6)
Vesicular Stomatitis	i.v.	+	+	(6)
West Nile	s.c.	+	+	(22)
West Nile	i.c.	+	+	(22)

Representative references are given. + indicates increased viral titer or lethality. i.c., intracranial; i.v., intravenous; p.o., peroral; s.c., subcutaneous; N.D., not determined.

them are IL-10 and PD-1 (programmed cell death 1). IL-10 is known to antagonize inflammatory activation on multiple immune cell types and its neutralization prevents chronic infection with LCMV (34). PD-1, a member of the CD28/CTLA4 family of T-cell regulators, is upregulated on exhausted T cells found in chronically infected mice. Its ligands, PD-1L and PD-2L, are broadly expressed and inducible by interferons (35). The interaction of PD-1 with PD-L1 acts to limit T-cell activity during chronic infection. Blockade of the PD-1–PD-L1 interaction using mAbs derepresses CD8 T-cell activity and leads to enhanced adaptive immune responses to LCMV infection (36).

In two recent publications, the effects of IL-10 and PD-1 in limiting the response to LCMV infection have been causally linked to IFN-I signaling (37, 38). During the initial stages of infection with CL13, the absence of IFN-I signaling allows for an increased viral titer and delayed clearance during the acute phase of the response (6, 18). Wild-type mice control the primary infection well but become chronic carriers. IFNAR$^{-/-}$ mice also become chronic carriers albeit at higher viral loads. The Cl13 strain induces higher levels of IFN-α and IFN-β than the acutely infective Armstrong strain (37). The major early producer of IFN-I are plasmacytoid DCs that are infected with the virus (37). The presence of IFN-I is associated with a prolonged signature of interferon-inducible genes in spleen cells (38). Despite having higher early titers of LCMV, IFNAR$^{-/-}$ mice show reduced IL-10 in serum and reduced PD-L1 expression on myeloid cells. In wild-type mice, blockade of IFNAR signaling with neutralizing mAbs replicates this effect, leading to reduction of IL-10 and PD-L1. Furthermore, neutralization of IFNAR after the establishment of chronic infection leads to reduced viral burden (37). Therefore, IFNAR plays a major role in the establishment of chronic infection with LCMV and neutralization of IFNAR has therapeutic potential for patients harboring chronic viral infections.

IFN-I protect against extracellular bacteria but are detrimental during intracellular bacterial infection

The response of IFNAR$^{-/-}$ mice to bacterial infections varies depending on the species and route of infection. Table 2 summarizes some of the findings of IFNAR$^{-/-}$ mice infected with several important pathogenic bacteria. In *Streptococcus*, *Escherichia coli*, and *Helicobacter* infections, IFNAR$^{-/-}$ mice have higher titers and/or lethality than wild-type controls. During *Brucella*, *Francisella*, *Salmonella*, *Chlamydia*, *Mycobacterium*, or *Yersinia* infections, IFNAR$^{-/-}$ mice control infection better than wild-type. The IFNAR$^{-/-}$ mice are more resistant to *L. monocytogenes* given systemically. A recent report has shown that during oral infection with *Listeria*, IFNAR signaling may be protective. Based on these initial studies, the simplest conclusion is that IFNAR signaling is beneficial during extracellular bacterial infection and detrimental during intracellular bacterial infection.

Type I IFN signaling provides increased protection during *Streptoccocus* infection by promoting upregulation of TNF-α, IFN-γ and nitric oxide (49). This is associated with restriction of bacterial growth. IFNAR$^{-/-}$ mice have bacteremia, increased systemic titers, and decreased survival. *In vitro*, *Streptococcus spp.* induce IFN-β production through cell-type-specific signaling pathways (52). *Strepcococcus* can trigger IFN-I via the complex of IRF3, stimulator of interferon genes (STING) and TANK-binding kinase 1 (TBK1). In *Streptococcus*-infected macrophages, IFN-β is induced through the IRF3–STING–TBK1 complex and this is partially dependent on MyD88 (IFN-I can also be produced in a MyD88-independent pathway). In contrast, *Streptococcus*-infected DCs induce IFN-β through IRF5 and MyD88. More mechanistic studies are still required to resolve the molecular triggers and *in vivo* cellular sources of IFN-I during *Streptoccocus* infection.

Helicobacter pylori-infected IFNAR$^{-/-}$ mice have higher titers, but the mechanism of IFN-I action in this infection remains unresolved (50). Further work needs to be done on the extracellular bacterial infections to determine how IFN-I is protective and what distinguishes IFN-I from IFN-II in these types of infections.

Following *Brucella* infection, there is IFNAR-dependent upregulation of TNF-related apoptosis-inducing ligand (TRAIL) and splenic apoptosis that is associated with increased susceptibility to infection (39). IFNAR$^{-/-}$ mice also express more IFN-γ and nitric oxide. In the case of *Salmonella enterica* and *Chlamydia muridarum*, IFN-I signaling sensitizes the infected macrophage to undergo cell death (47, 40). Prevention of macrophage cell death during *S. enterica* infection led to decreased bacterial titer. IFNAR$^{-/-}$ mice infected with *Francisella* have decreased titers and lethality compared with controls. This is attributed to the inhibitory effect of IFN-I signaling on IL-17A/F expression (41). IFNAR$^{-/-}$ mice express more IL-17A/F, have an expansion of IL-17^{+} γδ T cells and increased neutrophils at the site of infection.

Finally, treatment with IFN-I agonists such as poly(I:C) also promotes negative outcomes during bacterial infection. In the case of *Mycobacterium tuberculosis*, intranasal delivery of poly(I:C) throughout the course of infection led to increased inflammatory infiltrates and necrosis of lung tissue that was dependent of IFNAR signaling (53). Similar detrimental effects of poly(I:C) treatment are also seen following *Streptoccocus pneumoniae, Staphylococcus aureus* and *L. monocytogenes* infections (54) (see below).

IFN-I signaling is a negative regulator of the innate immune response to *L. monocytogenes*

The first example of the detrimental effect of IFN-I during bacterial infection was discovered following *L. monocytogenes* infection. To date, it remains the best examined system, yielding information on the mechanisms of IFN-I induction, cellular sources and targets of IFN-I, and the nature of biological outcomes.

Triggers and cellular sources of IFN-I during L. monocytogenes infection

Macrophages infected with *L. monocytogenes* induce expression of IFN-I that is dependent on bacterial expression of the pore-forming toxin listeriolysin O (LLO) (55, 56). LLO is important for the bacterial egress from the nascent phagosome to the cytosol (57). LLO alone does not induce strong levels of IFN-I production by the infected macrophage, suggesting that the presence of cytosolic bacteria is the driver of

Table 2. Phenotype of IFNAR$^{-/-}$ mice infected with bacterial species

Bacteria	Route	Titer	Lethality	References
Brucella abortus	i.p.	–	N.D.	(39)
Chlamydia muridarum	i.n.	–	N.D.	(40)
Francisella novicida	s.c.	–	–	(41)
Francisella novicida	i.n.	–	–	(41)
Francisella tularensis	i.n.	Same	N.D.	(41)
Listeria monocytogenes	i.p.	–	–	(42)
Listeria monocytogenes	i.v.	–	–	(43, 44)
Mycobacterium tuberculosis	i.n.	–	–	(45)
Mycobacterium tuberculosis	i.v.	–	N.D.	(46)
Salmonella enteric	i.v.	–	–	(47)
Yersinia pestis	i.n.	–	–	(48)
Escherichia coli	i.v.	N.D.	+	(49)
Helicobacter pylori	p.o.	+	N.D.	(50)
Listeria monocytogenes	p.o.	+	+	(51)
Streptococcus pyogenes	s.c.	N.D.	+	(52)
Streptococcus pyogenes	i.p.	+	+	(49)
Streptococcus pneumoniae	i.v.	+	+	(49)
Streptococcus pneumoniae	i.c	+	+	(49)

+ or – indicates increased or decreased bacterial titer or lethality, respectively. Shading indicates bacterial infections where IFN-I signaling is beneficial to the host. Representative references are given. i.c., intracranial; i.p., intraperitoneal; i.v., intravenous; p.o., peroral; s.c., subcutaneous; N.D., not determined.

IFN-I production (56). This is reinforced by experiments demonstrating that *Bacillus subtilis* expressing LLO gain access to the cytosol and also strongly induce IFN-responsive genes.

The major molecular driver of IFN-I induction by *L. monocytogenes* is the cyclic dinucleotide c-di-AMP (58). The cyclic dinucleotides were initially discovered in bacteria as a second messenger system that also doubles as a pathogen-associated molecular pattern (59). Interestingly, c-di-AMP is actively exported from the bacteria and the induced expression of a c-di-AMP synthesizing enzyme (di-adenylate cyclase) increases *Ifnb1* gene expression by infected macrophages (58). A sensor for cyclic dinucleotides has been identified as the helicase DDX41, which recruits STING, TBK1 and IRF3 (see above) to drive upregulation of IFN-I genes (60).

Splenic macrophages (CD11b$^+$CD11c$^-$PDCA1$^-$B220$^-$) and TNF/iNOS-producing DCs (TIP-DCs; CD11b$^+$CD11c$^+$Ly6c$^+$) produce IFN-I following *L. monocytogenes* infection *in vivo* (61, 62). Mice lacking CCR2 expression, which do not recruit TIP-DCs to the spleen, have reduced expression of IFN-α following *L. monocytogenes* infection (63). To date, there is no clear demonstration that a *L. monocytogenes*-infected myeloid cell population is producing IFN-I *in vivo*. On the basis of experiments using immunofluorescent colocalization, TIP-DCs appear not to be infected (62). The work that identified IFN-I production by splenic macrophages did not evaluate the infected status of the cells (61). Therefore, at this time, the connection between the molecular mechanisms of induction and *in vivo* cellular sources of IFN-I cannot be definitely established.

Biological outcomes of IFN-I signaling during L. monocytogenes infection

Listeria monocytogenes causes apoptotic cell death of macrophages that is enhanced by IFNAR signaling. Within 2 h of infection, bone marrow-derived macrophages upregulate IFN-β and phosphorylate STAT1 (64). Deletion of IFNAR on macrophages raises their resistance to *L. monocytogenes*-mediated killing significantly. The death induced by *L. monocytogenes* is dependent on bacterial expression of LLO (64). Since LLO is essential for virulence, it is unclear if it has a direct role in killing the infected macrophage or is only important for allowing egress of the bacteria to the cytosol. IFNAR-dependent macrophage death is also found following infection of mice with *L. monocytogenes* (43). A population of TNF-α-producing CD11b$^+$ macrophages is depleted following infection of wild-type mice. This population is maintained in IFNAR$^{-/-}$ mice, demonstrating a role for IFN-I in sensitization of macrophage death. It is not known at this time if the macrophages that die *in vivo* are infected by the bacteria.

The most profound IFNAR-dependent effect seen in mice infected with *L. monocytogenes* is the extensive depletion of white-pulp lymphocytes via apoptotic cell death (42). In wild-type mice, apoptosis begins in the periarteriolar lymphoid sheath (T-cell area) and extends to the entire white pulp in a dose-dependent manner (65). Removal of IFNAR significantly limits the number of apoptotic profiles and the extent of apoptotic death in any given white pulp (42). Treatment of T cells with IFN-α sensitizes them to LLO-induced apoptosis suggesting that secreted LLO may be a killer molecule *in vivo* (42). Additionally, IFN-I upregulate TRAIL on NK cells and TRAIL receptor (DR5) on the T cells and macrophages, providing a second potential mechanism for interferon-mediated lymphocyte and macrophage killing (66). TRAIL$^{-/-}$ mice harbor lower bacterial burdens than wild-type counterparts, have decreased splenic lymphocyte apoptosis, and increased accumulation of myeloid cells in the spleen following *L. monocytogenes* infection.

The reduction in lymphocyte death seen following *L. monocytogenes* infection is the major reason that IFNAR$^{-/-}$ mice are more resistant to infection (67). Several lines of evidence support this conclusion. First, mice deficient in lymphocytes (SCID/

RAG mice) are highly resistant to *L. monocytogenes* infection (68, 69). Second, mixed bone marrow chimeras that create mice that are IFNAR$^+$ in all cells except lymphocytes are also resistant to *L. monocytogenes* infection (69). This demonstrates the dominance of IFN-I signaling effects on lymphocytes. Third, induction of IFN-I using poly(I:C) increases the susceptibility to infection of wild-type but not SCID mice (69, 44). Finally, *L. monocytogenes* infection induces myeloid cell expression of IL-10 that is dependent on IFNAR expression by lymphocytes (69). The upregulation of IL-10 is a negative regulator of pathogen handling and IL-10$^{-/-}$ mice are more resistant to infection despite having normal lymphocyte apoptosis (69, 70).

As an aside, the work on IFNAR effects on *L. monocytogenes* infection was conducted on three different genetic backgrounds with different susceptibilities to infection. In all three strains—C57BL/6 (44), 129S6 (42) and Balb/c (43)—IFNAR signaling was detrimental to the outcome of infection. This demonstrates that IFNAR effects are dominant over the genetic susceptibilities of the mouse strains to *L. monocytogenes* infection. Further work needs to be done to determine if this applies to other bacterial infection models.

Conclusion

The initial paradigm of the IFN-I system is that it provides antiviral protection that sometimes goes awry in certain autoimmunities. This simplified view has been replaced with a more complex and interesting role for the interferons in regulating immune responses. Chronic viral infections are teaching us that while early IFN-I is important in controlling viremia, pathogens that can overcome this initial control benefit from the immune regulation that takes place following long-term interferon induction. The clinical relevance of this can be seen during infection of patients with HIV, where chronic IFN-I leads to TRAIL-mediated T-cell death and poor disease outcome (71). Future work needs to be done to determine the applicability of IFN-I modulation as a therapeutic to important chronic human viral infections.

Another important area of research is the interface between viral and bacterial coinfections. The clinical importance of severe bacterial infections occurring after a primary viral infection is well established (72). Respiratory bacterial infections are more dangerous to patients when they occur following infection with viruses such as influenza and respiratory syncytial virus. This observation has been replicated in mouse models of infection (73, 74). However, the interaction between viral and bacterial infection is not always deleterious. Infection with herpesvirus induces prolonged IFN-γ production that leads to protection against infection with *L. monocytogenes* and *Yersinia pestis* (75). The main distinguishing feature between the two potential outcomes (acute versus chronic virus) and (detrimental versus beneficial) appears to center on the balance between IFN-I and IFN-γ effects. This reinforces the need to understand the molecular effects of these cytokines during bacterial infection.

In the bacterial world, IFN-I were once believed to be relatively unimportant. This idea was reversed by research on *L. monocytogenes*. Careful examination of additional bacterial infections has demonstrated that both route and tropism of bacterial infections matter in the requirement of IFN-I. Future studies will be needed to determine cellular sources, molecular triggers and biological outcomes of IFN-I for many classes of bacterial pathogens. It will be interesting to see if bacteria have evolved mechanisms to manipulate the IFN-I system like some viruses do.

Recently, it has been shown that the balance of IFN-I and IFN-II may be important in the outcome of human mycobacterial infections (76). Reminiscent of chronic LCMV infection, IL-10 is also a key player in the IFN-I-mediated suppression of mycobacterial immunity. Future work will be needed to determine if chronic IFN-I production is a common determinant of negative outcomes in infectious diseases. Finally, we need a better understanding of how the genes specific for IFN-I lead to different outcomes from their close cousin, IFN-II.

Funding

National Institute of Allergy and Infectious Diseases (AI062832).

Acknowledgements

I wish to thank Dr Emil R. Unanue for his support and insightful discussions. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

References

1 Theofilopoulos, A. N., Baccala, R., Beutler, B. and Kono, D. H. 2005. Type I interferons (alpha/beta) in immunity and autoimmunity. *Annu. Rev. Immunol.* 23:307.
2 Stark, G. R. and Darnell, J. E., Jr. 2012. The JAK-STAT pathway at twenty. *Immunity* 36:503.
3 Platanias, L. C. 2005. Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat. Rev. Immunol.* 5:375.
4 Stark, G. R., Kerr, I. M., Williams, B. R., Silverman, R. H. and Schreiber, R. D. 1998. How cells respond to interferons. *Annu. Rev. Biochem.* 67:227.
5 Liu, S. Y., Sanchez, D. J., Aliyari, R., Lu, S. and Cheng, G. 2012. Systematic identification of type I and type II interferon-induced antiviral factors. *Proc. Natl Acad. Sci. USA* 109:4239.
6 Müller, U., Steinhoff, U., Reis, L. F. *et al.* 1994. Functional role of type I and type II interferons in antiviral defense. *Science* 264:1918.
7 Trinchieri, G. 2010. Type I interferon: friend or foe? *J. Exp. Med.* 207:2053.
8 Smith, P. L., Lombardi, G. and Foster, G. R. 2005. Type I interferons and the innate immune response–more than just antiviral cytokines. *Mol. Immunol.* 42:869.
9 Dunn, G. P., Koebel, C. M. and Schreiber, R. D. 2006. Interferons, immunity and cancer immunoediting. *Nat. Rev. Immunol.* 6:836.
10 Mordstein, M., Neugebauer, E., Ditt, V. *et al.* 2010. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. *J. Virol.* 84:5670.
11 Levy, D. E., Marié, I. J. and Durbin, J. E. 2011. Induction and function of type I and III interferon in response to viral infection. *Curr. Opin. Virol.* 1:476.
12 Shresta, S., Kyle, J. L., Snider, H. M., Basavapatna, M., Beatty, P. R. and Harris, E. 2004. Interferon-dependent immunity is essential for resistance to primary dengue virus infection in mice, whereas T- and B-cell-dependent immunity are less critical. *J. Virol.* 78:2701.
13 Panchanathan, V., Chaudhri, G. and Karupiah, G. 2005. Interferon function is not required for recovery from a secondary poxvirus infection. *Proc. Natl Acad. Sci. USA* 102:12921.
14 Gerlach, N., Schimmer, S., Weiss, S., Kalinke, U. and Dittmer, U. 2006. Effects of type I interferons on Friend retrovirus infection. *J. Virol.* 80:3438.
15 Barton, E. S., Lutzke, M. L., Rochford, R. and Virgin, H. W. IV. 2005. Alpha/beta interferons regulate murine gammaherpesvirus

latent gene expression and reactivation from latency. *J. Virol.* 79:14149.
16 Price, G. E., Gaszewska-Mastarlarz, A. and Moskophidis, D. 2000. The role of alpha/beta and gamma interferons in development of immunity to influenza A virus in mice. *J. Virol.* 74:3996.
17 García-Sastre, A., Durbin, R. K., Zheng, H. *et al.* 1998. The role of interferon in influenza virus tissue tropism. *J. Virol.* 72:8550.
18 Ou, R., Zhou, S., Huang, L. and Moskophidis, D. 2001. Critical role for alpha/beta and gamma interferons in persistence of lymphocytic choriomeningitis virus by clonal exhaustion of cytotoxic T cells. *J. Virol.* 75:8407.
19 Ireland, D. D., Stohlman, S. A., Hinton, D. R., Atkinson, R. and Bergmann, C. C. 2008. Type I interferons are essential in controlling neurotropic coronavirus infection irrespective of functional CD8 T cells. *J. Virol.* 82:300.
20 Johansson, C., Wetzel, J. D., He, J., Mikacenic, C., Dermody, T. S. and Kelsall, B. L. 2007. Type I interferons produced by hematopoietic cells protect mice against lethal infection by mammalian reovirus. *J. Exp. Med.* 204:1349.
21 Fiette, L., Aubert, C., Müller, U. *et al.* 1995. Theiler's virus infection of 129Sv mice that lack the interferon alpha/beta or interferon gamma receptors. *J. Exp. Med.* 181:2069.
22 Samuel, M. A. and Diamond, M. S. 2005. Alpha/beta interferon protects against lethal West Nile virus infection by restricting cellular tropism and enhancing neuronal survival. *J. Virol.* 79:13350.
23 Stetson, D. B. and Medzhitov, R. 2006. Type I interferons in host defense. *Immunity* 25:373.
24 Garcia-Sastre, A. and Biron, C. A. 2006. Type 1 interferons and the virus-host relationship: a lesson in detente. *Science* 312:879.
25 Nguyen, K. B., Salazar-Mather, T. P., Dalod, M. Y. *et al.* 2002. Coordinated and distinct roles for IFN-alpha beta, IL-12, and IL-15 regulation of NK cell responses to viral infection. *J. Immunol.* 169:4279.
26 Huber, J. P. and Farrar, J. D. 2011. Regulation of effector and memory T-cell functions by type I interferon. *Immunology* 132:466.
27 Sun, S., Zhang, X., Tough, D. F. and Sprent, J. 1998. Type I interferon-mediated stimulation of T cells by CpG DNA. *J. Exp. Med.* 188:2335.
28 Deal, E. M., Lahl, K., Narváez, C. F., Butcher, E. C. and Greenberg, H. B. 2013. Plasmacytoid dendritic cells promote rotavirus-induced human and murine B cell responses. *J. Clin. Invest.* 123:2464.
29 Jego, G., Palucka, A. K., Blanck, J. P., Chalouni, C., Pascual, V. and Banchereau, J. 2003. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity* 19:225.
30 Diamond, M. S. 2009. Mechanisms of evasion of the type I interferon antiviral response by flaviviruses. *J. Interferon Cytokine Res.* 29:521.
31 Taylor, K. E. and Mossman, K. L. 2013. Recent advances in understanding viral evasion of type I interferon. *Immunology* 138:190.
32 Salvato, M., Borrow, P., Shimomaye, E. and Oldstone, M. B. 1991. Molecular basis of viral persistence: a single amino acid change in the glycoprotein of lymphocytic choriomeningitis virus is associated with suppression of the antiviral cytotoxic T-lymphocyte response and establishment of persistence. *J. Virol.* 65:1863.
33 Moskophidis, D., Lechner, F., Pircher, H. and Zinkernagel, R. M. 1993. Virus persistence in acutely infected immunocompetent mice by exhaustion of antiviral cytotoxic effector T cells. *Nature* 362:758.
34 Moore, K. W., de Waal Malefyt, R., Coffman, R. L. and O'Garra, A. 2001. Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol.* 19:683.
35 Keir, M. E., Butte, M. J., Freeman, G. J. and Sharpe, A. H. 2008. PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.* 26:677.
36 Barber, D. L., Wherry, E. J., Masopust, D. *et al.* 2006. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* 439:682.
37 Teijaro, J. R., Ng, C., Lee, A. M. *et al.* 2013. Persistent LCMV infection is controlled by blockade of type I interferon signaling. *Science* 340:207.
38 Wilson, E. B., Yamada, D. H., Elsaesser, H. *et al.* 2013. Blockade of chronic type I interferon signaling to control persistent LCMV infection. *Science* 340:202.
39 de Almeida, L. A., Carvalho, N. B., Oliveira, F. S. *et al.* 2011. MyD88 and STING signaling pathways are required for IRF3-mediated IFN-β induction in response to *Brucella abortus* infection. *PLoS One* 6:e23135.
40 Qiu, H., Fan, Y., Joyee, A. G. *et al.* 2008. Type I IFNs enhance susceptibility to *Chlamydia muridarum* lung infection by enhancing apoptosis of local macrophages. *J. Immunol.* 181:2092.
41 Henry, T., Kirimanjeswara, G. S., Ruby, T. *et al.* 2010. Type I IFN signaling constrains IL-17A/F secretion by gammadelta T cells during bacterial infections. *J. Immunol.* 184:3755.
42 Carrero, J. A., Calderon, B. and Unanue, E. R. 2004. Type I interferon sensitizes lymphocytes to apoptosis and reduces resistance to Listeria infection. *J. Exp. Med.* 200:535.
43 Auerbuch, V., Brockstedt, D. G., Meyer-Morse, N., O'Riordan, M. and Portnoy, D. A. 2004. Mice lacking the type I interferon receptor are resistant to *Listeria monocytogenes*. *J. Exp. Med.* 200:527.
44 O'Connell, R. M., Saha, S. K., Vaidya, S. A. *et al.* 2004. Type I interferon production enhances susceptibility to *Listeria monocytogenes* infection. *J. Exp. Med.* 200:437.
45 Desvignes, L., Wolf, A. J. and Ernst, J. D. 2012. Dynamic roles of type I and type II IFNs in early infection with *Mycobacterium tuberculosis*. *J. Immunol.* 188:6205.
46 Stanley, S. A., Johndrow, J. E., Manzanillo, P. and Cox, J. S. 2007. The Type I IFN response to infection with *Mycobacterium tuberculosis* requires ESX-1-mediated secretion and contributes to pathogenesis. *J. Immunol.* 178:3143.
47 Robinson, N., McComb, S., Mulligan, R., Dudani, R., Krishnan, L. and Sad, S. 2012. Type I interferon induces necroptosis in macrophages during infection with *Salmonella enterica* serovar Typhimurium. *Nat. Immunol.* 13:954.
48 Patel, A. A., Lee-Lewis, H., Hughes-Hanks, J., Lewis, C. A. and Anderson, D. M. 2012. Opposing roles for interferon regulatory factor-3 (IRF-3) and type I interferon signaling during plague. *PLoS Pathog.* 8:e1002817.
49 Mancuso, G., Midiri, A., Biondo, C. *et al.* 2007. Type I IFN signaling is crucial for host resistance against different species of pathogenic bacteria. *J. Immunol.* 178:3126.
50 Watanabe, T., Asano, N., Fichtner-Feigl, S. *et al.* 2010. NOD1 contributes to mouse host defense against *Helicobacter pylori* via induction of type I IFN and activation of the ISGF3 signaling pathway. *J. Clin. Invest.* 120:1645.
51 Kernbauer, E., Maier, V., Rauch, I., Müller, M. and Decker, T. 2013. Route of infection determines the impact of type I interferons on innate immunity to *Listeria monocytogenes*. *PLoS One* 8:e65007.
52 Gratz, N., Hartweger, H., Matt, U. *et al.* 2011. Type I interferon production induced by *Streptococcus pyogenes*-derived nucleic acids is required for host protection. *PLoS Pathog.* 7:e1001345.
53 Antonelli, L. R., Gigliotti Rothfuchs, A., Gonçalves, R. *et al.* 2010. Intranasal Poly-IC treatment exacerbates tuberculosis in mice through the pulmonary recruitment of a pathogen-permissive monocyte/macrophage population. *J. Clin. Invest.* 120:1674.
54 Tian, X., Xu, F., Lung, W. Y. *et al.* 2012. Poly I:C enhances susceptibility to secondary pulmonary infections by gram-positive bacteria. *PLoS One* 7:e41879.
55 Stockinger, S., Materna, T., Stoiber, D. *et al.* 2002. Production of type I IFN sensitizes macrophages to cell death induced by *Listeria monocytogenes*. *J. Immunol.* 169:6522.
56 McCaffrey, R. L., Fawcett, P., O'Riordan, M. *et al.* 2004. A specific gene expression program triggered by Gram-positive bacteria in the cytosol. *Proc. Natl Acad. Sci. USA* 101:11386.
57 Schnupf, P. and Portnoy, D. A. 2007. Listeriolysin O: a phagosome-specific lysin. *Microbes Infect.* 9:1176.
58 Woodward, J. J., Iavarone, A. T. and Portnoy, D. A. 2010. c-di-AMP secreted by intracellular *Listeria monocytogenes* activates a host type I interferon response. *Science* 328:1703.
59 Bowie, A. G. 2012. Innate sensing of bacterial cyclic dinucleotides: more than just STING. *Nat. Immunol.* 13:1137.

60 Parvatiyar, K., Zhang, Z., Teles, R. M. *et al*. 2012. The helicase DDX41 recognizes the bacterial secondary messengers cyclic di-GMP and cyclic di-AMP to activate a type I interferon immune response. *Nat. Immunol*. 13:1155.
61 Stockinger, S., Kastner, R., Kernbauer, E. *et al*. 2009. Characterization of the interferon-producing cell in mice infected with *Listeria monocytogenes*. *PLoS Pathog*. 5:e1000355.
62 Dresing, P., Borkens, S., Kocur, M., Kropp, S. and Scheu, S. 2010. A fluorescence reporter model defines "Tip-DCs" as the cellular source of interferon β in murine listeriosis. *PLoS One* 5:e15567.
63 Serbina, N. V., Salazar-Mather, T. P., Biron, C. A., Kuziel, W. A. and Pamer, E. G. 2003. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity* 19:59.
64 Zwaferink, H., Stockinger, S., Hazemi, P., Lemmens-Gruber, R. and Decker, T. 2008. IFN-beta increases listeriolysin O-induced membrane permeabilization and death of macrophages. *J. Immunol*. 180:4116.
65 Merrick, J. C., Edelson, B. T., Bhardwaj, V., Swanson, P. E. and Unanue, E. R. 1997. Lymphocyte apoptosis during early phase of Listeria infection in mice. *Am. J. Pathol*. 151:785.
66 Zheng, S. J., Jiang, J., Shen, H. and Chen, Y. H. 2004. Reduced apoptosis and ameliorated listeriosis in TRAIL-null mice. *J. Immunol*. 173:5652.
67 Carrero, J. A. and Unanue, E. R. 2012. Mechanisms and immunological effects of apoptosis caused by *Listeria monocytogenes*. *Adv. Immunol*. 113:157.
68 Bancroft, G. J., Bosma, M. J., Bosma, G. C. and Unanue, E. R. 1986. Regulation of macrophage Ia expression in mice with severe combined immunodeficiency: induction of Ia expression by a T cell-independent mechanism. *J. Immunol*. 137:4.
69 Carrero, J. A., Calderon, B. and Unanue, E. R. 2006. Lymphocytes are detrimental during the early innate immune response against *Listeria monocytogenes*. *J. Exp. Med*. 203:933.
70 Dai, W. J., Köhler, G. and Brombacher, F. 1997. Both innate and acquired immunity to *Listeria monocytogenes* infection are increased in IL-10-deficient mice. *J. Immunol*. 158:2259.
71 Herbeuval, J. P. and Shearer, G. M. 2007. HIV-1 immunopathogenesis: how good interferon turns bad. *Clin. Immunol*. 123:121.
72 Beadling, C. and Slifka, M. K. 2004. How do viral infections predispose patients to bacterial infections? *Curr. Opin. Infect. Dis*. 17:185.
73 Li, W., Moltedo, B. and Moran, T. M. 2012. Type I interferon induction during influenza virus infection increases susceptibility to secondary *Streptococcus pneumoniae* infection by negative regulation of γδ T cells. *J. Virol*. 86:12304.
74 Kim, Y. G., Park, J. H., Reimer, T. *et al.* 2011. Viral infection augments Nod1/2 signaling to potentiate lethality associated with secondary bacterial infections. *Cell Host Microbe*. 9:496.
75 Barton, E. S., White, D. W., Cathelyn, J. S. *et al*. 2007. Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* 447:326.
76 Teles, R. M., Graeber, T. G., Krutzik, S. R. *et al.* 2013. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. *Science* 339:1448.