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Targeting of Type I Interferon in Systemic Autoimmune Diseases

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Abstract

Increased blood levels of type I interferon (IFN-I) and expression of a broad signature of gene transcripts that reflect induction by IFN-I are observed in many patients with systemic autoimmune diseases, and that pattern is most striking in systemic lupus erythematosus (SLE). Persistent production of IFN- α , the most abundant subtype measured in these patients, is an important feature of the immunopathogenesis of lupus and has stimulated current efforts to develop and test therapeutics that either block IFN-I or its receptor directly or target components of the IFN-I pathway involved in induction of or response to IFN-I. This review will describe data from animal models of chronic viral infection, examples of lupus-like syndromes associated with single-gene mutations that impact the IFN-I pathway, and longitudinal studies from lupus patients to support the rationale for therapeutic targeting of the IFN-I pathway in SLE. However, the complexity of IFN-I regulation and the diversity of its effects on immune system function suggest that the definitive demonstration of that pathway as a valid and productive therapeutic target will only come from clinical trials of agents tested in patients with systemic autoimmune disease, with lupus patients likely to be the most informative.

Introduction

Among the multitude of immunologic aberrations and mediators that have been documented in patients with the prototype systemic autoimmune disease, systemic lupus erythematosus, elevated type I interferon (IFN-I) and its associated signature of highly correlated mRNA transcripts encoded by IFN-I-stimulated genes have gained considerable attention.^{1,2} The IFN-I's comprise products of a gene family encoded on human chromosome 9p and include 13 IFN- α 's, IFN- β , IFN- ϵ , IFN- κ and IFN- ω . The IFN-I's bind to a common receptor, IFNAR, that is composed of two chains, IFNAR1 and IFNAR2, and they signal through

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members of the Janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway to induce expression of hundreds of gene transcripts that generate anti-viral and immunomodulatory proteins. Building on longstanding observations of increased serum IFN-I activity in lupus patients, extensive recent studies assessing gene expression in lupus peripheral blood,^{3–7} *in vitro* analyses of the functional impact of IFN-I in serum and plasma on immune function,^{8–10} and murine studies in which administration of IFN-I accelerates lupus-related pathology¹¹ have all supported the hypothesis that IFN-I is a pathogenic mediator in lupus. Additional data derived from histopathologic and gene expression analyses of skin, kidney biopsies and synovial tissue from patients with clinical involvement in the relevant tissues have identified the presence of plasmacytoid dendritic cells (pDC's), active producers of IFN-I, in close proximity to cells expressing classic IFN-I-stimulated gene products, such as MX1, further supporting active production of IFN-I in association with tissue pathology.^{12,13} Studies characterizing the subtype of IFN-I most relevant to lupus have identified IFN- α as the predominant product,¹⁰ although IFN- β may be a significant, although less abundant, mediator as well.¹⁴ Genetic association studies have identified specific components of molecular pathways responsible for IFN-I production or response. Those include interferon regulatory factor 5 and Tyk2, associated with a diagnosis of SLE, and point to mechanisms, including activation of Toll-like receptor (TLR) pathways, that might contribute to the chronic activation of the IFN-I pathway observed in patients.^{15,16}

Taken together, the extensive data associating IFN-I, the cells that produce IFN-I, and the products induced by IFN-I with a majority of patients with SLE – approximately 65% of adult patients and virtually all patients with pediatric SLE - provide a strong case for IFN-I as a central mediator relevant to lupus disease and identify components of the pathway as rational therapeutic targets. However, in view of the complex functional effects of IFN-I on immune system function, it remains possible that the production of IFN-I in the context of systemic autoimmune disease represents a response to immune system triggers that induce autoimmunity. At least some activities of IFN-I may serve to dampen the pathologic immune activation that contributes to inflammation and tissue damage. In addition, even if the pathway is supported as a rational therapeutic target, it remains uncertain whether modulating IFN- α , IFN- β , their receptor, mediators of IFN-I induction, or other components of the pathway might be the most productive therapeutic approach.

Predicting and supporting the validity of IFN-I and its molecular pathway as therapeutic targets in SLE can begin with an assessment of the extensive literature that has carefully characterized the beneficial vs. pathologic roles of IFN-I in the context of host defense in response to virus infection, although the most informative information to date has come from animal models rather than human studies. Data from patients with single gene mutations that impact the IFN-I pathway and result in characteristic clinical syndromes with similarities to SLE are also informative. Data from SLE patients that link production of IFN-I to future development of significant disease manifestations, rather than abrogation of disease, would provide additional support for targeting IFN-I therapeutically. Of course, most definitive will be results from clinical trials using agents that effectively block the IFN-I pathway. While no single therapeutic approach is likely to be sufficient to control the

extensive autoimmunity and immune system alterations that generate disease in lupus, documenting an important pathogenic role for the IFN-I pathway in lupus disease based on abrogation of some aspects of disease activity in interventional clinical trials would be an important step toward more effective management of this significant and life-altering disease. Data from lupus patients might also support development of new therapeutics for other systemic autoimmune diseases characterized by IFN-I pathway activation. This review will summarize information from models of viral infection, patients with single-gene mutations, our data from lupus patients studied longitudinally, and the limited available data from clinical trials to support the validity of components of the IFN-I pathway as promising therapeutic targets.

Lessons from animal models of chronic virus infection

IFN-I represents a family of immune system products that are essential for defense of the host against viral infections.¹⁷ The redundant nature of the IFN- α 's, with 13 family members encoded by distinct but related genes, suggests an expansion of that gene family over evolutionary time, perhaps driven by threats to host survival posed by viruses. In fact, the multiplicity of mechanisms by which the IFN-I system is regulated reflects the capacity of viruses to subvert the host immune response.¹⁸

In the setting of acute virus infection, a very low level of constitutive IFN-I production is rapidly amplified to control virus replication, with inhibition of protein translation and generation of cytotoxic cells, initially natural killer cells, often effective. However, in the case of viruses that persist and are not sufficiently controlled by early immune responses, a complex interplay between host and virus orchestrated by the IFN-I pathway plays out, with implications for survival of the virus and also for host tissue inflammation and damage. Recent publications have described the distinct immune system functions that are activated in the setting of acute production of IFN-I early after infection with some viruses vs. the sustained IFN-I production that is seen when a virus sets up a chronic infection. An etiologic microbial agent has not been identified in patients with lupus, although evidence of infection with the common Epstein Barr virus appears to be present in nearly all lupus patients.¹⁹ Nonetheless, the immunologic profile characteristic of lupus patients bears striking similarity to that characterized in animal models of chronic viral infection, supporting a predominantly pathologic role for persistent high level IFN-I.

In the case of lymphocytic choriomeningitis virus (LCMV), two informative recent studies dissected the immune system correlates of acute and chronic IFN-I pathway activation in mice infected with two distinct viral strains.^{20,21} A virus that causes persistent infection and tissue damage also induces persistent IFN-I production, along with IL-10 and PD-L1 expression by splenic dendritic cells, viewed as suppressive factors that inhibit the induction of T cell-mediated viral clearance. Pro-inflammatory mediators and damaged lymphoid architecture are also associated with sustained IFN-I production. Blockade of IFN-I with an anti-receptor antibody permitted induction of a T cell-mediated anti-viral response and resulted in clearance of virus and restoration of lymphoid architecture. In an extension of this work, Osokine et al. demonstrated that in the setting of chronic LCMV infection, sustained production of IFN-I inhibits the differentiation of activated T cells to T helper1

(T_{H1}) effector cells, thereby preferentially expanding T follicular helper (T_{FH}) cells, a situation supportive of B cell differentiation and possible autoantibody production, rather than providing support for development of cytotoxic CD8 cells that might help to clear the viral infection.²² Protective T_{H1} cells were restored after blocking the IFN-I receptor with an antibody.

In patients with human immunodeficiency virus-1 (HIV-1) infection, an inflammatory response, assessed based on early elevations of IFN-I-induced gene products such as the pro-inflammatory chemokine CXCL10 (IP-10), is predictive of disease progression.^{23,24} In fact, higher levels of IFN-I and an IFN-I-stimulated gene signature characterize those patients whose disease progresses compared to relative non-progressors.²⁵ Studies of the related simian immunodeficiency virus (SIV) are informing understanding of the consequences of IFN-I pathway activation for the immunologic response to the infection and its impact on outcome.^{26–29} Natural hosts of SIV, African green monkeys, tolerate the virus infection but do not develop the chronic immune activation, including T cell activation and production of inflammatory mediators, that characterizes humans infected with HIV. Recent data from studies in the African green monkey model suggest that high levels of IFN- α contribute to but may not be sufficient to promote the immune system activation and inflammation that are associated with sustained viral infection and clinical disease in humans with HIV-1 infection. Administration of recombinant IFN- α 2 early following SIV infection did not induce T cell activation, alter production of inflammatory mediators such as IP-10, or induce cytokines, including IL-6, IL-18 and TNF, associated with pathologic disease in other species.²⁹ Other IFN-I subtypes or mechanisms that regulate the response to IFN-I might be required to generate the sustained high IFN-I-stimulated gene expression signature that characterizes those species that do progress after infection with SIV or HIV-1 infection in humans. Responses to IFN-I by distinct cell populations, for example myeloid cells vs. pDC's, might also impact the subsequent immune activity and persistence of inflammation that can be important for disease outcome.³⁰ HIV-1 can traffic to early endosomes in pDC's and serve as a TLR7 agonist, resulting in persistent IFN- α production and weak capacity to stimulate T cell responses.³¹ In SLE, a comparable mechanism mediated by RNA-containing immune complexes, such as those containing anti-Ro or anti-RNP antibodies, might provide the stimulus for persistent IFN-I pathway activation and the consequent inflammation and tissue damage.^{1,2,32}

In hepatitis C infection, often associated with clinical features common in rheumatic diseases and SLE, including arthritis and vasculitis, IFN-I production is also associated with persistent viral infection.³³ In those patients, sustained production of endogenous IFN-I is associated with immune system activation, yet those with the high levels of baseline IFN-I pathway activation, possibly driven by relatively high concentrations of endogenous IFN-I, show a relatively poor response to administration of recombinant IFN- α . That effect is at least in part mediated by high expression of several IFN-I-stimulated genes, including ISG15 and USP18, that are negative regulators of the IFN-I pathway and contribute to persistence of virus.^{34,35} These mediators, which are among the IFN-I-stimulated genes overexpressed in lupus, might provide negative feedback regulation of the IFN-I pathway in some settings, but might be insufficient to control IFN-I production and tissue damage in SLE patients with persistent activation of pDCs mediated by nucleic acid-containing

immune complexes. Those immune complexes can trigger production of pro-inflammatory mediators as well as IFN-I, and might preferentially drive pathologic rather than protective pathways.

The data from these animal models and, to some extent, human patients present a fairly consistent scenario in which acute infection with some viruses induces production of IFN-I that has the potential to limit viral replication and control infection. However, in some cases, likely dependent on combinations of viral and host genetic factors, activation of the IFN-I pathway is sustained with several consequences. Immunosuppressive factors are produced, such as IL-10 and cell surface PD-L1, and generation of Th1 effector cells is inhibited, limiting the host's capacity to generate the cytotoxic T cells needed to clear remaining virus. At the same time, pro-inflammatory mediators, such as IL-6 and IP-10, are produced, augmenting tissue inflammation and immune system activation. CD4 T cells show a relative shift toward T_{FH} cells, providing support for B cell differentiation (Table 1). In addition, in Th17-mediated diseases, IFN-I can promote inflammation and amplify tissue damage.^{36,37} While the molecular mechanisms that account for the consequences of chronic IFN-I production are only partially understood, to the extent that these models of virus infection reflect mechanisms that might also be operative in patients with SLE, we suggest that IFN-I pathway blockade would be predicted to limit the excessive production of pro-inflammatory mediators and shift the balance of CD4 effector cells away from T_{FH} cells. Both results should be productive in limiting autoimmunity, inflammation and tissue damage.

Drawing an analogy between immune system mechanisms relevant to chronic viral infection and the immunopathogenesis of SLE raises obvious questions regarding a potential role for a viral etiology in SLE. While such an etiology is conceivable, it has not been demonstrated over many decades of study. Alternative mechanisms that might achieve a comparable immunologic profile, characterized by chronic IFN-I pathway activation, might include impaired regulation of endogenous viral-like elements, impaired degradation of potentially stimulatory endogenous nucleic acids, or the activation of endosomal TLR's by nucleic acid-containing immune complexes in an individual with genetically-conferred capacity for generation of self-directed adaptive immune responses. Whatever the molecular basis of the sustained production of IFN-I and IFN-I-stimulated gene-encoded proteins, these models of virus infection suggest that blockade of IFNAR, the IFN-I receptor, or pathways that sustain the production of IFN-I and pro-inflammatory mediators, as through the endosomal TLR's, might be beneficial in SLE.

Clinical syndromes associated with single-gene mutations that impact the IFN-I pathway

Additional rationale for considering IFN-I as a therapeutic target in lupus is provided by studies of clinical syndromes with some features of lupus, along with increased IFN-I and IFN-I-stimulated gene expression. Important insights regarding molecular pathways that can mediate these clinical syndromes come from documentation of single-gene mutations identified through detailed genetic analyses of affected patients and families. Each of the relevant gene products can impact the activation of cytoplasmic receptors for nucleic acids and induce IFN-I production.³⁸ These include a DNase encoded by TREX1 that is required

to metabolize potentially stimulatory reverse-transcribed DNA, and SAMHD1, encoding an enzyme that removes phosphates from dNTP's, reducing available nucleotides for reverse transcription. SAMHD1 deficiency can trigger a DNA damage response and IFN-I production. Members of the RNASEH2 family remove ribonucleotides from RNA-DNA hybrids. ADAR1 encodes an RNA-specific adenosine deaminase that converts adenosine to inosine in dsRNAs, particularly those enriched in Alu sequences, and typically functions as a suppressor of the cell intrinsic IFN-I response.³⁹ Each of these products plays a role in control of the quality of endogenous nucleic acids, reduces the risk to the genome of production of endogenous virus-like transposons, and appears to be important for avoiding aberrant activation of an innate immune response characterized by IFN-I pathway activation. Many patients with Aicardi-Goutieres syndrome, characterized by lupus-like features such as skin rash, neurologic manifestations and anti-DNA antibodies, have been documented to have mutations in genes encoding one or those proteins,⁴⁰ and a polymorphism in TREX1 has been associated with a diagnosis of SLE.⁴¹ An IFN-I signature has been documented in many patients with Aicardi-Goutieres syndrome.³⁸ Although therapeutic inhibition of IFN-I production has not been reported in patients with that syndrome, data from a TREX1-deficient murine model support a contribution of IFN- β to autoimmunity and pathology.⁴²

Recent data from young children with mutations in TMEM173, encoding STING, an essential component of the TLR-independent pathway of immune system activation, develop a syndrome with some features consistent with the vasculopathy that characterizes many patients with SLE or systemic sclerosis.⁴³ Skin rash, a livedo-like vascular pattern, distal extremity ulcerations, interstitial lung disease, markers of systemic inflammation, and low-titer antinuclear antibodies are among the clinical characteristics of patients with STING gain-of-function genetic alterations. These patients show increased transcription of IFN- β and other ISGs and constitutive phosphorylation of STAT1, a signaling component of the JAK-STAT pathway that is activated downstream of IFNAR, the IFN-I receptor. In vitro studies using a JAK inhibitor supported targeting the effector arm of the IFN-I pathway in this fascinating syndrome.⁴³

While the studies of chronic LCMV, HIV-1 and hepatitis C virus infection draw attention to mechanisms that confer sustained production of IFN-I and pro-inflammatory cytokines, as might be driven through endosomal TLRs, the clinical syndromes associated with single-gene mutations in regulators of TLR-independent pathways, some with features consistent with the vascular pathology characteristic of lupus, suggest that blockade of components of that pathway might also hold some promise as therapeutic targets in SLE. We might predict that effective therapeutic targeting of the TLR-independent STING-dependent IFN-I pathway might modify those clinical manifestations of lupus that are related to its underlying vasculopathy. Additional study will be needed to dissect the potential implications of STING activation vs. inhibition as recent studies point to STING- and IFN-I-dependent induction of indoleamine 2,3-dioxygenase 1 and augmented T regulatory cell function that contributes to control of T cell-mediated tissue damage in some murine models.⁴⁴

Association of IFN-I with future lupus nephritis

Type I interferon (IFN-I) is elevated in many patients with SLE and is associated with more severe disease. However, the relationship between elevated levels of IFN-I and disease activity over time has not been well defined, and the significance of elevated IFN-I for development of future significant clinical manifestations of lupus has not been studied. Identification of elevated IFN-I as a risk factor for future disease flares or organ system involvement would further support IFN-I and its pathway as a rational therapeutic target in SLE.

We evaluated the biological activity of IFN-I retrospectively in plasma samples collected longitudinally from SLE patients meeting ACR classification criteria and related those results to clinical and serologic data collected over time. The study was approved by the Institutional Review Board of Hospital for Special Surgery, and all patients provided signed consent for participation in the study. These patients visited our clinic on average 9 times (range 2–20), and a total of 568 data points were collected. The median number of years patients were followed equaled 2.8 (0.3–5.3) years. IFN-I activity in plasma was determined based on the response of the WISH epithelial cell line, which is sensitive to IFN-I stimulation and has a minimum detection level of 6 IU/ml.¹⁰

SLE patients with high IFN-I plasma activity at study initiation showed increased IFN-I plasma activity during follow up visits ($p < 0.01$). Patients with high plasma IFN-I activity at the time of the first visit were prone to overall greater disease activity during the study, as measured by SLEDAI ($p < 0.02$) or BILAG ($p < 0.05$).^{45,46} Although there was no significant difference at visit 1 in the proportion of patients with renal involvement based on the BILAG Renal score between patients with high and low plasma IFN-I activity, strikingly, SLE patients with high IFN-I activity in plasma at study initiation were more likely (1.0 vs. 0.4 incident per year $p < 0.001$) to demonstrate renal BILAG activity during the course of follow-up.⁴⁷

Because of the importance of renal involvement in SLE, we performed multivariate analysis and developed a mixed model predicting future renal disease activity. From all available laboratory parameters the following parameters showed significance in the final model: IFN-I plasma activity, anti-dsDNA level, serum albumin and total serum protein. According to our model, SLE patients who had high levels of anti-dsDNA antibodies and high IFN-I plasma activity at their first visit showed an increased rate of subsequent renal disease activity for up to several years of follow up (Figure 1).⁴⁷

Lupus nephritis is the most common severe manifestation of SLE and confers an increased risk of death and end-stage renal disease. Our data suggest that IFN-I activity in SLE plasma could predict future disease activity, particularly involving the kidney. While elevated IFN-I is only one of many factors that contribute to renal pathology and development of nephritis, our data provide additional support for considering IFN-I inhibition as a therapeutic approach that might reduce risk of future renal disease. A role for IFN-I in lupus nephritis is supported by data in murine lupus models as well as demonstration of the IFN-I-induced protein MX1 in glomeruli of patients with lupus nephritis.^{11,48–51}

Clinical studies of IFN-I pathway inhibition

As described, the strong case for the IFN-I pathway playing a central pathogenic role in SLE provides the rationale for therapeutic targeting of IFN- α and other IFN-I pathway components in patients with lupus.⁵²

The most direct approach to therapeutic inhibition of the IFN-I pathway involves blockade of its major stimulus, IFN- α , with a monoclonal antibody (mAb). Three distinct anti-IFN- α mAbs are in development. Based on safety data, these agents are generally well tolerated. Partial inhibition of expression of ISG's in whole blood cells and in skin was observed in some patients receiving sifalimumab (MEDI-545),⁵³ but the degree of inhibition of the IFN signature was greater in a phase I study of patients with moderate disease (mean SLE Disease Activity Index, SLEDAI, 5.2) than in a phase II study of patients with more active disease (mean SLEDAI of 11.0).^{53–55} Encouraging progress is suggested by the recent announcement that a phase IIb study of sifalimumab met its primary endpoint, based on the SLE Response Index-4, in patients with moderate or severe lupus (<http://www.astrazeneca.com/Media/Press-releases/Article/20140512--astrazeneca-announces-medimmunes-mavrilimumab-sifalimumab-met-primary-endpoints-Phase-IIb-studies>). Clinically important improvement in skin and joint symptoms and in patient-reported outcomes was noted in the public release.

Most patients who received a 3 mg/kg or 10 mg/kg IV dose of rontalizumab (with mean SLEDAI of 3.4) demonstrated > 50% reduction of IFIGs in whole blood but did not successfully achieve a level comparable to healthy donors or patients with a low IFN score.⁵⁶ Interestingly, some evidence of clinical efficacy was observed in those patients with a “low” IFN-I score, perhaps suggesting that more effective neutralization of IFN-I activity can be achieved in those patients with functionally important but relatively low level production of IFN-I. Of note, all patients who had received single or multiple doses of that mAb recovered their IFN signature by six months after the last dose, suggesting that the stimulus for induction of IFN-I remained operative *in vivo*. Higher doses of antibody might provide more effective blockade, however, a potential role for additional IFN types, including IFN- β or others, must be considered as an explanation for the incomplete blockade noted. IFN- β induces most of the same IFIGs that are regulated by IFN- α , and neither sifalimumab nor rontalizumab has activity against IFN- β or other IFN-I's. In contrast to the inhibition of IFN-I-stimulated gene expression in lupus skin by anti-IFN- α mAb, the IFN signature seen in psoriatic skin was not inhibited by sifalimumab, nor was any indication of clinical efficacy noted in psoriasis patients.⁵⁷ IFN- κ , an IFN-I that is expressed in skin, might be important in psoriasis and be responsible for the lack of effect of a mAb specific for IFN- α in the psoriasis study. The data presented so far from clinical trials of IFN- α -specific mAb's suggest that effective therapies will require higher doses to successfully reduce induction of IFN-I-regulated gene expression or inhibition of a broader spectrum of IFN-I's, their receptor or components of their signaling pathway.

An interesting strategy for generating endogenous polyclonal anti-IFN- α , with the goal of inhibiting pathogenic IFN-I, has been reported in preclinical studies and more recently in a first in human study of a so-called IFN-kinoid, a complex of recombinant IFN- α with

keyhole limpet hemocyanin.⁵⁸ Injection of the IFN-kinoid resulted in T cell-dependent production of neutralizing IFN- α -specific antibody that decreased expression of IFN-I-stimulated genes in blood.

In view of suggestions that IFN- β , as well as IFN- α , might contribute to SLE pathogenesis, blockade of IFNAR, the IFN-I receptor, might provide more effective therapy for systemic autoimmune disease than mAb's that target only one subtype. The limited disease observed in male BXSB lupus mice receiving an antibody specific for IFNAR, along with data from NZB mice genetically deficient in IFNAR support that approach.⁵⁹ A mAb specific for subunit 1 of IFNAR, MEDI-546, prevents association of subunit 1 of IFNAR with subunit 2, thereby blocking downstream signaling events. In contrast to the partial effects on IFN-I-stimulated gene expression in the sifalimumab and rontalizumab studies, this anti-IFNAR mAb resulted in nearly complete inhibition of ISG expression in peripheral blood and skin of patients with systemic sclerosis.⁶⁰ This more complete blockade of the IFN-I pathway should be pursued with caution, bearing in mind the central role of IFN-I in host defense during the acute phase of viral infection.

As nucleic acid-containing immune complexes are potent triggers of endosomal TLRs that signal transcription of IFN-I and other pro-inflammatory gene products, therapeutic approaches that degrade the nucleic acid components of those complexes or inhibit TLR activation and downstream signaling might be particularly promising as they might decrease levels of IFN-I, limit the capacity of immune complexes to induce new IFN-I and might also reduce production of autoantibodies.^{61–64} Along those lines, hydroxychloroquine, documented to inhibit IFN-I production induced by lupus immune complexes in vitro, is now standard of care due to its demonstrated reduction of lupus flares.⁶⁵ Studies in progress are investigating the safety of several oligonucleotide inhibitors of endosomal TLRs. A related concept that might reduce signaling mediated by endosomal TLRs and TLR-dependent IFN-I production would involve disruption of the stimulatory nucleic acid-containing immune complexes with nucleases. Overexpression of RNase in a murine lupus model proved beneficial in reducing disease.⁶⁶

Other therapeutic approaches might target kinases, adaptors and other components of TLR-dependent or TLR-independent pathways that are important for effective induction of IFN-I, such as PI3K, IKK ϵ , cGAS, or STING.^{1,2,43,67} While not specific for IFN-I, inhibition of the JAK-STAT signaling pathway with kinase inhibitors that target relevant JAKs or Tyk2 might reduce the induction of IFN-I-stimulated genes and their many downstream effects on immune function that could contribute to tissue pathology.^{43,68}

Conclusion

The complexity of the human immune system, and particularly the protective as well as potentially destructive effects of IFN-I, have raised many questions regarding the validity of the IFN-I pathway as a productive target for development of therapeutic agents for important diseases such as SLE. The highly informative and provocative data gleaned from literature describing studies of chronic virus infections show that among those gene products that comprise the IFN-I signature are some that can amplify activation of the pathway as well as

contribute to its regulation through negative feedback mechanisms. However, taking available information together, the parallels between the immunologic correlates of chronic IFN-I production in animal models of chronic virus infection and the immunopathogenesis of SLE strongly support the hypothesis that on the whole, the sustained production of IFN-I and induction of its downstream gene products contribute to disease pathology. Our own data identifying elevated plasma IFN-I as associated with future renal disease is additional support for pursuing IFN-I pathway regulation. Although any number of possible therapeutic approaches might prove to be effective, data presented to date suggest that targeting IFN- α may be less efficacious than more broadly modulating the inducers or downstream effectors of IFN-I. Pursuit of the IFN-I pathway as a central immunopathogenic mechanism in systemic autoimmune disease as well as a compelling therapeutic target will continue to engage the efforts of translational scientists and clinical investigators.

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Abbreviations

IFN-I	type I interferon
IFNAR	type I interferon receptor
LCMV	lymphocytic choriomeningitis virus
pDC	plasmacytoid dendritic cell
SIV	simian immunodeficiency virus
SLE	systemic lupus erythematosus
TLR	Toll-like receptor

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Figure 1. Graphic depiction of predicted probability of developing renal disease activity over time based on longitudinal data obtained from 60 SLE patients

Multiple parameters were studied, and the minimum multivariate model included: plasma IFN-I activity based on reporter cell assay, level of anti-dsDNA antibodies, absolute leukocyte count, and serum total protein and serum albumin. Renal disease activity was defined as any BILAG score greater than C. The high plasma IFN-I cut-off corresponds to 12.5 IU/ml. A high level of anti-dsDNA antibodies is defined as ++ and +++ based on C. luciliae assay. Predicted values for development of renal disease activity were plotted for four patient groups based on their IFN-I and anti-dsDNA antibody status. The group with both high IFN-I and positive anti-dsDNA antibody had the highest probability of developing renal disease activity during follow up visits.

Table 1

Chronic viral infections associated with persistent IFN-I production provide a model for SLE immunopathogenesis (see text).

Disease Models	LCMV Armstrong	LCMV Clone 13	SLE
	SIV African green monkey	HIV-1	
Clinical Outcome	Resolution of acute infection	Chronic infection with organ damage	Chronic, with variable course and organ damage
Cytokines	IP-10, PD-L1 in acute phase, followed by resolution	Early and persistent IP-10 and PD-L1, followed by TNF, IL-6	High IP-10, TNF, IL-6
IFN-I Pathway	Early IFN-I, ISG's, followed by resolution	Early and persistent IFN-I and ISG's	High and persistent IFN-I and ISG's
T Effector Cells	Generate effective T _{H1} and CD8 cytotoxic cells	Fail to expand T _{H1} while generating T _{FH} ; in HIV-1 infection T _{FH} cells harbor virus	T _{FH} provide help for B cell differentiation to autoantibody forming plasma cells