Type I Interferons in Autoimmune Disease

Mary K. Crow, Mikhail Olferiev, and Kyriakos A. Kirou

Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, New York 10021, USA; email: crowm@hss.edu

Keywords
systemic lupus erythematosus, systemic autoimmune disease, type I interferon, interferon-α, nucleic acid, Toll-like receptor

Abstract
Type I interferons, which make up the first cytokine family to be described and are the essential mediators of antivirus host defense, have emerged as central elements in the immunopathology of systemic autoimmune diseases, with systemic lupus erythematosus as the prototype. Lessons from investigation of interferon regulation following virus infection can be applied to lupus, with the conclusion that sustained production of type I interferon shifts nearly all components of the immune system toward pathologic functions that result in tissue damage and disease. We review recent data, mainly from studies of patients with systemic lupus erythematosus, that provide new insights into the mechanisms of induction and the immunologic consequences of chronic activation of the type I interferon pathway. Current concepts implicate endogenous nucleic acids, driving both cytosolic sensors and endosomal Toll-like receptors, in interferon pathway activation and suggest targets for development of novel therapeutics that may restore the immune system to health.
INTRODUCTION

The discovery in 1957 of type I interferon (IFN-I) as a cytokine family mediating host defense against virus infection initiated 60 years of compelling investigation illuminating complex mechanisms of immune cell function. The IFN-I locus on human chromosome 9p encodes 13 IFN-α genes, IFN-β, IFN-ε, IFN-ω, and IFN-κ, with both gene conversion and gene duplication contributing to the evolution of this gene family (1). The hundreds of IFN-I-regulated gene products that implement a coordinated response to virus invasion, along with the multiple regulatory mechanisms that control this response, have a dark side; they are recognized to be important mediators in two categories of disease that are not obviously attributable to virus infection: systemic autoimmune disease and the monogenic interferonopathies. Studies of patients with the prototype systemic autoimmune disease systemic lupus erythematosus (SLE), along with studies of rare patients with Aicardi-Goutières syndrome (AGS), continue to enhance our understanding of the immunopathogenesis of those disorders, as well as the mechanisms of activation and control of the innate and adaptive immune response in health and disease.

The notion that IFN-I might play a pathogenic role in SLE was first raised in 1969 in an insightful and prescient paper by Steinberg et al. (2) describing the acceleration of autoimmune disease in the (NZB × NZW) F1 murine lupus model following administration of polyinosinic:polycytidylic acid, an inducer of IFN-I. The authors suggested a role for nucleic acid as a driver of IFN-I production in lupus and identified an association between IFN-I and the induction of anti-RNA autoantibodies, two observations that are supported by studies performed decades later. Skurkovich and colleagues (3, 4) and then Hooks et al. (5) documented elevated IFN-I in the serum of patients with SLE as well as other systemic autoimmune diseases, including rheumatoid arthritis, systemic sclerosis and Sjogren’s syndrome. Additional early studies demonstrated the capacity of immune complexes containing antigen and antibody to induce IFN-I by immune system cells (6). This has proved to be an important mechanism relevant to the high levels of circulating IFN-I seen in patients with RNA-containing immune complexes and documented in an important series of in vitro studies led by Ronnblom (7) and later supported by studies from our group demonstrating a strong association between the presence of autoantibodies targeting RNA-binding proteins and activation of the IFN-I pathway (8).

A role for IFN-I in the tissue pathology of SLE was suggested by the studies of Rich and colleagues (9, 10), which demonstrated the capacity of both recombinant IFN-α and SLE sera to induce intracellular microtubular structures that were termed lupus inclusions. These structures had been observed in the glomerular endothelial cells of patients with SLE and dermatomyositis (11), and Rich et al.’s studies implicated IFN-I rather than virus in their development (10). Many subsequent studies, in spontaneous murine models of lupus and in lupus patients, supported a pathogenic rather than a protective role of IFN-I in many systemic autoimmune diseases. Overexpression of IFN-α using an adenovirus construct accelerated autoimmunity and disease in the (NZB × NZW) F1 model and implicated an essential role for T cells in that effect, indicating that IFN-I has broad immune system effects (12). Serendipitous observations of the development of lupus autoantibodies and clinical lupus-like disease in some patients receiving recombinant IFN-α provided a similar demonstration in human patients that IFN-I could play a pathogenic role in SLE but also suggested that the genetic profile of the recipient of IFN-α is a determinant of whether pathology developed (13).

THE INTERFERON SIGNATURE

This robust record of investigation implicating IFN-I in the pathogenesis of SLE, and to some extent in other systemic autoimmune diseases, drew attention to the IFN-I cytokine family as a
likely contributor to the immunopathology of those diseases. However, it was the availability of microarray platforms for assessment of global gene expression that led researchers to consider IFN-I, along with its broad signature of IFN-I-induced gene products, as a core mechanism in the immunopathogenesis of SLE. In 2003, three laboratories used microarray analysis of gene expression in peripheral blood cells of patients with SLE to demonstrate a striking overexpression of hundreds of gene transcripts that suggested induction by IFN-I (14–16). The following year, we used real-time polymerase chain reaction analysis of transcripts preferentially induced by either IFN-I (IFN-α) or IFN-γ to demonstrate that the observed transcript profile in microarray-based studies was attributable to IFN-I rather than IFN-γ and that the induced gene transcripts are coordinately expressed in the cells of lupus patients. Expression of each of the transcripts highly correlated with expression of the others, suggesting that IFN-α, or a stimulus that behaved in a similar manner to IFN-α, was responsible for the striking interferon signature present in most SLE patients studied (17) (Figure 1a). The contribution of IFN-α to the IFN-I signature was confirmed when assay of IFN-I activity in sera from SLE patients was measured using a reporter cell line, WISH cells, that express the IFN-I receptor, IFNAR, and respond to IFN-I with expression of IFN-I-regulated gene products (18). When an antibody specific to IFN-α was included in the assay culture, most of the IFN-I activity was inhibited, whereas anti-IFN-γ did not significantly reduce the capacity of the sera to induce IFN-I-regulated gene products. The demonstration of the IFN signature has not only provided a tool for assessing involvement of the IFN-I pathway in SLE and related autoimmune diseases, as well as in the monogenic interferonopathies, but has also driven new understanding of the mechanisms that account for the protean immunologic alterations that

![Figure 1](image_url)

**Figure 1**

Expression and induction of the type I interferon (IFN-I) signature. (a) IFN-I-induced gene expression was assessed in peripheral blood mononuclear cells (PBMCs) from patients with systemic lupus erythematosus (SLE) by reverse transcription polymerase chain reaction analysis of IFIT1, IFI44, MX1, and PKR. Coordinate expression of the IFN-I-regulated genes is shown based on relative expression compared to housekeeping gene controls. (b) Healthy donor (HD) PBMCs were cultured with plasma from HDs or SLE patients expressing autoantibodies (Abs) specific to RNA-binding proteins (anti-RBP) and/or DNA, and induction of IFN-I was measured.
characterize patients with lupus. Investigation of the inducers of the IFN signature has identified several rational therapeutic targets that are now under study, and significant therapeutic trials of targeted therapies will soon be completed. Based on extensive study of the induction, regulation, and impact of the IFN-I signature in SLE, it is our view that activation of the IFN-I pathway represents a fundamental feature of lupus pathogenesis, as well as an important but perhaps less central contributor to the immunopathogenesis of Sjögren’s syndrome, systemic sclerosis, and dermatomyositis and perhaps other systemic autoimmune diseases (19).

EXOGENOUS AND ENDOGENOUS TRIGGERS OF TYPE I INTERFERON

Endosomal Toll-Like Receptor Ligands

Among the most significant challenges that limit understanding of the etiology of SLE is characterization of the stimuli and pathways through which production of IFN-I is induced. Two categories of receptors and related molecular pathways—the endosomal Toll-like receptors (TLRs) and the cytosolic nucleic acid sensors—suggest triggers that are potentially relevant to lupus pathogenesis. A common theme is that nucleic acids, both RNA and DNA, have the potential to drive IFN-I production.

Historically, as suggested by the insightful 1969 paper by Steinberg et al. (2), researchers considered viruses to be the most obvious inducers of innate immune system activation. It is possible that activation of latent Epstein-Barr virus (EBV) could be responsible for production of IFN-I (20, 21). Recent studies show that expression of latent membrane protein 1 (LMP1), but not other EBV-encoded transcripts, is correlated with expression of IFN-I-regulated genes, and SLE patients have increased levels of antibodies against EBV early antigen, suggestive of reactivation (22). Potential mechanisms whereby EBV might induce IFN-I are suggested by the demonstration that intact EBV can trigger TLR9 in a major histocompatibility complex (MHC) class II–dependent manner, and small RNAs encoded by EBV, EBERs, activate TLR7 and stimulate IFN-I production (23–25). At least at the level of EBV-specific CD8\(^+\) T cells, which are impaired in their anti-EBV cytotoxic function, flare of lupus disease activity precedes EBV reactivation (26). It is thus not clear if the functional effects of EBV on the IFN-I pathway and other immune system functions reflect a primary etiologic role for EBV or are a consequence of lupus disease.

While viral nucleic acids, whether related to acute or to reactivated latent infection, may induce IFN-I expression, the significant insight relevant to SLE pathogenesis is that endogenous nucleic acid can also trigger IFN-I expression and the IFN-I signature. The laboratory of Lars Ronnblom performed a series of experiments that documented the capacity of immune complexes containing material derived from necrotic and apoptotic cells, along with SLE immunoglobulin G (IgG), to induce production of IFN-\(\alpha\) by plasmacytoid dendritic cells (pDCs) (7, 27). The activity of the necrotic material depended on the presence of RNA, and the activity of the SLE IgG correlated with the presence of antibodies specific for RNA-binding proteins. In our laboratory, we studied plasma derived from patients with autoantibodies specific for RNA-binding proteins (RBPs; Ro, La, Sm, or RNP) and/or anti-double-stranded DNA autoantibodies and found that induction of IFN-I in healthy donor peripheral blood mononuclear cells (PBMCs) depended on the presence of anti-RBP autoantibodies (Figure 1b). Barrat et al. implicated endosomal TLR7 and TLR9 in this response to nucleic acid–containing immune complexes using novel TLR oligonucleotide inhibitors (28). Identification of lupus-associated genetic polymorphisms in the IFN regulatory factor 5 (IRF5) gene, a transcription factor that is phosphorylated after endosomal TLR activation, further implicated this pathway as important in IFN-I production (29). Our demonstration that, in
patients expressing anti-RBP or anti-DNA antibodies, the risk allele of IRF5 was associated with increased serum IFN-I activity further supported the significant role played by the endosomal TLR pathway in the IFN-I produced by many SLE patients (30). MyD88, IRAK1, IRAK4, IRF7, IKKβ, and prolyl isomerase 1 are additional components of the TLR7 signaling pathway that participate in driving IFN-I production (31–35). More recent studies have shown that both T and B lymphocytes can amplify the production of IFN-I by immune complex–activated pDCs (36, 37), and IgE and the kallikrein–kinin system can inhibit that pathway (38, 39). Given these results, as well as those of studies of anti-RBP antibody, the current view is that TLR7 recognizes cell debris–associated RNA. In the case of SLE, RNA is in the form of immune complexes that access the TLR7 compartment after engaging cell surface Fc receptors on pDCs and act as immunopathogenic mediators that drive IFN-α production (Figure 2a). While mitochondrial DNA can activate TLR9, stimulate its downstream signaling components, and induce IFN-I, it is not yet clear how TLR9-induced IFN-I contributes to the IFN-I signature in vivo (40). However, rare mutations in DNASE1, encoding an extracellular protein that degrades circulating DNA, or in DNASE1L3, encoding an enzyme that digests DNA confined in microparticles, are associated with production of anti-DNA antibodies, and the DNA may be recognized by TLR9 (41, 42). This important body of work established new roles for autoantibodies and the complexes that they form beyond their well-established contribution to disease through passive deposition in target organs such as the kidney.

### Ligands of Cytosolic Nucleic Acid Sensor Signaling Pathways

In addition to the clear contribution of RNA-containing immune complexes to IFN-I production in patients with SLE, advances in defining sensors of cytosolic nucleic acids and their ligands have raised the possibility that alterations in nucleic acid localization or degradation might engage cytosolic pathways that can induce IFN-I (43). However, in contrast to the well-documented role of lupus immune complexes in driving endosomal TLRs, defining the most relevant ligands for the cytosolic RNA and DNA sensors is a work in progress. The retinoic acid–inducible gene I (RIG-I)-like receptors (RLRs) recognize replicating RNA viruses and induce IFN-I through a signaling pathway that involves mitochondrial antiviral signaling protein (MAVS), an adaptor that associates with mitochondria and then activates TANK binding kinase 1 (TBK1) and nuclear factor κB (NF-κB) subunit 1. Cyclic GMP–AMP synthase (cGAS) recognizes cytosolic DNA, generates 2′,3′-cyclic GMP–AMP (cGAMP) and activates the adaptor STING, encoded by TMEM173, also resulting in TBK1 activation and, ultimately, transcription of IFN-β and other proinflammatory genes (44) (Figure 2b).

A current research focus is the investigation of a potential role for these cytosolic nucleic acid sensing pathways in the immunopathogenesis of SLE. Some similarities between the clinical manifestations of AGS and SLE, with common features including high levels of IFN-I, central nervous system disease, skin lesions, and some autoantibodies, have suggested that, in some patients with SLE, single-gene mutations in mediators of nucleic acid degradation or signaling might contribute to innate immune activation and autoimmunity (45). Mutations in TREX-1 (DNASE3), SAMHD1, RNASEH2A, B, or C; or ADAR have all been associated with AGS and are associated in various ways with defects in nucleic acid degradation or metabolism. Only a small percentage of SLE patients have been documented to have damaging mutations in AGS-associated genes (46–48), but the collective data on AGS point to a need for studies of cytosolic nucleic acids and the signaling pathways that they trigger in patients with SLE.

Polymorphisms in interferon induced with helicase domain 1 (IFIH1), encoding the RNA sensor MDA5, are associated with SLE and increased IFN-I and CXCL10 production (49–51).
a TLR-mediated induction of IFN-I

b Cytosolic sensor–mediated induction of IFN-I

Caption appears on following page
εSTING and TBK1/IKK
TRAF6, TBK1/IKK
SAMHD1
EBV-encoded small RNA; EBV, Epstein-Barr virus; IFN, interferon; IKK
 cyclic GMP–AMP synthase; cGAMP, cyclic GMP–AMP; dsRNA, double-stranded RNA; EBER,
acids and drive increased signaling through RNA and DNA sensors. Abbreviations: Ab, antibody; cGAS,
sensing pathway induces IFN-β
ε
transcription of IFN-β
and was associated with activation of DNA damage pathways, and silencing of MAVS
aggregation observed in the PBMCs of one-third of SLE patients studied (53). MAVS aggregation
was typically engaged by RNA-activated RIG-I, a RIG-I-independent pathway of MAVS
activation and aggregation can be induced by mitochondrial oxidative stress (54). The relevance of
RNA sensing and MAVS to cell function is supported by a recent study of bone marrow–derived
mesenchymal stem cells from SLE patients (55). MAVS expression was highly correlated with
IFN-β and was associated with activation of DNA damage pathways, and silencing of MAVS
reduced IFN-β and p53.

The DNA-triggered cGAS signaling pathway is also under current study in SLE. Keith Elkon’s
laboratory has documented increased expression of cGAS in PBMCs of SLE patients and a
correlation of cGAS levels with IFN-I signature score (56). As cGAS is an IFN-I-stimulated gene
product, its elevated expression could merely be a reflection of IFN-I pathway activation, although
it should be noted that 15% of the patients studied also showed detectable cGAMP, an activa-
tor of STING. However, a study of a family with members expressing lupus-like autoimmune
disease and increased IFN-I production found a gain-of-function mutation in TMEM173 that re-
sulted in constitutive activation of STING, providing a proof of principle that the cGAS–STING
pathway can contribute to a lupus phenotype (57). cGAMP can also provide a priming signal to
the AIM2 inflammasome, an innate immune system pathway that generates caspase-1-dependent
interleukin-1β (58). As is noted above for the RNA sensing pathway, oxidative modification of
DNA can promote induction of IFN-I due to the DNA’s resistance to TREX1 degradation, sug-
uggesting that environmental factors generating reactive oxygen species could also augment the
likelihood that the cGAS–STING pathway might be activated and trigger IFN-I production (59). Extracellular sources of oxidized mitochondrial DNA can derive from neutrophils that have undergone NETosis and stimulate cGAS if the material gains access to the intracellular compartment (60–63).

The potential role of STING in the immunopathogenesis of SLE is complicated by recent data identifying an isoform of STING, STING-β, that inhibits binding of TBK1 and 2',3'-cGAMP to STING-α and is inversely related to IFN-β levels (64). STING-β levels were reduced in cells from SLE patients, indicating a mechanism that might allow more robust IFN-I production. No information is currently available on how the relative expression of the two relevant isoforms of STING are regulated and whether STING-β deficiency might be a significant contributor to IFN-I pathway activation in SLE.

In spite of tremendous progress in defining the sensors and related signaling pathways that induce IFN-I, the nucleic acid ligands for those pathways that are most relevant to SLE are not known. Perhaps the most compelling potential ligand is oxidized mitochondrial DNA, which, as noted above, is particularly resistant to degradation and can activate cGAS and STING and drive TBK1 and IRF3 activation (59). In contrast to nuclear DNA, mitochondrial DNA is relatively hypomethylated, similar to microbial DNA. Herpesvirus infection can induce mitochondrial DNA stress, which is of interest with regard to the potential mechanisms by which EBV infection might mediate IFN-I pathway activation in SLE (65, 66).

An intriguing mechanism of IFN-I induction implicates genome-derived retroelements that are either nuclear DNA or mitochondrial DNA derived. A recent study of mechanisms of tissue damage in age-related macular degeneration provides a model system for considering contributions of genomic elements to inflammatory disease (67). In that condition, a relative deficiency of DICER (ribonuclease III) in the retinal pigment epithelium results in expression of RNAs encoded by Alu retroelements, members of the short interspersed nuclear element repetitive element family. These RNAs increase the permeability of mitochondrial pores, allowing escape of mitochondrial DNA into the cytosol, activation of cGAS, and induction of IFN-β in a STING-dependent manner. In this system, the release of mitochondrial DNA results in activation of the noncanonical NLRP3 inflammasome pathway and inflammation-mediated tissue damage. A similar mechanism involving both RNA and DNA sensing pathways is suggested by the host response to dengue virus, an RNA virus (68). Dengue RNA, like the Alu RNAs described above, mediates release of mitochondrial DNA, providing ligands for the cGAS pathway and induction of IFN-β. Thus, in addition to mitochondrial stress, Alu RNA and, perhaps, some virus RNAs can contribute to cGAS activation by altering mitochondrial pore permeability and extrusion of mitochondrial DNA, a ligand for cGAS. A role for Alu RNAs in the IFN-I response has also been demonstrated in ADAR1-deficient human cells (69). ADAR1 is required for editing of RNA polymerase II-transcribed RNAs, including Alus, and deficiency of ADAR1 is associated with MDA5-dependent spontaneous IFN-I production. Notably, Alu RNA is bound by Ro60, a common autoantigen targeted by autoantibodies in SLE, Sjogren’s syndrome, and rheumatoid arthritis, and is found in SLE immune complexes (70). Ro60 deletion results in increased Alu and IFN-I-induced gene expression, suggesting a regulatory role for Ro60.

We have studied a different family of retroelements, long interspersed nuclear elements (L1 or LINE-1), in blood and tissue samples from patients with SLE and Sjogren’s syndrome (71). In contrast to Alu elements, full-length L1 are present in multiple copies (approximately 70, but variable from person to person) in the genome, and those full-length elements can be transcribed to generate a full-length mRNA with two open reading frames that encode an RBP, an endonuclease, and a reverse transcriptase. Suspecting that impaired regulation of L1 might contribute to innate immune system activation, we demonstrated expression of L1 transcripts in kidney tissue from
patients with class IV lupus glomerulonephritis and in salivary gland tissue from patients with Sjögren’s syndrome (72). While we documented decreased methylation of several of the CpG elements in the 5′ regulatory region of L1 in DNA from patient samples, additional alterations in mechanisms that control L1 transcription are also possible (73). L1 RNA expression was highly correlated with IFN-α transcripts, and in vitro transcribed RNA derived from the 5′ untranslated region of L1 induced expression of IFN-I mRNA and protein. Although the cellular sensors that recognize the L1 RNA have not been identified, a TBK1 inhibitor abrogated the induction of IFN-I by the in vitro–transcribed L1 RNA, suggesting that RNA sensors and MAVS might be involved (72). Alternatively, as was observed in the age-related macular degeneration scenario described above, L1 RNA might have the capacity to promote transfer of cell-intrinsic mitochondrial DNA to the cytosol, providing ligands for the cGAS pathway.

Many contributors and mechanisms relevant to the induction of IFN-I by endogenous nucleic acids remain to be elucidated. The nature of the nucleic acid ligands for cytosolic RNA and DNA sensors, the regulatory mechanisms that lead to impaired control of endogenous retroelements in systemic autoimmune disease, the fidelity of the regulators of metabolism and degradation of endogenous stimulatory nucleic acids, and the role of mitochondrial integrity in allowing access of mitochondrial DNA are all topics needing further investigation. Our view is that, while each individual with a systemic autoimmune disease, for which we use SLE as a prototype, may take a distinct route toward activation of the IFN-I pathway, the excessive and sustained production of IFN-I represents a core pathogenic mechanism, at least in SLE. We also suspect that both endosomal TLR and cytosolic nucleic acid sensing pathways are active in these diseases. The recent accumulating data implicating genomic retroelements and mitochondria in IFN-I pathway activation suggest productive new directions that might ultimately provide new insights into the role of environmental stresses in inducing or amplifying innate immune system activation. Barbara McClintock (74) first conceived of activation of endogenous retrotransposons as a genomic defense mechanism that responded to environmental stresses, providing a mechanism to generate genomic diversity. While, at the population level, these stress responses may be beneficial, at the individual level, sensing of self-nucleic acids can represent a trigger for autoimmunity and inflammation.

**CELLS PRODUCING TYPE I INTERFERON**

The major IFN-I-producing cells were first isolated by Siegal et al. (75) in 1999 and described as type 2 dendritic cell precursors and later as pDCs. Reizis and colleagues (76, 77) have studied the development of pDCs in detail and concluded that they have a common origin with antigen-presenting DCs, with the transcription factor TCF4 (E2-2) determining their differentiation program. pDCs express BDCA2, a type II C-type lectin that inhibits IFN-I production when ligated, and ILT7, and their extraordinarily abundant production of IFN-I is facilitated by their expression of IRF7. Their development is dependent on Flt3 and mTOR, and treatment with rapamycin, an mTOR inhibitor, can impact their development (78).

The important role of pDCs as the major producers of IFN-α is generally accepted, and genetic studies in mice support the theory that pDCs are the most significant cell population responsible for production of IFN-I in lupus (79, 80). pDCs have also been implicated in studies of skin and blood from patients with systemic sclerosis, although in this case, TLR8 rather than TLR7 mediates cell activation and induction of IFN-I (81). A recent study using a sensitive assay for IFN-α confirmed that pDCs were the major producers of IFN-α in several autoimmune diseases but also implicated monocytes in patients with gain-of-function STING mutations (82). Neutrophils stimulated with immune complexes may also contribute to production of IFN-α (83). Identification and study of pDCs are challenging due to their low numbers in peripheral blood.
Ronnblom’s laboratory documented decreased numbers of circulating IFN-I-producing cells in SLE blood samples and proposed that those cells had been recruited to tissue following activation by an inducer of IFN-I—nucleic acid–containing immune complexes—in serum (84).

Although IFN-α is the major IFN-I found in SLE patient sera, there is also increasing interest in the contribution of the protein products of other IFN-I genes and their cell sources to the immunopathogenesis of systemic autoimmune disease. IFN-β is of particular interest; its transcripts have been demonstrated in mesenchymal stem cells (55), and serum levels of IFN-β are highly correlated with disease activity in patients with dermatomyositis (85). Mavragani et al. (72) stained salivary gland tissue of patients with Sjogren’s syndrome and renal tissue from patients with lupus nephritis and observed IFN-β protein in glandular epithelial cells and renal tubular cells, respectively. Study of skin from patients with cutaneous lupus shows production of IFN-κ by keratinocytes (86). IFN-λ, a type III IFN, can be produced by gut and lung epithelial cells, as well as by myeloid dendritic cells, and while it is probably not a product of pDCs, it can influence their production of IFN-I (87).

Identifying the most relevant cells producing IFN-I and the subspecies of IFN-I that they generate will help to unravel the impact of the IFNs on the immunopathogenesis of disease and design of effective therapeutics. For example, although the families of IFN-I-regulated genes transcribed in response to IFN-α and IFN-β are largely the same, some studies point to the special capacity of IFN-β, but not other IFN-Is, to induce the immunosuppressive molecules IL-10 and PD-L1 (88). In murine models of virus infection, IFN-α and IFN-β appear to have distinct roles in control of virus dissemination early in the course of the infection. While promoting an immunosuppressive T cell phenotype might intuitively seem desirable in an autoimmune disease characterized by chronic immune system activation, the specific roles of IFN-α versus IFN-β activity in the immunopathogenesis of systemic autoimmune diseases require further study. Monoclonal antibodies specific to BDCA2 target pDCs and would be likely to preferentially inhibit IFN-α production. Although IFN-α may be the most abundantly produced IFN-I in most of the systemic autoimmune diseases, current data suggest that a therapeutic approach that more broadly targets the IFN-I family, including IFN-β and IFN-ω, may be more efficacious (89).

**THE TYPE I INTERFERON RECEPTOR AND THE CELLULAR RESPONSE**

The heterodimeric IFN-I receptor comprises two transmembrane proteins, IFNAR2, which has high binding affinity for the cytokine, and IFNAR1, which has lower affinity (90, 91). Although the differences between them may be subtle, each of the IFN-I subspecies and subtypes is likely to have a different binding profile, with IFN-β having the highest affinity (92). IFNAR is expressed on most cells, although, as is relevant to mechanisms of neuropsychiatric lupus, expression of IFNAR2 is relatively low in the human brain (91). Our unpublished data indicate that expression of both IFNAR1 and IFNAR2 transcripts are comparable in PBMCs, as well as in isolated CD4 and CD8 T cells and B cells from SLE patients and healthy donors, although these data do not rule out differences in stability, trafficking, or degradation of the receptor. Binding of ligand to the receptor activates the Janus family kinases Jak1 and Tyk2, leading to phosphorylation of associated members of the signal transducer and activator of transcription (STAT) family. In antiviral responses, STAT1 and STAT2 are mainly involved in signaling downstream, associating with IRF9 to regulate hundreds of IFN-I-induced genes, but other STATs, as well as MAP kinases, may also be involved in IFNAR signaling in a manner that may differ in different cell types. Engagement of IFNAR by IFN-I leads to induction of SOCS genes and a negative feedback loop limiting signaling through IFNAR, but the documented decrease in SOCS1 expression in SLE.
patients and in murine lupus models suggests reduced negative regulation of IFNAR signaling (93). Ubiquitin-specific protease 18 (USP18) is an additional gene product regulating IFN-I signaling that is potentially relevant to altered signaling in systemic autoimmune disease and is interesting in that it preferentially blocks signaling by IFN-α while sparing inhibition of signaling induced by IFN-β (94).

INTERFERON-INDUCED GENES AND THEIR FUNCTIONAL SIGNIFICANCE

After binding to its receptor and triggering the Jak-STAT signaling pathway, IFN-I induces transcription of hundreds of genes. Many have antiviral activity and can be categorized based on their impact on inhibition of translation, degradation of RNA, and other important functions relevant to control of viral load and infectivity (Figure 3). Other IFN-I-induced genes are more involved in regulatory activity relevant to immune function, including antiproliferative activity. In contrast

![Diagram](https://example.com/diagram.png)

**Figure 3**

Induction of type I IFN-inducible genes. Type I IFNs bind to IFNAR, the type I IFN receptor, with IFN-β having a higher affinity for IFNAR than does IFN-α. In general, binding to IFNAR initiates a signaling cascade through Jak1 and Tyk2, activating STAT1 and STAT2, which translocate to the nucleus in association with IRF9 and induce new gene transcription. In some cases additional STATs may be activated, or protein kinase B may mediate gene transcription initiated by IFNAR binding. Studies of IFN-induced gene expression have identified two general categories of IFN-induced genes, those that are readily induced and mediate many antiviral effects and those that mediate antiproliferative and immunomodulatory functions. The antiviral or robust IFN-induced genes tend to be expressed in a relatively stable manner over time in many SLE patients. Expression of the immunomodulatory or tunable IFN-induced genes can fluctuate over time in relation to lupus disease activity. Abbreviations: IFN, interferon; IRF9, interferon regulatory factor 9; ISRE, interferon-sensitive response element; Jak1, Janus kinase 1; Tyk2, tyrosine kinase 2; SLE, systemic lupus erythematosus; STAT1/2, signal transducer and activator of transcription 1/2.
to those genes with antiviral activity, which often depend on regulation by STAT1/STAT2/IRF9 complexes binding to interferon-sensitive response elements in gene promoters, IFN-I-induced genes with antiproliferative and immune-modulating activity may use other regulatory elements and may be more dependent on higher concentrations of IFN-I.

A study led by Gideon Schreiber used a mutant IFN-α that bound well to IFNAR2 but not to IFNAR1 to characterize IFN-I-induced genes as either antiviral (robust) or antiproliferative and immunomodulatory (tunable) (95). Antiviral IFN-I-regulated genes include some that are well-known components of the IFN-I signature assessed by many investigators (e.g., MX1, IFIT1), and the antiproliferative genes include some of those encoding inflammatory mediators (e.g., CXCL10, IL8). The SOCS1 protein, an inhibitor of IFN-α signaling, is among the products of the antiviral (robust) IFN-I-induced genes.

Chiche et al. (96) analyzed gene expression data from microarray analysis of blood cells from SLE patients and identified three distinct modules of IFN-regulated gene transcripts. Two of the modules are IFN-I related, with module M1.2 generally comparable to the robust module described above and present in most SLE patients. Module M3.4 was less prevalent, fluctuated over time, and was described as including transcripts induced by IFN-β in other studies. While transcripts in module M3.4 are of interest, it appears that they are not specific to IFN-β. We performed K-means clustering of differentially expressed transcripts in SLE compared to healthy donor PBMCs based on the Affymetrix microarray platform and also defined two IFN-I clusters with considerable overlap with the robust and tunable transcripts defined by Schreiber’s group (M. Olferiev & M.K. Crow, unpublished data). In addition to genes encoding chemokines and other proinflammatory mediators (e.g., CXCL10, CXCL11), the cluster resembling Schreiber’s tunable transcripts included transcripts involved in signaling or regulation of the cytosolic nucleic acid sensing pathway (e.g., DDX58/RIG-I, ADAR, TREX1), as well as transcripts documented to regulate expression of genomic retroelements (e.g., APOBEC3A, BST2, ISG20). While they were often highly expressed early in the course of lupus disease, transcripts in this second cluster sometimes peaked in expression weeks or months prior to a clinical disease flare. Detailed analysis of the longitudinal expression of these IFN-I-related transcripts is ongoing in our laboratory, but transcripts studied to date support the relevance of the cytosolic nucleic acid sensing pathways to the immunopathogenesis of SLE and warrant further longitudinal study to relate regulation of those transcripts to serologic features of autoimmunity, protein biomarkers, and clinical manifestations of disease.

**THE CONTRIBUTION OF TYPE I INTERFERON TO HOST DEFENSE AND IMMUNOPATHOLOGY**

Chronic activation of the IFN-I pathway, as demonstrated in most patients with SLE, has numerous and complex effects on both innate and adaptive immune system function, as well as on target organ pathology (97–99) (Figure 4). The capacity of IFN-I to alter antigen-presenting cell function, B cell differentiation and class switching, and chemokine production has been well documented (100–102), but the impact of IFN-I on T effector cell function and tissue immunopathology is still being investigated. In that regard, murine models of chronic virus infection, as well as studies of patients with chronic HIV infection, have been particularly informative in dissecting the effects of acute versus sustained expression of IFN-I on immune regulation and tissue damage (103–107). In fact, the many parallels between the immunopathogenic mechanisms described in HIV-infected patients and those in SLE patients are striking. Nucleic acid-containing immune complexes are potent inducers of IFN-I through TLR7 in pDCs of SLE patients, and virus-containing immune complexes drive IFN-I production by pDCs in HIV-infected patients in a TLR7-dependent manner (108).
Innate immune functions
- Augments APC function
- activates microglial cells
- alters endothelial cell function
- inhibits angiogenesis
- induces chemokines and myeloid cell recruitment
- promotes apoptosis

Clinical consequences
- autoimmunity
- neuropsychiatric manifestations
- premature atherosclerosis
- preeclampsia
- inflammation, including synovial and renal inflammation
- skin rash

B cell functions
- promotes B cell differentiation and immunoglobulin class switching

Immune complex-mediated multiorgan pathology, including glomerulonephritis
- Antibody-mediated cytopenias
- Cellular infiltration contributes to organ damage

T cell functions
- promotes T follicular helper cell expansion
- induces partial CD8 T cell exhaustion
- regulates NK cell function

Promotes autoimmune
- Impairs antiviral immunity
- Cellular infiltration contributes to organ damage

Figure 4
Protean immunopathologic effects of type I interferon contribute to many of the clinical and pathologic manifestations of disease in systemic lupus erythematosus. Abbreviations: APC, antigen-presenting cell; NK, natural killer.

Murine models of chronic lymphocytic choriomeningitis virus (LCMV) and HIV infection have been particularly informative in dissecting the broad immune-modulating effects of chronic IFN-I exposure. Many studies from the Ahmed and Oldstone laboratories have made important contributions to understanding how chronic virus infection, and the accompanying sustained IFN-I production, can shape the T cell effector profile to promote T cell–dependent B cell differentiation and inflammation (88, 104, 109), and several recent reviews summarize the immune dysregulation associated with chronic IFN-I availability (97–99). Chronic IFN-I production may shift the CD4 T cell effector phenotype from a Th1 functional phenotype toward a dominant T follicular helper cell phenotype, promoting B cell differentiation, and may also directly or indirectly contribute to the partially exhausted CD8 T cell phenotype that has been observed in SLE (CD4+ Th1 cells are necessary for effective development of CD8 cytotoxic T cells). The lessons learned from these murine studies are highly relevant to the development of hypotheses regarding the contribution of IFN-I to altered immune system function in SLE and other autoimmune diseases associated with an IFN-I signature.

Two studies comparing the pathology induced by two LCMV strains—clone 13 and Armstrong—are particularly notable (103, 104). While the production of IFN-I after virus infection is rapidly controlled in mice infected with the Armstrong strain, clone 13 leads to long-term elevation of IFN-I and tissue pathology. In these studies, blockade of IFNAR in the animals infected with clone 13 reduced levels of proinflammatory mediators and corrected alterations in splenic architecture, reducing tissue pathology. Two additional studies published in 2017 used humanized mice infected with HIV to show that blockade of IFNAR, together with antiretroviral therapy, during chronic infection decreased markers of CD8 T cell exhaustion; reduced the extent of HIV replication, perhaps due to improved CD8 T cell function; and decreased the reservoir of cells harboring HIV (105, 106). Together, these and other studies of chronic virus infection indicate that the immune dysregulation and tissue pathology associated with sustained IFN-I production can be corrected by inhibition of IFNAR, an important lesson that is highly relevant to the design of therapeutics for SLE and other systemic autoimmune diseases characterized by IFN-I pathway activation.
TISSUE PATHOLOGY AND DISEASE MANIFESTATIONS ASSOCIATED WITH TYPE I INTERFERON

Production of IFN-I in target tissues and organs in patients with SLE and related diseases is consistent with the documented contribution of the IFN-I pathway to the inflammation and disruption of the architecture of lymphoid tissue in murine models characterized by sustained IFN-I production. pDCs have been observed in skin and renal tissue from SLE patients, and expression of the protein products of IFN-I-induced genes—typically MX1—are documented in those tissues (72, 80, 110–112). Ultraviolet light, a well-known inducer of lupus flare, promotes recruitment of pDCs to skin (113). Mavragani et al. (72) stained kidney tissue from patients with lupus nephritis and salivary gland tissue from patients with Sjogren’s syndrome with anti-BDCA2 antibody to identify pDCs, and they observed infiltration of pDCs in both tissues. Both IFN-α and IFN-β can be seen in both tissues. Keratinocyte-derived IFN-κ is present in skin of patients with cutaneous lupus, and synovial tissue from SLE patients with arthritis is strongly positive for IFN-I-regulated gene transcripts (86, 114). IFN-I likely contributes to the premature atherosclerosis that is characteristic of patients with SLE, and the IFN-I signature is associated with impaired endothelial function, accelerated thrombosis, and platelet activation (115, 116). Neuropsychiatric lupus is one of the more prevalent manifestations of the disease, and it has a significant impact on quality of life. Recent studies implicate IFN-I generated in the periphery in microglial activation and altered synaptic pruning in murine lupus, and preliminary data from pathologic brain specimens from patients with SLE indicate increased microglial activation and synaptic pruning (117). Elevated levels of IFN-I are also associated with risk of preeclampsia and poor pregnancy outcomes in patients with SLE (118).

Collectively, the broad expression of IFN-I and IFN-I-regulated gene products, in association with most of the clinical manifestations that characterize SLE, provides strong support for the immunopathologic relevance of this cytokine family. It is likely that all subspecies of IFN-I are implicated, although some questions remain regarding the relative roles of IFN-α and IFN-β in the different organs affected. This issue could be of clinical significance, as IFN-I may play protective as well as pathogenic roles in the central nervous system (119).

While the documentation of local production of IFN-I is not as extensive in other systemic autoimmune diseases as it is in SLE, it is likely that IFN-I also contributes to immune dysregulation in those disorders that are characterized by autoantibodies targeting nucleic acids and nucleic acid–binding proteins. As noted above, IFN-α and IFN-β are expressed in Sjogren’s syndrome salivary glands, with immunohistochemistry data suggesting that IFN-α is primarily expressed in pDCs, while IFN-β is present in glandular epithelial cells (72, 120). The IFN-I signature is also present in PBMCs from those patients. Muscle tissue from patients with dermatomyositis shows the presence of IFN-I and IFN-I-induced protein; IFN-β is proposed to be the predominant species of IFN-I in this disease (85, 121, 122). The role of the IFN-I pathway in systemic sclerosis is an area of active current investigation (123); pDCs are likely to be the important producers, but they may act via an unusual signaling pathway transduced through TLR8 (81). The IFN-I signature is not prominent in most patients with rheumatoid arthritis, although the signature has been demonstrated in treatment-naïve patients and may identify patients refractory to initial therapy (124). A common theme that applies to several, if not most, of these systemic autoimmune diseases is the association of IFN-I pathway activation and the IFN-I signature with autoantibodies targeting RNA and RNA-associated proteins (8, 125, 126). These observations support the significant role of nucleic acid–containing immune complexes in driving production of IFN-I, with pDCs and TLR7 likely playing a key role.
RELATIONSHIP BETWEEN THE TYPE I INTERFERON SIGNATURE AND DISEASE ACTIVITY

Early studies in patients with SLE showed a statistical association of the IFN-I signature in peripheral blood with important clinical manifestations of disease, such as lupus nephritis, and an association with the SLE disease activity index in cross-sectional data (14, 17). However, more recent data have questioned the utility of the IFN-I signature as a biomarker of disease activity, as longitudinal data demonstrate stability of the IFN-I score over time in most patients (127). In our view, the assessment of a relationship between the IFN-I signature and clinical disease activity and lupus flare requires further study. In studies that evaluated all patients meeting classification criteria for a diagnosis of SLE, most participants show stability of the IFN-I score. However, in a study designed by Kyriakos Kirou that selected SLE patients to enrich the study population in those who demonstrated a disease flare in the year prior to enrollment and that analyzed multiple longitudinal samples, several longitudinal patterns of IFN-I pathway activation were found (Figure 5) (K.A. Kirou, M. Olferiev & M.K. Crow, unpublished data). Stable patterns of IFN-I score in relation to disease activity were observed, but 40% of patients studied showed a peak in IFN-I score 1–6 months before an increase in disease activity. Some patients did show concurrence of the IFN-I score and disease activity scores, suggesting, at least, that exogenous or endogenous drivers of IFN-I production might contribute to the immune dysregulation that results in the clinical manifestations of disease.

While we do see stable expression of the IFN-I score in many patients, more refined dissection of the IFN-I pathway may reveal clinically relevant associations. As described above, the IFN-I-regulated transcripts can be clustered into groups of transcripts that can be differentiated statistically, and transcripts from the cluster described by Schreiber’s group as robust, roughly comparable to Chiche’s module M1.2, are often used to measure activation of the IFN-I pathway (95, 96). A characteristic of these transcripts is that they are sensitive to induction and relatively

Figure 5

Longitudinal expression of an IFN-I signature in relation to disease activity in patients with SLE. An IFN-I score was generated based on RT-PCR analysis of three genes (IFIT1, IFI44, and PKR) in longitudinal PBMC samples from two patients with SLE, and this was related to disease activity scores (SLEDAI and BILAG). (a) Patient IF2 demonstrated an IFN-I score that paralleled the disease activity. (b) Patient IF6 initially had inactive disease and a limited autoantibody profile (anti-Ro). The patient developed community-acquired pneumonia approximately 5 months after recruitment into the study, developed an acute IFN-I spike approximately 8 months after recruitment, and extended the autoantibody profile to include anti-Sm/RNP 16 months after recruitment. The asterisks indicate the peak of disease activity. Abbreviations: BILAG, British Isles Lupus Assessment Group; IFN-I, type I interferon; PBMC, peripheral blood mononuclear cell; RT-PCR, reverse transcription polymerase chain reaction; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.
stable over time, regardless of disease activity. A second cluster of IFN-I-regulated transcripts that we have defined using K-means clustering, which has some overlap with the Schreiber group’s (95) tunable transcript cluster and includes representatives from Chiche et al.’s (96) modules M3.4 and M5.12, may be more useful in predicting future disease flares, as we have observed that these transcripts fluctuate over time. We are currently analyzing extensive longitudinal data to understand the relationship of those transcripts to serologic and clinical measures of disease activity.

One subpopulation of patients that requires further study includes those that do not demonstrate an IFN-I signature. Observations from interventional clinical trials, most notably the study of the anti-IFNAR monoclonal antibody anifrolumab (89), demonstrated a significant response to the agent in patients with a high IFN-I score, but not in those with a score that overlapped with that of healthy donors, compared with patients treated with placebo. In view of the nearly universal presence of an IFN-I signature in pediatric lupus patients prior to therapy, it remains possible that acquired alterations in the immune system might contribute to a blunting of the IFN-I signature in some adult lupus patients. In most studies describing patients considered to have a low IFN-I score, many still show a level of IFN-I pathway activation that is greater than that of healthy individuals. One potential mechanism that might account for consistently low IFN-I activity in patients bearing a clear diagnosis of SLE is the development of endogenous anti-IFN-I antibodies. These antibodies have been identified in patients with rare mutations in the autoimmune regulator AIRE but are also documented among the anticytokine antibodies detected in patients with SLE and Sjogren’s syndrome (128–130). Some data have documented a low IFN-I score in some SLE patients with anti-IFN-I antibodies (129), but additional investigation will be needed to determine the role of these antibodies in the IFN-I-low patient group more generally. Of interest, one therapeutic approach in current clinical trials aims to induce endogenous anti-IFN-I antibody using a vaccination protocol (131).

**THERAPEUTIC APPROACHES TARGETING THE TYPE I INTERFERON PATHWAY**

The strong evidence that IFN-I is a central mediator of the immunopathogenesis of SLE, and perhaps of additional systemic autoimmune diseases, is driving active preclinical and clinical drug development programs, including testing of agents that might address afferent and efferent arms of the IFN-I pathway. We do not provide a comprehensive summary of the therapeutic agents relevant to this cytokine pathway, as others have reviewed many of the agents of current interest (132). However, we highlight several therapeutic approaches based on the results of both murine and human studies, including data reviewed in this article.

Antimalarial drugs are currently used in most patients with SLE and in patients with some other autoimmune diseases, and their utility in decreasing the frequency of future disease flares is well established (133). Recent data indicate that agents in the antimalarial family can inhibit signaling through both TLR and cytosolic sensor pathways (134). If these drugs could be made more potent, then they could prove even more efficacious than the commonly used hydroxychloroquine. The potential promise of targeting pDCs is suggested by the abundant IFN-α produced by those cells, the association of IFN-I production with RNA-containing immune complexes that stimulate pDCs through TLR7, and genetic studies in murine systems that demonstrate abrogation of disease when pDCs are diminished. Anti-BDCA2 antibodies are specific for pDCs, so they might deplete and/or have the potential to provide an inhibitory signal to those cells (135). Kinases involved in the TLR7 signaling pathway are also of interest (136). Inhibitors of IRAK4 have been tested in murine lupus models and reduce disease through actions on multiple pathogenic pathways (137). The cytosolic nucleic acid sensors and their signaling pathways also represent promising therapeutic targets in
view of the recognition that intracellular nucleic acids, as well as extracellular immune complexes, can serve as relevant drivers of IFN-1 production. cGAS inhibitors are in development, and several studies have provided support for inhibition of TBK1 as an approach to reduce the IFN-1-regulated gene signature (138, 139).

Inhibitors of the efferent arm of the IFN-1 pathway are particularly promising for the treatment of autoimmune diseases because they can target IFN-1 signaling, as well as signaling induced by other cytokine ligands. Jak1 inhibitors have been used in patients with monogenic disorders of IFN-1 pathway regulation and are currently being studied in patients with SLE (140). Targeting Jak1 should abrogate IFN-1 signals but also reduce the production of IL-12, an effect that might have a beneficial impact on T cell function (141).

In addition, inhibition of IFNAR with the anti-IFNAR monoclonal antibody anifrolumab is promising given its successful Phase II clinical trial, although initial reports of Phase III studies are disappointing (89). The Phase II study met its clinical end point across multiple clinical parameters and was particularly effective in patients demonstrating a high IFN-1 gene signature. In view of the protean immunologic alterations that characterize the autoimmune disease of patients with SLE and the iterative and complex amplification of immune system alterations that typically develop over time in SLE, it is more than likely that targeting only one molecular pathway, even one as central to immunopathology as the IFN-1 pathway, will not be sufficient to gain control of this disease, as well as other related systemic autoimmune diseases associated with an IFN-1 signature. However, approaches that target components of this pathway represent the most promising and advanced therapeutic strategy to date.

PERSPECTIVE

The complex genomic structure of the IFN-1 locus, encoding multiple members of the IFN-1 cytokine family, reflects the ongoing struggle between the host and the multitude of viral pathogens that challenge host integrity. In SLE and related diseases, this rigorously regulated system escapes its controls, resulting in induction of the IFN-1 genes, activation of the molecular pathways that they trigger, and induction of the hundreds of genes that they regulate. A complex molecular program driven by IFN-1 modulates many aspects of immune function, contributing to the autoimmunity, inflammation, and tissue damage that play central roles in generating the clinical manifestations of SLE; this molecular program likely also contributes to related systemic autoimmune diseases. A notable feature of the IFN-1 pathway in SLE is that its activation is sustained over time, raising many questions yet to be addressed. Potential roles for exogenous viral triggers or latent infection with EBV remain possibly relevant, and the potential contribution of intracellular nucleic acids, including those encoded by genomic repeat elements, that escape proper metabolism or degradation is only beginning to come into focus.

We contend that excess IFN-1 represents a core immunopathogenic mechanism in SLE. While the murine models of chronic virus infection associated with sustained IFN-1 production provide informative demonstrations of the immune sequelae of excessive IFN-1 signaling, additional concepts are needed to address the early events that might contribute to IFN-1 production. We suggest a conceptual model that can guide continued investigation of the immunologic mechanisms that account for development of SLE, informed by the clear role for genetic variations that decrease the threshold for immune activation and shape development of autoantibody specificities in an individual patient (Figure 6). As was demonstrated in a comprehensive and insightful study combining examination of patients with severe malaria infection and a murine model of malaria infection that demonstrates similar pathology, IFN-1 serves as an essential mediator determining disease outcomes (142). In a first phase of disease following infection, macrophages activated by malaria
parasites in a STING-dependent manner, presumably based on signaling from cytosolic nucleic acid receptors, produced small amounts of IFN-I and prime pDCs to respond to malaria parasites through the TLR7 pathway, resulting in robust IFN-I production, immune system activation, and tissue inflammation. Disease pathology was abrogated in the absence of IFNAR. Continued investigation of patients with systemic autoimmune disease, along with murine models, may similarly demonstrate requirements for both cytosolic sensors and the endosomal TLR pathways in initiating and perpetuating IFN-I production and its myriad downstream sequelae. Such a scenario would provide many candidate therapeutic targets and opportunities to gain control of disease in patients.

**DISCLOSURE STATEMENT**

M.K.C. has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Lilly, and Neovacs. K.A.K. serves as an investigator in clinical trials sponsored by AstraZeneca, Aurinia Pharmaceuticals, and the Lupus Clinical Investigators Network (LuCIN). M.O. is not aware of any affiliations, memberships, funding, or other financial holdings that might be perceived as affecting the objectivity of this review.

**ACKNOWLEDGMENTS**

The authors have received funding from the National Institutes of Health, the Lupus Research Alliance, and the Emerald Foundation. They acknowledge the contributions of Jing Hua, PhD, who performed experiments assessing the contributions of anti-DNA and anti-RBP antibodies to induction of IFN-I.


Contents

Polyglutamine Repeats in Neurodegenerative Diseases
Andrew P. Lieberman, Vikram G. Shakkottai, and Roger L. Albin ......................... 1

Epstein–Barr Virus and Cancer
Paul J. Farrell ................................................................. 29

Exposure to Ultraviolet Radiation in the Modulation of Human Diseases
Prue H. Hart, Mary Norval, Scott N. Byrne, and Lesley E. Rhodes ......................... 55

Insights into Pathogenic Interactions Among Environment, Host, and Tumor at the Crossroads of Molecular Pathology and Epidemiology
Shuji Ogino, Jonathan A. Nowak, Tsuyoshi Hamada, Danny A. Milner Jr., and Reiko Nishihara ................................................................. 83

Pathological Issues in Dystrophinopathy in the Age of Genetic Therapies
Nazima Shahnoor, Emily M. Siebers, Kristy J. Brown, and Michael W. Lawlor .... 105

Pathogenesis of Rickettsial Diseases: Pathogenic and Immune Mechanisms of an Endotheliotropie Infection
Abha Sahni, Rong Fang, Sanjeev K. Sabni, and David H. Walker ......................... 127

Innate Immune Signaling in Nonalcoholic Fatty Liver Disease and Cardiovascular Diseases
Jingjing Cai, Meng Xu, Xiaojing Zhang, and Hongliang Li ................................. 153

Immunological Basis for Recurrent Fetal Loss and Pregnancy Complications
Hitesh Deshmukh and Sing Sing Wiy ............................................ 185

Opportunities for microRNAs in the Crowded Field of Cardiovascular Biomarkers
Perry V. Halushka, Andrew J. Goodwin, and Marc K. Halushka ......................... 211

Molecular Pathogenesis of the Tauopathies
Jürgen Götz, Glenda Halliday, and Rebecca M. Nisbet ..................................... 239
Pathophysiology of Sickle Cell Disease
Prithu Sundd, Mark T. Gladwin, and Enrico M. Novelli ........................................ 263

Malformations of Cerebral Cortex Development: Molecules and Mechanisms
Gordana Juric-Sekhar and Robert F. Hevner ....................................................... 293

Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection
Wei Gu, Steve Miller, and Charles Y. Chiu ....................................................... 319

Molecular Genetics of Endometrial Carcinoma
Daphne W. Bell and Lora Hedrick Ellenson ....................................................... 339

Type I Interferons in Autoimmune Disease
Mary K. Crow, Mikhail Olferiev, and Kyriakos A. Kirou ........................................ 369

Systems-Wide Approaches in Induced Pluripotent Stem Cell Models
Edward Lau, David T. Paik, and Joseph C. Wu ....................................................... 395

Pathology and Pathogenesis of Chagas Heart Disease
Kevin M. Bonney, Daniel J. Luthringer, Stacey A. Kim, Nisha J. Garg, and David M. Engman ............................................................... 421

Modeling Disease with Human Inducible Pluripotent Stem Cells
Rodrigo Grandy, Rute A. Tomaz, and Ludovic Vallier ........................................ 449

RNA Binding Proteins and the Pathogenesis of Frontotemporal Lobar Degeneration
Jeffrey W. Hofmann, William W. Seeley, and Eric J. Huang ........................................ 469

Cellular and Molecular Mechanisms of Prion Disease
Christina J. Sigurdson, Jason C. Bartz, and Markus Glatzel ........................................ 497

Errata

An online log of corrections to Annual Review of Pathology: Mechanisms of Disease articles may be found at http://www.annualreviews.org/errata/pathmechdis