Published in final edited form as:

Nat Rev Rheumatol. 2010 January ; 6(1): 40–49. doi:10.1038/nrrheum.2009.237.

Type I interferons: crucial participants in disease amplification in autoimmunity

John C. Hall and

Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Mason F. Lord Building, Center Tower, Suite 5300, Baltimore, MD 21224, USA

Antony Rosen

Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Mason F. Lord Building, Center Tower, Suite 4100, Room 412, Baltimore, MD 21224, USA

Abstract

A significant body of data implicates the type I interferon (IFN) pathway in the pathogenesis of autoimmune rheumatic diseases. In these disorders, a reinforcing cycle of IFN production can contribute to immunopathology through multiple mechanisms. The type I IFN cytokines are pleiotropic in their effects, mediating anti-viral and anti-tumor activities, and possessing numerous immunomodulatory functions for both the innate and adaptive immune responses. A key principle of the type I IFN system is rapid induction and amplification of the signaling pathway, which generates a feed-forward loop of IFN production, ensuring that a vigorous anti-viral immune response is mounted. While such feed-forward pathways are highly adaptive when it comes to rapid and effective virus eradication, this amplification can be maladaptive in immune responses directed against host tissues. Such feed-forward loops, however, create special opportunities for therapy.

INTRODUCTION

Systemic autoimmune diseases, which include systemic lupus erythematosus (SLE), myositis, Sjögren's syndrome (SS) and systemic sclerosis (SSc), are a complex group of heterogeneous disorders that are characterized by an antigen-driven immune response against self with the destruction of host tissue. A hallmark of these diseases is their self-sustaining and auto-amplifying nature, in which immune-mediated tissue damage and tissue repair collaborate in a feed-forward loop to provide the destructive power and the fuel that sustain the process. In this regard, different modes of cell death and enhanced autoantigen expression in regenerating cells seem to have key roles.^{1,2} The disease phenotypes are quite distinct in terms of the primary tissues targeted, the specific autoantibodies elaborated, and the inflammatory and immune effector pathways that predominate. Nevertheless, in spite of the different nature of each disease, they clearly share some pathogenic mechanisms.

Over the past 3 decades, a significant body of data has accumulated that implicates type I IFN in the pathogenesis of systemic autoimmune diseases. Type I IFN cytokines are pleiotropic in their effects, mediating anti-viral and anti-tumor activities, and possessing

CORRESPONDENCE TO: arosen@jhmi.edu.

COMPETING INTERESTS

The authors declare no competing interests.

numerous immunomodulatory functions, with the capacity to amplify both innate and adaptive immune responses. Understanding which of these effects contributes to autoimmune disease pathogenesis, and whether these effects can be exploited therapeutically, remain important questions.

In this Review article, we will introduce the evidence implicating the type I IFN pathway in the initiation and propagation of systemic autoimmune disease and examine the mechanisms that regulate type I IFN production. The self-amplifying features of this pathway and its relevance to autoimmunity will be highlighted, and the opportunities and potential pitfalls in targeting type I IFN therapeutically will be addressed.

THE IFN FAMILY

IFNs were initially identified as secreted factors capable of inhibiting viral replication. Later studies, however, revealed three distinct classes of IFN, each capable of mediating a wide array of biological functions. The three members of the IFN family—type I, type II and type III—are classified based on structural homology and chromosomal localization, and each signals through a unique receptor complex (Table 1). Type I IFN (comprising IFN- α , - β , - ω , - ϵ and - κ) and type III IFN (IFN- λ) can be produced by almost all nucleated cells. They activate identical signaling pathways, induce an overlapping set of genes, and mediate potent anti-viral effects.^{3–6} A major difference between type I and type III IFN is that the former's receptor is ubiquitously expressed, rendering all cells capable of responding to type I IFN, whereas the type III IFN receptor seems to have limited distribution (primarily on epithelial cells and plasmacytoid dendritic cells),^{7,8} suggesting that a limited array of cells respond to type III IFN.

Type II IFN (IFN- γ) is quite distinct from types I and III IFN. Only natural killer cells (NK), NK T cells and T cell populations produce IFN- γ , and signaling through the IFN- γ receptor activates some pathways that are shared with types I and III IFN, as well as some distinct pathways.⁹ The primary role of IFN- γ is to modulate the adaptive immune response,¹⁰ although it is also capable of mediating limited anti-viral effects. Although all three classes of IFN can have a pathogenic role in autoimmunity, this Review will focus on type I IFN.

THE ROLES OF TYPE I IFN

The type I IFN system constitutes a family of cytokines that can be produced by all nucleated cells upon recognition of conserved viral and bacterial structures (Table 1).^{11–13} Interestingly, although the family members are largely similar, there are some nuances to the downstream effects of each type I IFN cytokine.¹⁴ The considerable redundancy of the type I IFN genes is thought to signify the evolutionary importance of this pathway. *In vivo* observations in humans and mice underscore the critical role of type I IFN in the antiviral response. Many viruses encode inhibitors of type I IFN signaling and production,¹⁵ highlighting the selective pressure that the IFN system places on viral success. In addition, human deficiencies in IFN signaling pathway genes render individuals highly susceptible to various infections. For example, mutations in tyrosine kinase 2 (TYK2), a type I and type III IFN receptor-associated Janus kinase that is necessary for signal transduction through the IFN receptors, renders individuals susceptible to viral, bacterial and fungal infections.¹⁶ Deficiency in signal transducers and activators of transcription 1 (STAT1), which is activated downstream of all IFN receptors and is critical for the induction of IFN-stimulated genes, results in early lethality from viral disease.¹⁷

Studies in mice are consistent with these findings. Mice deficient in the type I IFN receptor quickly succumb to sublethal challenge with a variety of viruses.^{18,19} In addition to its

effects on viral infection, signaling through the type I IFN receptor prevents tumor growth,²⁰ probably via the activation of NK cells and cytolytic T cells.^{21,22} The role of type I IFN in the anti-viral and anti-tumor response is further highlighted by the clinical efficacy of IFN compounds in the treatment of chronic viral infections (such as hepatitis C) and some malignancies (such as hairy cell leukemia and melanoma).

Although type I IFN is critical for the host immune response, several lines of evidence strongly suggest that these cytokines are directly involved in the pathogenesis of systemic autoimmune disease. First, it is known that IFN immunotherapy can induce autoimmunity. Second, circulating immune complexes can initiate IFN production and dendritic cell (DC) maturation. Third, studies have shown a high level of IFN-regulated gene expression in patients with systemic autoimmunity. Finally, polymorphisms in IFN pathway genes are associated with an increased risk of systemic autoimmune disease.

IFN therapy can induce autoimmunity

High-dose IFN therapy is effective in treating chronic viral disease and malignancy. In some patients, however, this treatment has been associated with the generation of autoimmunity.²³ The autoimmune phenomena that manifest are quite diverse, ranging from the induction of autoantibodies, to the development of autoimmune diseases, including SLE, polymyositis, and rheumatoid arthritis (RA). Although IFN immunotherapy is directly related to the development of autoimmunity, the development of overt autoimmune disease in these individuals is rare, suggesting that additional genetic and environmental susceptibility factors are necessary to induce disease. Interestingly, the autoimmune symptoms that manifest can resolve after the cessation of treatment,²⁴ suggesting that although type I IFN can initiate symptoms of autoimmunity, additional factors are required for the initiation of a self-propagating loop. These findings have implications for the treatment of autoimmune disease, whereby inhibiting the self-propagating cycle of tissue destruction and regeneration could stop disease flares.

Immune complexes and IFN production

Elevated type I IFN levels in the serum of patients with systemic autoimmunity were described several decades ago,²⁵ but were largely ignored. Significant momentum for a pathogenic role of type I IFN was provided by Rönnblom and colleagues when they demonstrated that elevated serum IFN- α levels could be driven by immune complexes. In their study, when immunoglobulin from patients with SLE was combined with plasmid DNA or apoptotic cells and added to peripheral blood mononuclear cells (PBMCs), IFN was produced.^{26,27} Similar findings have been described in patients with SS and SSc.^{28,29} Subsequently, Banchereau and colleagues demonstrated that serum from patients with SLE was capable of inducing the maturation of monocytes into DCs in an IFN- α -dependent manner.³⁰ As prominent regulators of T cell activation, DCs occupy a central position in the immune system. Chronic DC maturation in the presence of increased IFN levels might have a central role in autoimmunity by activating autoreactive T cells to drive the autoimmune destruction of target tissues. The ability of self antigen-containing immune complexes to stimulate IFN production further contributes to a self-propagating loop of tissue damage.

Expression of IFN-regulated genes

Studies from multiple groups have demonstrated increased expression of a subset of type I IFN-regulated genes in PBMCs from patients with SLE compared with healthy controls.^{31–34} Furthermore, expression of this so-called ‘IFN signature’ correlated with disease severity and activity in a portion of these patients.^{31,32,35} Consistent with the fact that IFN immunotherapy can induce a multitude of autoimmune diseases, other studies have demonstrated that the IFN signature is expressed broadly across the rheumatic diseases. For

example, PBMCs from patients with dermatomyositis, SS and SSc express a similar group of IFN-regulated genes at high levels.³⁶⁻³⁹ In addition, studies on tissue from patients with dermatomyositis or SS demonstrated that IFN-regulated genes and proteins are expressed at high levels in the relevant disease microenvironment.^{40,41} Professional type I IFN-producing plasmacytoid dendritic cells (pDCs) are enriched in the inflamed muscle and salivary glands of patients with dermatomyositis and SS, respectively,^{40,41} providing evidence for IFN expression in inflamed tissues. Of importance, despite a positive association between increased IFN-regulated gene expression and disease activity and/or severity, this signature is only expressed in a subset of patients with active disease, suggesting that other mechanisms contribute to disease pathogenesis. As viral infections can be difficult to distinguish from disease flares, further studies are necessary to determine how the different signatures observed in disease subsets differ from those observed during acute or chronic viral infection, or during IFN therapy.

Gene polymorphisms of the IFN pathway

Studies have identified polymorphisms within genes of the IFN pathway that confer an increased risk for several systemic autoimmune diseases. These genetic effects should be viewed as gain switches, which influence the nature or magnitude of a response, rather than as binary switches, which are either 'on' or 'off'. Gain switches are particularly relevant in diseases where feed-forward loops contribute to pathogenesis.

Interferon regulatory factor 5 (IRF5) is a member of a family of transcription factors that regulate the production of type I IFN (discussed below). The original description of an association between *IRF5* and SLE⁴² has been widely replicated, and several single nucleotide polymorphisms have been identified that regulate both splicing and expression of the *IRF5* gene.^{43,44} Furthermore, the risk haplotype of IRF5 is associated with increased serum IFN- α activity in patients with SLE.⁴⁵ However, the presence of this haplotype is clearly not the only mechanism regulating the IFN response, as anti-RNA binding protein and/or anti-double-stranded DNA (dsDNA) antibodies in these individuals can also predict increased serum IFN- α activity.⁴⁵ In addition, studies have suggested that *IRF5* polymorphisms are associated with an increased risk of SS and SSc.^{46,47}

STAT4 is activated downstream of a number of cytokines, including type I IFN, and contributes to T cell differentiation and IFN- γ production.^{48,49} Polymorphisms within *STAT4* have been linked with an increased risk of RA and SLE.⁵⁰ Patients with SLE and the *STAT4* risk haplotype have a more severe disease phenotype and seem to have increased sensitivity to type I IFN, than patients lacking this haplotype.^{52,52} The functional significance of these polymorphisms on activation of the type I IFN pathway requires further attention.

SELF-AMPLIFYING IFN PRODUCTION

The self-amplifying nature of autoimmune diseases has an interesting counterpart in the type I IFN system, which is characterized by its striking capacity to amplify rapidly. Many of the receptors, signal transduction molecules and transcription factors that drive IFN production are themselves regulated by IFN.^{53,54} This creates a feed-forward mechanism whereby the production of type I IFN further increases the expression of molecules that drive IFN production in the responding and neighboring cells. Although such feed-forward loops are highly adaptive in allowing the host to respond rapidly and broadly to viral infection, they also create the potential for amplifying immunopathology in systemic autoimmunity. Additionally, several antigens targeted in systemic autoimmune diseases are highly responsive to IFN, potentially augmenting antigen drive in these diseases (see below).

INDUCTION OF IFN EXPRESSION

To initiate an effective anti-viral immune response all cells should be capable of sensing and responding appropriately to infection. In this regard, the host encodes a number of germ-line pattern recognition receptors (PRRs) that are expressed on immune and non-immune cells. These receptors are capable of recognizing a wide array of conserved pathogen-associated molecular patterns (PAMPs) that do not occur under normal circumstances in the host. The PRRs sense specific viral and bacterial structures and induce the production of type I IFN. There are two types of PRR: ubiquitously expressed cytoplasmic nucleic acid-sensing molecules and membrane-bound Toll-like receptors (TLRs). The expression of the latter is more limited than that of the cytoplasmic receptors (Table 2).

Cytoplasmic nucleic acid-sensing receptors

The retinoic-acid-inducible gene I (RIG-I)-like RNA helicases, which include RIG-I and melanoma differentiation-associated gene 5 (MDA5; also known as IFIH1), are a ubiquitously expressed group of cytoplasmic receptors that recognize and bind unique viral RNA structures, and induce IFN- β production.^{55–57} RIG-I is activated by 5' triphosphate single-stranded RNA (ssRNA) and short dsRNA,⁵⁸ whereas MDA5 recognizes long dsRNA structures.⁵⁹ Both forms of RNA are very unusual during normal host conditions. RIG-I and MDA5, therefore, respond to different viral species and provide coverage against a broad array of viruses. Accordingly, mice deficient in RIG-I or MDA5 are susceptible to distinct viral infections.^{60–62} Binding of viral RNA enables interaction between the RIG-I-like helicases and downstream signaling molecules, which activate transcription factors and regulate the production of type I IFN.

In addition, cytoplasmic sensors of DNA are important for the recognition of bacterial, and probably also viral nucleic acid.⁶³ Studies have identified DNA-dependent activator of IFN-regulatory factors as a receptor for bacterial DNA that induces type I IFN production.⁶⁴ The cytoplasmic nucleic acid-sensing receptors enable cell-autonomous initiation of IFN production upon recognition of viral and bacterial nucleic acid. Although their expression is low in the steady state, these receptors are strikingly induced by type I IFN, enhancing their capacity to recognize viral and bacterial nucleic acid and to propagate the anti-viral response.

Recognition of nucleic acids by TLRs

TLRs are distinct from the cytoplasmic nucleic acid receptors in several ways, including the cells that express them, their subcellular localization, and the signaling pathways that are activated by them. Nine TLRs have been identified in humans, of which three (TLR3, TLR7 and TLR9) recognize nucleic acid components and stimulate type I IFN production. Interestingly, TLR expression is also regulated by IFNs, further highlighting the amplifying principle of the IFN response.⁵³ TLR3 is triggered by dsRNA, whereas TLR7 recognizes guanosine and uridine-rich ssRNA, and TLR9 senses unmethylated CpG motifs.^{65–69} TLR8 is also a receptor for ssRNA, but primarily elicits proinflammatory cytokine production.⁷⁰ TLR4, which is expressed on the cell surface, recognizes lipopolysaccharide,⁷¹ and can stimulate type I IFN production. TLRs have been shown to mediate the recognition of viral structures in apoptotic debris and to initiate type I IFN production. In this regard, TLR7 recognizes nucleic acid from ssRNA viruses, whereas TLR9 facilitates the recognition of certain DNA viruses.^{72–74}

TLRs are primarily expressed on hematopoietic cells, but within this group, their distribution varies widely by cell type. For instance, B cells and pDCs express TLR7 and TLR9, whereas myeloid dendritic cells primarily express TLR3 and TLR8.^{75–77} The

subcellular restriction of TLRs to surface membranes and endosomes skews their sampling to extracellular material and is thought to prevent TLR signaling from within healthy hematopoietic cells. Clearly, however, self components derived from dying host cells and taken up by antigen-presenting cells could pose a challenge, particularly as some of the molecular patterns that are recognized by TLRs are also present in host nucleic acid (albeit at a lower density than found in pathogen-derived nucleic acid).

PROPAGATION OF THE IFN RESPONSE

Numerous distinct signaling pathways are activated downstream of the nucleic acid sensing receptors, which converge at the activation of the IRF family of transcription factors, upstream of IFN production.⁷⁸ Four IRF family members (IRF1, IRF3, IRF5 and IRF7) are positive regulators of type I IFN production. These molecules regulate transcription at distinct type I IFN loci, determining which type I IFN subtypes are expressed in the initiation and propagation of the IFN response.⁷⁹ IRF3 is constitutively expressed in the cytoplasm of cells, and when activated translocates to the nucleus to induce transcription primarily at the IFN- β locus.⁸⁰ IRF7, which is normally expressed at low levels in lymphoid cells but is induced by type I IFN, is activated downstream of the same pathways that activate IRF3, and preferentially stimulates IFN- α gene transcription.⁸¹ In the initiation phase, therefore, recognition of viral or bacterial PAMPs induces IRF3 activation and IFN- β production. IFN- β can induce the expression of IRF7, as well as the receptors and signal transduction molecules that activate IRF7, enabling a feed-forward loop, whereby further recognition of PAMPs induces IFN- α gene transcription.^{54,82}

pDCs have the unique capacity to rapidly secrete large quantities of type I IFN upon recognition of nucleic acid structures by TLR7 or TLR9.^{72–74,83} These cells constitutively express high levels of IRF7, making them ideally suited to respond rapidly to PAMPs in the absence of prior IFN exposure. pDCs are, therefore, thought to have a central role in the self-amplifying nature of autoimmune disease through the production of large quantities of type I IFN, which mediates numerous downstream functional effects on target cells and cells of the immune system (see below). In addition, pDCs express IRF5, which induces transcription of IFN- α genes distinct from IRF7.^{84,85} As previously discussed, polymorphisms in the gene encoding IRF5 are associated with an increased risk of SLE, SS and SSc,^{42–44,46,47} suggesting that *IRF5* polymorphisms could affect IFN secretion by pDCs in response to TLR ligands. However, the functional significance and role of these polymorphisms in disease are not yet well understood.

The IRFs are critical regulators of the type I IFN response, controlling both the qualitative (that is, the subtypes expressed) and quantitative features of the response. Interestingly, both IRF5 and IRF7 are induced by type I IFN,^{54,84} again reinforcing the self-amplifying capacity of this pathway. Inhibiting the feed-forward nature of IFN production, therefore, represents a potential therapeutic approach to systemic autoimmune diseases. Moreover, selective inhibition of IRF5 or IRF7 could leave basal IFN- β production intact whilst limiting amplification of this pathway.

DOWNSTREAM EFFECTS OF IFN

Once produced, type I IFN acts in an autocrine and paracrine manner to trigger the heterodimeric type I IFN receptor (IFNAR), which is expressed on all nucleated cells. In molecular terms, binding of type I IFN to the receptor complex induces dimerization of the IFNAR1 and IFNAR2 chains and the phosphorylation of associated Janus kinase family members TYK2 and JAK1. This enables activation of members of the STAT family, which autophosphorylate and homodimerize or heterodimerize, and translocate to the nucleus. There, they initiate transcription of hundreds of IFN-stimulated genes, resulting in direct and

indirect anti-viral effects.⁸⁶ Furthermore, the activities of type I IFN regulate the global immune response.⁸⁷ In physiological terms, type I IFN regulates pathways in target cells, antigen-presenting cells (which direct the scope of the immune response) and effector cells (which mediate anti-viral effects and tissue damage).

Induction of an anti-viral state

IFN-stimulated proteins mediate a variety of direct and indirect anti-viral effects that are critical for inhibiting viral replication and enhancing clearance (Figure 1). The IFN-regulated anti-viral proteins of importance include the APOBEC family of DNA-editing enzymes, which are packaged in nascent virions and mutate viral genomes, the Mx GTPases, which associate with viral polymerases and inhibit viral gene transcription, and members of the tripartite motif family (which includes the frequently targeted autoantigen Ro/SSA 52kD [also known as TRIM21, or tripartite-motif-containing 21]), which can inhibit viral replication at multiple stages in the life cycle.^{88–90} Other molecules inhibit viral replication indirectly through broad effects on cellular processes. For example, RNA-activated protein kinase (PKR) inhibits viral protein synthesis by blocking cap-dependent messenger RNA translation. Furthermore, immune recognition is enhanced in cells exposed to type I IFN. The induction of major histocompatibility complex (MHC) class I expression results in enhanced presentation of viral and self antigens for recognition by the immune system, and is important for the effector phase of the immune response. Other changes include the induction of molecules (such as p53)⁹¹ that increase susceptibility to cell death-inducing stimuli, thus enhancing the killing of virally infected cells by the immune system.

Although it was initially believed that autoantigens targeted in systemic autoimmunity were ubiquitously expressed, it has now become clear that these molecules are expressed at significantly high levels in the target tissues of patients with systemic autoimmune disease.² Some of these molecules are expressed at low levels under normal circumstances, but are highly expressed upon exposure to IFN. One such autoantigen is Ro/SSA 52 kD, which is broadly targeted in systemic autoimmunity.⁹² Once targeted by the immune system, enhanced Ro/SSA 52 kD expression in cells responding to IFN signaling can increase the presentation of immunostimulatory Ro/SSA 52 kD epitopes in the context of MHC class I molecules, facilitating recognition by autoreactive T cells. Other autoantigens, although targeted in only a subset of the rheumatic diseases, are similarly regulated by type I IFN, and their expression in the setting of elevated type I IFN levels might propagate the autoimmune response against them in specific phenotypes. For example, a member of the HIN-200 family, IFI16, is targeted in patients with SLE and SSc.^{93,94} By contrast, MDA5, which binds viral RNA and initiates type I IFN production, is frequently targeted in patients with dermatomyositis.⁹⁵ Defining the basis for the distinct phenotypic associations of antigens induced by type I IFN is an important research priority.

Maturation of antigen-presenting cells

The subtypes of type I IFN have the capacity to influence the generation of an adaptive immune response through their ability to activate and mature DCs. In the steady state, immature DCs maintain peripheral tolerance through the presentation of exogenously derived antigens in the absence of co-stimulation. When activated, mature DCs are efficient stimulators of T-cell-dependent immune responses. Type I IFN induces the expression MHC class I and class II, as well as co-stimulatory molecules, on DCs, enabling these cells to efficiently activate T cells.^{96,97} DC activation by type I IFN also induces the expression of the chemokine receptor, CCR7, which is necessary for homing to lymphoid organs,⁹⁸ where DCs interact with T cells and initiate an adaptive immune response. Steinman and colleagues have shown that type I IFN acts directly on DCs to induce their maturation, and that IFN is necessary for the efficient generation of CD4 T cell responses.⁹⁹ Similarly, type I

IFN enhances CD8 T cell responses through activation of DCs.¹⁰⁰ In the setting of chronic IFN production, therefore, increased levels of immunostimulatory DCs³⁰ could challenge tolerance by continuously presenting self antigen in a proimmune context, potentially activating autoreactive cells that have survived negative selection in the thymus and periphery.

Activation of effector cells

In addition to its ability to influence the initiation of an adaptive immune response, type I IFN has the capacity to enhance the survival and effector functions of cells that mediate immunopathology in systemic autoimmunity, potentiating amplification. Type I IFN has been shown to promote T cell survival,^{22,101,102} and to increase the cytolytic activity of NK cells and cytotoxic T cells (CTLs).^{22,103} Evidence directly implicates cytotoxic lymphocytes, which kill virally infected and transformed cells via the granzyme B (GrB) pathway, in the effector arm of tissue damage in systemic autoimmunity. Polarized CTLs surrounding myofibers that express MHC class I have been found in muscle biopsies from patients with polymyositis.¹⁰⁴ Similarly, effector lymphocytes expressing GrB are present at high levels in patients with SLE, and have been shown to correlate with disease activity.¹⁰⁵ Many autoantigens are GrB substrates, and cleavage by GrB generates peptide fragments that are distinct from those generated by caspases during normal homeostatic cell death.¹⁰⁶ These novel fragments might not be tolerized during immune development, and could stimulate autoreactive T cells when presented by activated DCs. Enhanced effector functions of CTLs in response to type I IFN could lead to increased tissue damage and augmented antigen load, propagating the autoimmune response.

In addition, type I IFN has the ability to promote B cell differentiation and antibody production.^{107,108} Many of the autoantigens that are frequently targeted in systemic autoimmune diseases are nucleic acid–protein complexes. In both human and murine systems, there is extensive evidence that signaling by nucleic acid-containing immune complexes through TLRs induces IFN production. This suggests that the ability to ligate and activate TLRs might be a critical property of self antigens, constituting an additional element of the feed-forward loop. For example, autoantigen complexes that can co-ligate both B cell receptors and TLRs on B cells induce B cell activation and IFN secretion, further enhancing autoantibody production.^{109,110} In humans, co-ligation of Fc receptor and TLR9 by immune complexes in pDCs induces IFN secretion.¹¹¹ In mice, immune complexes that co-ligate Fc receptor and TLRs induce myeloid DC activation and IFN secretion.¹¹² In a murine model of lupus, TLR7 and TLR9 were shown to be critical for autoantibody production. TLR7-deficient animals had less-severe disease and failed to produce autoantibodies against ribonucleoprotein autoantigens, whereas TLR9-deficient animals did not produce anti-DNA antibodies.^{113,114} The ability of IFNs to enhance TLR expression, and the ability of TLR ligation by systemic autoimmune disease autoantigens to generate IFN secretion, creates a self-reinforcing cycle. The likelihood that additional components (for example, enhanced cytotoxicity pathways, increased sensitivity to cell death, increased autoantigen expression) contribute to this cycle is high. These additional components are included in the model of the potential activity of type I IFNs in systemic autoimmunity shown in Figure 2.

CONCLUSIONS

The type I IFN response is a rapidly-inducing, self-amplifying pathway that has the capacity to regulate both innate and adaptive immune responses. The feed-forward nature of IFN production ensures that a vigorous anti-viral immune response is mounted. While such feed-forward pathways are highly adaptive to rapid and effective virus eradication, these functions could be maladaptive in immune responses directed against host tissues. These

self-amplifying loops are particularly hazardous if the ligands that drive the response are derived from self antigens contained within dying cells. Such reinforcing cycles should, however, be highly amenable to therapy.

Effectively impacting the type I IFN pathway and predicting the side effects of treatment is dependent upon understanding the many reinforcing components of this system. Inhibitors of TLR signaling could prevent amplification of the IFN pathway by immune complexes. In this regard, it is relevant that hydroxychloroquine is used for the treatment of a variety autoimmune rheumatic diseases (such as SLE and RA), and has been shown to inhibit TLR signaling.^{115,116} Short-term use of IFNAR inhibitors could be useful to break the self-amplifying cycle of tissue damage and IFN production. However, selective inhibitors might prevent potentially catastrophic infections in chronically treated individuals. Inhibitors of IRF5 or IRF7 could block the production of IFN- α , which is closely tied to disease activity/severity, leaving the anti-viral and/or anti-tumor effects of IFN- β unaltered. Neutralizing antibodies directed against IFN- α species are currently being evaluated and could be highly effective at inhibiting the amplifying nature of the IFN response. Preliminary studies demonstrate that a single dose of IFN- α -neutralizing antibody decreases the expression of IFN- α -inducible genes in whole blood from patients with SLE, and these effects persists for up to 12 weeks.¹¹⁷ The IFN system might be therapeutically tractable in many other ways in systemic autoimmunity. Defining the key points of control and minimum basal function for safety in terms of antiviral and anti-tumor activities are essential areas for future research.

References

1. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J. Exp. Med.* 1994; 179:1317–1330. [PubMed: 7511686]
2. Casciola-Rosen L, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J. Exp. Med.* 2005; 201:591–601. [PubMed: 15728237]
3. Sheppard P, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat. Immunol.* 2003; 4:63–68. [PubMed: 12469119]
4. Kotenko SV, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat. Immunol.* 2003; 4:69–77. [PubMed: 12483210]
5. Doyle SE, et al. Interleukin-29 uses a type 1 interferon-like program to promote antiviral responses in human hepatocytes. *Hepatology.* 2006; 44:896–906. [PubMed: 17006906]
6. Ank N, et al. Lambda interferon (IFN-lambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo. *J. Virol.* 2006; 80:4501–4509. [PubMed: 16611910]
7. Ank N, et al. An important role for type III interferon (IFN-lambda/IL-28) in TLR-induced antiviral activity. *J. Immunol.* 2008; 180:2474–2485. [PubMed: 18250457]
8. Sommereyns C, Paul S, Staeheli P, Michiels T. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. *PLoS Pathog.* 2008; 4:e1000017. [PubMed: 18369468]
9. Der SD, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. *Proc. Natl. Acad. Sci. U. S. A.* 1998; 95:15623–15628. [PubMed: 9861020]
10. Boehm U, Klamp T, Groot M, Howard JC. Cellular responses to interferon-gamma. *Annu. Rev. Immunol.* 1997; 15:749–795. [PubMed: 9143706]
11. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. *Immunol. Rev.* 2004; 202:8–32. [PubMed: 15546383]
12. Stetson DB, Medzhitov R. Type I interferons in host defense. *Immunity.* 2006; 25:373–381. [PubMed: 16979569]

13. van Boxel-Dezaire AH, Rani MR, Stark GR. Complex modulation of cell type-specific signaling in response to type I interferons. *Immunity*. 2006; 25:361–372. [PubMed: 16979568]
14. Foster GR, et al. Different relative activities of human cell-derived interferon-alpha subtypes: IFN-alpha 8 has very high antiviral potency. *J. Interferon Cytokine Res.* 1996; 16:1027–1033. [PubMed: 8974005]
15. Randall RE, Goodbourn S. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *J. Gen. Virol.* 2008; 89:1–47. [PubMed: 18089727]
16. Minegishi Y, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*. 2006; 25:745–755. [PubMed: 17088085]
17. Dupuis S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat. Genet.* 2003; 33:388–391. [PubMed: 12590259]
18. Muller U, et al. Functional role of type I and type II interferons in antiviral defense. *Science*. 1994; 264:1918–1921. [PubMed: 8009221]
19. Hwang SY, et al. A null mutation in the gene encoding a type I interferon receptor component eliminates antiproliferative and antiviral responses to interferons alpha and beta and alters macrophage responses. *Proc. Natl. Acad. Sci. U. S. A.* 1995; 92:11284–11288. [PubMed: 7479980]
20. Dunn GP, et al. A critical function for type I interferons in cancer immunoediting. *Nat. Immunol.* 2005; 6:722–729. [PubMed: 15951814]
21. Swann JB, et al. Type I IFN contributes to NK cell homeostasis, activation, and antitumor function. *J. Immunol.* 2007; 178:7540–7549. [PubMed: 17548588]
22. Curtsinger JM, Valenzuela JO, Agarwal P, Lins D, Mescher MF. Type I IFNs provide a third signal to CD8 T cells to stimulate clonal expansion and differentiation. *J. Immunol.* 2005; 174:4465–4469. [PubMed: 15814665]
23. Ioannou Y, Isenberg DA. Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. *Arthritis Rheum.* 2000; 43:1431–1442. [PubMed: 10902743]
24. Okanoue T, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. *J. Hepatol.* 1996; 25:283–291. [PubMed: 8895006]
25. Hooks JJ, et al. Immune interferon in the circulation of patients with autoimmune disease. *N. Engl. J. Med.* 1979; 301:5–8. [PubMed: 449915]
26. Vallin H, Perers A, Alm GV, Ronnblom L. Anti-double-stranded DNA antibodies and immunostimulatory plasmid DNA in combination mimic the endogenous IFN-alpha inducer in systemic lupus erythematosus. *J. Immunol.* 1999; 163:6306–6313. [PubMed: 10570325]
27. Bave U, Alm GV, Ronnblom L. The combination of apoptotic U937 cells and lupus IgG is a potent IFN-alpha inducer. *J. Immunol.* 2000; 165:3519–3526. [PubMed: 10975873]
28. Bave U, et al. Activation of the type I interferon system in primary Sjogren's syndrome: a possible etiopathogenic mechanism. *Arthritis Rheum.* 2005; 52:1185–1195. [PubMed: 15818675]
29. Kim D, et al. Induction of interferon-alpha by scleroderma sera containing autoantibodies to topoisomerase I: association of higher interferon-alpha activity with lung fibrosis. *Arthritis Rheum.* 2008; 58:2163–2173. [PubMed: 18576347]
30. Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. *Science*. 2001; 294:1540–1543. [PubMed: 11711679]
31. Baechler EC, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc. Natl. Acad. Sci. U. S. A.* 2003; 100:2610–2615. [PubMed: 12604793]
32. Bennett L, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J. Exp. Med.* 2003; 197:711–723. [PubMed: 12642603]
33. Han GM, et al. Analysis of gene expression profiles in human systemic lupus erythematosus using oligonucleotide microarray. *Genes Immun.* 2003; 4:177–186. [PubMed: 12700592]
34. Kirou KA, et al. Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus. *Arthritis Rheum.* 2004; 50:3958–3967. [PubMed: 15593221]

35. Kirou KA, et al. Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. *Arthritis Rheum.* 2005; 52:1491–1503. [PubMed: 15880830]
36. Baechler EC, et al. An interferon signature in the peripheral blood of dermatomyositis patients is associated with disease activity. *Mol. Med.* 2007; 13:59–68. [PubMed: 17515957]
37. Walsh RJ, et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. *Arthritis Rheum.* 2007; 56:3784–3792. [PubMed: 17968926]
38. Emamian ES, et al. Peripheral blood gene expression profiling in Sjogren's syndrome. *Genes Immun.* 2009; 10:285–296. [PubMed: 19404300]
39. Tan FK, et al. Signatures of differentially regulated interferon gene expression and vasculotropism in the peripheral blood cells of systemic sclerosis patients. *Rheumatology (Oxford).* 2006; 45:694–702. [PubMed: 16418202]
40. Greenberg SA, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. *Ann. Neurol.* 2005; 57:664–678. [PubMed: 15852401]
41. Gottenberg JE, et al. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjogren's syndrome. *Proc. Natl. Acad. Sci. U. S. A.* 2006; 103:2770–2775. [PubMed: 16477017]
42. Sigurdsson S, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am. J. Hum. Genet.* 2005; 76:528–537. [PubMed: 15657875]
43. Graham RR, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat. Genet.* 2006; 38:550–555. [PubMed: 16642019]
44. Graham RR, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc. Natl. Acad. Sci. U. S. A.* 2007; 104:6758–6763. [PubMed: 17412832]
45. Niewold TB, et al. Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. *Arthritis Rheum.* 2008; 58:2481–2487. [PubMed: 18668568]
46. Miceli-Richard C, et al. The CGGGG insertion/deletion polymorphism of the IRF5 promoter is a strong risk factor for primary Sjogren's syndrome. *Arthritis Rheum.* 2009; 60:1991–1997. [PubMed: 19565491]
47. Dieude P, et al. Association between the IRF5 rs2004640 functional polymorphism and systemic sclerosis: a new perspective for pulmonary fibrosis. *Arthritis Rheum.* 2009; 60:225–233. [PubMed: 19116937]
48. Nishikomori R, et al. Activated STAT4 has an essential role in Th1 differentiation and proliferation that is independent of its role in the maintenance of IL-12R beta 2 chain expression and signaling. *J. Immunol.* 2002; 169:4388–4398. [PubMed: 12370372]
49. Nguyen KB, et al. Critical role for STAT4 activation by type 1 interferons in the interferon-gamma response to viral infection. *Science.* 2002; 297:2063–2066. [PubMed: 12242445]
50. Remmers EF, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N. Engl. J. Med.* 2007; 357:977–986. [PubMed: 17804842]
51. Taylor KE, et al. Specificity of the STAT4 genetic association for severe disease manifestations of systemic lupus erythematosus. *PLoS Genet.* 2008; 4:e1000084. [PubMed: 18516230]
52. Kariuki SN, et al. Cutting edge: autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. *J. Immunol.* 2009; 182:34–38. [PubMed: 19109131]
53. Miettinen M, Sareneva T, Julkunen I, Matikainen S. IFNs activate toll-like receptor gene expression in viral infections. *Genes Immun.* 2001; 2:349–355. [PubMed: 11607792]
54. Sato M, et al. Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7. *FEBS Lett.* 1998; 441:106–110. [PubMed: 9877175]
55. Yoneyama M, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat. Immunol.* 2004; 5:730–737. [PubMed: 15208624]

56. Andrejeva J, et al. The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter. *Proc. Natl. Acad. Sci. U. S. A.* 2004; 101:17264–17269. [PubMed: 15563593]
57. Yoneyama M, et al. Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. *J. Immunol.* 2005; 175:2851–2858. [PubMed: 16116171]
58. Hornung V, et al. 5'-Triphosphate RNA is the ligand for RIG-I. *Science.* 2006; 314:994–997. [PubMed: 17038590]
59. Kato H, et al. Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. *J. Exp. Med.* 2008; 205:1601–1610. [PubMed: 18591409]
60. Kato H, et al. Cell type-specific involvement of RIG-I in antiviral response. *Immunity.* 2005; 23:19–28. [PubMed: 16039576]
61. Kato H, et al. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature.* 2006; 441:101–105. [PubMed: 16625202]
62. Gitlin L, et al. Essential role of mda-5 in type I IFN responses to polyriboinosinic:polyribocytidylic acid and encephalomyocarditis picornavirus. *Proc. Natl. Acad. Sci. U. S. A.* 2006; 103:8459–8464. [PubMed: 16714379]
63. Stetson DB, Medzhitov R. Recognition of cytosolic DNA activates an IRF3-dependent innate immune response. *Immunity.* 2006; 24:93–103. [PubMed: 16413926]
64. Takaoka A, et al. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. *Nature.* 2007; 448:501–505. [PubMed: 17618271]
65. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature.* 2001; 413:732–738. [PubMed: 11607032]
66. Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science.* 2004; 303:1529–1531. [PubMed: 14976261]
67. Heil F, et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science.* 2004; 303:1526–1529. [PubMed: 14976262]
68. Hemmi H, et al. A Toll-like receptor recognizes bacterial DNA. *Nature.* 2000; 408:740–745. [PubMed: 11130078]
69. Bauer S, et al. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. *Proc. Natl. Acad. Sci. U. S. A.* 2001; 98:9237–9242. [PubMed: 11470918]
70. Gorden KB, et al. Synthetic TLR agonists reveal functional differences between human TLR7 and TLR8. *J. Immunol.* 2005; 174:1259–1268. [PubMed: 15661881]
71. Poltorak A, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science.* 1998; 282:2085–2088. [PubMed: 9851930]
72. Lund JM, et al. Recognition of single-stranded RNA viruses by Toll-like receptor 7. *Proc. Natl. Acad. Sci. U. S. A.* 2004; 101:5598–5603. [PubMed: 15034168]
73. Lund J, Sato A, Akira S, Medzhitov R, Iwasaki A. Toll-like receptor 9-mediated recognition of Herpes simplex virus-2 by plasmacytoid dendritic cells. *J. Exp. Med.* 2003; 198:513–520. [PubMed: 12900525]
74. Krug A, et al. Herpes simplex virus type 1 activates murine natural interferon-producing cells through toll-like receptor 9. *Blood.* 2004; 103:1433–1437. [PubMed: 14563635]
75. Kadowaki N, et al. Subsets of human dendritic cell precursors express different toll-like receptors and respond to different microbial antigens. *J. Exp. Med.* 2001; 194:863–869. [PubMed: 11561001]
76. Hornung V, et al. Quantitative expression of toll-like receptor 1–10 mRNA in cellular subsets of human peripheral blood mononuclear cells and sensitivity to CpG oligodeoxynucleotides. *J. Immunol.* 2002; 168:4531–4537. [PubMed: 11970999]
77. Ito T, et al. Interferon-alpha and interleukin-12 are induced differentially by Toll-like receptor 7 ligands in human blood dendritic cell subsets. *J. Exp. Med.* 2002; 195:1507–1512. [PubMed: 12045249]

78. Honda K, Takaoka A, Taniguchi T. Type I interferon [corrected] gene induction by the interferon regulatory factor family of transcription factors. *Immunity*. 2006; 25:349–360. [PubMed: 16979567]
79. Barnes BJ, Moore PA, Pitha PM. Virus-specific activation of a novel interferon regulatory factor, IRF-5, results in the induction of distinct interferon alpha genes. *J. Biol. Chem.* 2001; 276:23382–23390. [PubMed: 11303025]
80. Schafer SL, Lin R, Moore PA, Hiscott J, Pitha PM. Regulation of type I interferon gene expression by interferon regulatory factor-3. *J. Biol. Chem.* 1998; 273:2714–2720. [PubMed: 9446577]
81. Honda K, et al. IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature*. 2005; 434:772–777. [PubMed: 15800576]
82. Marie I, Durbin JE, Levy DE. Differential viral induction of distinct interferon-alpha genes by positive feedback through interferon regulatory factor-7. *EMBO J.* 1998; 17:6660–6669. [PubMed: 9822609]
83. Siegal FP, et al. The nature of the principal type 1 interferon-producing cells in human blood. *Science*. 1999; 284:1835–1837. [PubMed: 10364556]
84. Izaguirre A, et al. Comparative analysis of IRF and IFN-alpha expression in human plasmacytoid and monocyte-derived dendritic cells. *J. Leukoc. Biol.* 2003; 74:1125–1138. [PubMed: 12960254]
85. Barnes BJ, et al. Global and distinct targets of IRF-5 and IRF-7 during innate response to viral infection. *J. Biol. Chem.* 2004; 279:45194–45207. [PubMed: 15308637]
86. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat. Rev. Immunol.* 2005; 5:375–386. [PubMed: 15864272]
87. Biron CA. Interferons alpha and beta as immune regulators--a new look. *Immunity*. 2001; 14:661–664. [PubMed: 11420036]
88. Harris RS, Liddament MT. Retroviral restriction by APOBEC proteins. *Nat. Rev. Immunol.* 2004; 4:868–877. [PubMed: 15516966]
89. Turan K, et al. Nuclear MxA proteins form a complex with influenza virus NP and inhibit the transcription of the engineered influenza virus genome. *Nucleic Acids Res.* 2004; 32:643–652. [PubMed: 14752052]
90. Ozato K, Shin DM, Chang TH, Morse HC 3rd. TRIM family proteins and their emerging roles in innate immunity. *Nat. Rev. Immunol.* 2008; 8:849–860. [PubMed: 18836477]
91. Takaoka A, et al. Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence. *Nature*. 2003; 424:516–523. [PubMed: 12872134]
92. Strandberg L, et al. Interferon-alpha induces up-regulation and nuclear translocation of the Ro52 autoantigen as detected by a panel of novel Ro52-specific monoclonal antibodies. *J. Clin. Immunol.* 2008; 28:220–231. [PubMed: 18071879]
93. Seelig HP, Ehrfeld H, Renz M. Interferon-gamma-inducible protein p16. A new target of antinuclear antibodies in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1994; 37:1672–1683. [PubMed: 7526871]
94. Mondini M, et al. A novel autoantigen to differentiate limited cutaneous systemic sclerosis from diffuse cutaneous systemic sclerosis: the interferon-inducible gene IFI16. *Arthritis Rheum.* 2006; 54:3939–3944. [PubMed: 17133607]
95. Sato S, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: Association with rapidly progressive interstitial lung disease. *Arthritis Rheum.* 2009; 60:2193–2200. [PubMed: 19565506]
96. Luft T, et al. Type I IFNs enhance the terminal differentiation of dendritic cells. *J. Immunol.* 1998; 161:1947–1953. [PubMed: 9712065]
97. Gallucci S, Lolkema M, Matzinger P. Natural adjuvants: endogenous activators of dendritic cells. *Nat. Med.* 1999; 5:1249–1255. [PubMed: 10545990]
98. Parlato S, et al. Expression of CCR-7, MIP-3beta, and Th-1 chemokines in type I IFN-induced monocyte-derived dendritic cells: importance for the rapid acquisition of potent migratory and functional activities. *Blood*. 2001; 98:3022–3029. [PubMed: 11698286]
99. Longhi MP, et al. Dendritic cells require a systemic type I interferon response to mature and induce CD4+ Th1 immunity with poly IC as adjuvant. *J. Exp. Med.* 2009; 206:1589–1602. [PubMed: 19564349]

100. Le Bon A, et al. Cross-priming of CD8+ T cells stimulated by virus-induced type I interferon. *Nat. Immunol.* 2003; 4:1009–1015. [PubMed: 14502286]
101. Marrack P, Kappler J, Mitchell T. Type I interferons keep activated T cells alive. *J. Exp. Med.* 1999; 189:521–530. [PubMed: 9927514]
102. Kolumam GA, Thomas S, Thompson LJ, Sprent J, Murali-Krishna K. Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection. *J. Exp. Med.* 2005; 202:637–650. [PubMed: 16129706]
103. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu. Rev. Immunol.* 1999; 17:189–220. [PubMed: 10358757]
104. Goebels N, et al. Differential expression of perforin in muscle-infiltrating T cells in polymyositis and dermatomyositis. *J. Clin. Invest.* 1996; 97:2905–2910. [PubMed: 8675705]
105. Blanco P, et al. Increase in activated CD8+ T lymphocytes expressing perforin and granzyme B correlates with disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2005; 52:201–211. [PubMed: 15641052]
106. Casciola-Rosen L, Andrade F, Ulanet D, Wong WB, Rosen A. Cleavage by granzyme B is strongly predictive of autoantigen status: implications for initiation of autoimmunity. *J. Exp. Med.* 1999; 190:815–826. [PubMed: 10499920]
107. Le Bon A, et al. Type I interferons potently enhance humoral immunity and can promote isotype switching by stimulating dendritic cells in vivo. *Immunity.* 2001; 14:461–470. [PubMed: 11336691]
108. Jegu G, et al. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity.* 2003; 19:225–234. [PubMed: 12932356]
109. Leadbetter EA, et al. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature.* 2002; 416:603–607. [PubMed: 11948342]
110. Lau CM, et al. RNA-associated autoantigens activate B cells by combined B cell antigen receptor/Toll-like receptor 7 engagement. *J. Exp. Med.* 2005; 202:1171–1177. [PubMed: 16260486]
111. Means TK, et al. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. *J. Clin. Invest.* 2005; 115:407–417. [PubMed: 15668740]
112. Boule MW, et al. Toll-like receptor 9-dependent and -independent dendritic cell activation by chromatin-immunoglobulin G complexes. *J. Exp. Med.* 2004; 199:1631–1640. [PubMed: 15197227]
113. Christensen SR, et al. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity.* 2006; 25:417–428. [PubMed: 16973389]
114. Christensen SR, et al. Toll-like receptor 9 controls anti-DNA autoantibody production in murine lupus. *J. Exp. Med.* 2005; 202:321–331. [PubMed: 16027240]
115. Sun S, Rao NL, Venable J, Thurmond R, Karlsson L. TLR7/9 antagonists as therapeutics for immune-mediated inflammatory disorders. *Inflamm. Allergy Drug Targets.* 2007; 6:223–235. [PubMed: 18220957]
116. Rutz M, et al. Toll-like receptor 9 binds single-stranded CpG-DNA in a sequence- and pH-dependent manner. *Eur. J. Immunol.* 2004; 34:2541–2550. [PubMed: 15307186]
117. Yao Y, et al. Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an anti-interferon-alpha monoclonal antibody in systemic lupus erythematosus. *Arthritis Rheum.* 2009; 60:1785–1796. [PubMed: 19479852]
118. Ank N, West H, Paludan SR. IFN-lambda: novel antiviral cytokines. *J. Interferon Cytokine Res.* 2006; 26:373–379. [PubMed: 16734557]
119. Bach EA, Aguet M, Schreiber RD. The IFN gamma receptor: a paradigm for cytokine receptor signaling. *Annu. Rev. Immunol.* 1997; 15:563–591. [PubMed: 9143700]
120. Toshchakov V, et al. TLR4, but not TLR2, mediates IFN-beta-induced STAT1alpha/beta-dependent gene expression in macrophages. *Nat. Immunol.* 2002; 3:392–398. [PubMed: 11896392]

Biographies

John C Hall

John Hall received his PhD from the Immunology Graduate Program at the Johns Hopkins University School of Medicine in Baltimore, MD, USA. He is currently a post-doctoral research fellow focusing on the role of interferon in autoimmune rheumatic disease.

Antony Rosen

Antony Rosen is the Mary Betty Stevens Professor of Medicine, and Director of Rheumatology at the Johns Hopkins University School of Medicine in Baltimore, MD, USA. He obtained his medical degree from the University of Cape Town in 1984, and performed post-doctoral studies at the Rockefeller University in New York. He works on the mechanisms of autoimmune rheumatic diseases.

KEY POINTS

The type I interferon (IFN) system constitutes a highly redundant group of cytokines that are of critical importance to host survival

The production of type I IFN *in vivo* is regulated by numerous mechanisms that have the capacity to rapidly self-amplify upon recognition of IFN-inducing ligands

Type I IFN regulates both innate and adaptive immune responses, and can activate cells and effector pathways of pathogenic significance in systemic autoimmunity

Inhibition of the feed-forward nature of IFN production might inhibit the self-amplifying loops of tissue damage in systemic autoimmune diseases

REVIEW CRITERIA

We searched PubMed for full-text articles and reviews focusing on interferon and autoimmunity written in English. We analyzed the reference lists of selected papers for further leads. Search terms, used either alone, or in combination included “interferon”, “IFN”, “IFNAR”, “autoimmunity”, “autoantibody”, “SLE”, “myositis”, “Sjogren’s syndrome”, “scleroderma”, “autoantigen”, “IRF”, “IRF5”, “TLR”, “RIG-I”, “MDA5”, “IFN therapy”, “pDC”, “T cell”, and “B cell”.

Figure 1. Steps in the induction of an anti-viral state

1. Endocytosis of viral particles leads to the release of viral nucleic acid into the cytoplasm.
2. Cytoplasmic nucleic acid sensing receptors (such as RIG-I, MDA5 and DAI) bind nucleic acid within the cytoplasm and initiate a signal transduction cascade which results in phosphorylation of IRF3.
3. Phosphorylated IRF3 dimerizes and translocates to the nucleus where it associates with additional transcription factors to induce transcription primarily at the *IFNβ* locus.
4. *IFN-β* is produced and secreted from the infected cell.
5. Secreted *IFN-β* functions in an autocrine and paracrine manner to trigger IFNAR expressed on the infected and neighboring cells.
6. IFNAR signaling leads to the formation of phosphorylated STAT1/STAT2 heterodimers which associate with IRF9 to form the ISGF3 complex.
7. ISGF3 translocates to the nucleus and initiates transcription at ISRE binding sites, inducing transcription of hundreds of ISGs.
8. Expression of ISGs leads to induction of anti-viral state through the expression of direct and indirect inhibitors of viral replication, increases expression of MHC class I molecules on cell surface, enhancing antigen presentation to cytotoxic lymphocytes, and increases sensitivity to cell-death-inducing stimuli.

Abbreviations DAI, DNA-dependent activator of interferon regulatory factors; IFNAR, interferon- α receptor; *INF-β*, interferon β ; ISG, IFN-stimulated genes; ISGF3, IFN-stimulated gene factor 3; ISRE, interferon-stimulated response element; IRF, interferon regulatory factor; JAK, Janus kinase; MDA5, melanoma differentiation-associated gene 5; MHC, major histocompatibility complex; PKR, RNA-activated protein kinase; RIG-I, retinoic acid inducible gene I; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase; TRIM, tripartite motif.

Figure 2. The self-amplifying nature of type I IFN production and tissue damage in systemic autoimmunity

1. Recognition of viral nucleic acid in apoptotic debris by pDCs induces rapid production of large quantities of type I IFN. 2. Type I IFN induces self-amplification of the TLR pathway in pDCs and induces an anti-viral state in target cells. 3. Type I IFN influences monocyte differentiation and subsequent activation of dendritic cells, which, 4. process and present self and viral antigens derived from dying cells. 5. Autoreactive CD4 and CD8 T cells are activated by DCs expressing self antigens, and signaling through the type I IFN receptor promotes their survival and enhances the cytotoxic activity of CTLs. 6. CTLs kill uninfected host cells, which express high levels of autoantigens, via the granzyme B pathway. Debris from dying cells is taken up by dendritic cells and presented for recognition by T cells in a self-amplifying loop. 7. Type I IFN also induces the differentiation of autoreactive B cells into plasma cells and promotes antibody production. 8. Autoantibodies can form immune complexes with self molecules in cell debris, which 9. bind Fc receptors and TLRs on pDCs, further amplifying IFN production.

Abbreviations BCR, B cell receptor; CTL, cytotoxic T lymphocytes; IFN, interferon; IFNAR, interferon- α receptor; MDA5, melanoma differentiation-associated gene 5; pDC, plasmacytoid dendritic cells; Ro52, Ro/SSA 52 kD; TLR, Toll-like receptors.

Table 1

Members of the IFN family of cytokines

	Type I IFN	Type II IFN	Type III IFN	References
Subtypes	IFN α - 13 subtypes	IFN γ	IFN λ -1(IL-29)	3, 4, 11, 86
	IFN β		IFN λ -2 (IL-28A)	
	IFN ω		IFN λ -3 (IL-28B)	
	IFN ϵ			
	IFN κ			
Chromosome localization	9p22	12q14	19q13	3, 4, 11
Produced by	All nucleated cells	NK cells	all nucleated cells	10, 118
		NKT cells		
		T cells		
Receptor subunits	IFNAR1, IFNAR2	IFNGR1, IFNGR2	IFNLR1, IL-10R2	3, 4, 11
Receptor expression	all nucleated cells	all nucleated cells	epithelial cells	7, 8, 119
			pDCs	
Signaling molecules	JAK1 and TYK2	JAK1 and JAK2	JAK1 and TYK2	3, 4, 11, 86
Transcription factors	STAT1/STAT2/IRF9	STAT1/STAT1	STAT1/STAT2/IRF9	3, 4, 11, 86
	STAT1/STAT1		STAT1/STAT1	

Abbreviations: IFN, interferon; IFNAR, interferon- α receptor; IFNGR, interferon- γ receptor; IFNLR, interferon- λ receptor; IL-10R, interleukin-10 receptor; IRF, interferon regulatory factor; JAK, Janus kinase; NK, natural killer; NKT, natural killer T; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase

Table 2

Activating receptors of the type I IFN cytokines

Receptor	Expression	Localization	Primary ligand(s)	References
Nucleic acid-sensing receptors				
RIG-I	Ubiquitous	Cytoplasm	Short dsRNA	55, 57–59
			5' triphosphate ssRNA	
MDA5	Ubiquitous	Cytoplasm	Long dsRNA	56, 57, 59
DAI	Ubiquitous	Cytoplasm	DNA	64
Unnamed	Ubiquitous	Cytoplasm	DNA	63
Toll-like receptors				
TLR3	mDCs	Endosomes	dsRNA	65, 75–77
TLR4	Monocytes	Cell surface	Lipopolysaccharide	71, 75–77, 120
	Macrophages			
TLR7	B cells	Endosomes	Guanosine-rich or uridine-rich ssRNA	66, 67, 75–77
	pDCs			
TLR8	Monocytes	Endosomes	Guanosine-rich or uridine-rich ssRNA	67, 75–77
	mDCs			
TLR9	B cells	Endosomes	Unmethylated CpG DNA	68, 69, 75–77
	pDCs			

Abbreviations: DAI, DNA-dependent activator of interferon regulatory factors; dsRNA, double-stranded RNA; MDA5, melanoma differentiation associated gene 5; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; RIG-I, retinoic acid inducible gene I; ssRNA, single-stranded RNA; TLR, Toll-like receptor