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Type I interferon in the pathogenesis of systemic lupus erythematosus

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Abstract

Type I interferon (IFN) is a primary pathogenic factor in systemic lupus erythematosus (SLE). Gain-of-function genetic variants in the type I IFN pathway have been associated with risk of disease. Common polygenic as well as rare monogenic influences on type I IFN have been demonstrated, supporting a complex genetic basis for high IFN in many SLE patients. Both SLE-associated autoantibodies and high type I IFN can be observed in the pre-disease state. Patients with SLE and evidence of high type I IFN have more active disease and a greater propensity to nephritis and other severe manifestations. Despite the well-established association between type I IFN and SLE, the specific triggers of type I IFN production, the mechanisms by which IFNs help perpetuate the cycle of autoreactive cells and autoantibody production are not completely clear. This review provides an updated overview of type I IFN in SLE pathogenesis, clinical manifestations, and current therapeutic strategies targeting this pathway.

Keywords

Type I Interferon; genetics; pathogenesis; systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease resulting from defects in both the innate and adaptive immune systems [1, 2]. Both genetic and environmental factors are important determinants of the different phenotypes observed in SLE [3]. Type I interferon (IFN) levels are chronically and persistently elevated in blood in approximately 50% of SLE patients [4]. An even greater percentage of patients demonstrate over-expression of type I IFN pathway genes in their peripheral blood cells [5–7], referred to as the “IFN signature”. Type I and Type II IFN can induce many of the same genes, which may explain why more patients demonstrate the signature than have high functional circulating type I IFN in their blood [5]. In addition, other pathways and downstream effectors can induce IFN signature genes [8–10]. Interestingly, a high type I IFN activity is associated with the presence of other cytokines, such as B-cell activating factor (BAFF) and type II IFN [11, 12], specific autoantibodies [13], and certain clinical manifestations, such as lupus nephritis [12].

Despite the well-established association between type I IFN and SLE, the specific triggers of type I IFN production, the mechanisms by which IFNs help perpetuate the cycle of autoreactive cells and autoantibody production, and the clinical relevance of targeting type I IFN in SLE are less clear. In this review, we will provide an updated overview of recent evidence on mechanisms of type I IFN production, genetic associations, the relevance of impaired nucleic acid processing in animal models of lupus and human SLE, as well as the emergence of successful therapeutic agents targeting type I IFN pathways.

Mechanisms of Type I IFN production

Plasmacytoid dendritic cells (pDCs) have been a focus of interest in SLE ([14], reviewed in [15]). Each pDC can produce as many as 10^9 IFN-α molecules in 12 hours [16]. This striking feature, along with the skewing of blood type I IFNs toward IFN-α over IFN-β in SLE [17], suggest pDCs as the potential cellular IFN source in this disease. Accordingly, pDC deficiency has been shown to ameliorate murine lupus models [18, 19]. However, isolating IFN-α-producing pDCs from SLE patients’ blood and tissue has remained challenging [20, 21]. Although other cell types, including macrophages and fibroblasts, are also a source of type I IFN, these cells primarily synthesize IFN-β [22].

Type I IFN production is mainly triggered by the activation of nucleic acid-binding pattern recognition receptors, including the endosomal toll-like receptors (TLR) 3 4, 7 and 9, the cytosolic sensor cyclic GMP-AMP synthase (cGAS), and the RNA-sensor RIG-I–like receptors (RLRs)-MAVS [23]. Under normal conditions, these nucleic-acid sensing pathways are subject to strict regulation and are required to form an appropriate antiviral response [24], but many SLE patients demonstrate chronic overactivity in these pathways. A recent study suggests this chronic type I IFN pathway activation may actually blunt the response to additional endosomal TLR stimulation, while responses to LPS in patients with chronic type I IFN elevation were augmented [20].

The role of TLR7 in SLE is well established, as its overexpression is associated with severe lupus in mice, and TLR7 inhibition is protective (reviewed in [25]). Conversely, the effect of TLR9 in SLE has remained controversial and a net tolerogenic role has been suggested [26, 27]. In agreement with these observations, recent evidence has shown that the TLR-trafficking chaperone UNC93B1 protects from TLR7-driven autoimmunity in mice, without affecting TLR9 [28]. UNC93B1 limits TLR7 signaling in response to self RNA *via* binding to the adaptor protein Syntenin-1 and sorting TLR7 into intraluminal vesicles [28]. Similarly, a model of persistent lymphocytic choriomeningitis virus infections in lupus-prone mice has been shown to enhance systemic autoimmunity in a pDC- and endosomal TLR-dependent manner [29]; interestingly, UNC93B1$^{3d/3d}$ mutant NZB mice were used to corroborate the requirement for TLR-dependent responses, indirectly suggesting a key role of TLR7 in this model [28, 29].

Mechanisms that impact nucleic acid metabolism are also thought to influence the threshold of activation and triggering of type I IFN production. This is well illustrated in the interferonopathies, a set of monogenic disorders involving genes related to nucleic acid handling (*see section on Genetic Influences on Type I IFN in SLE*). In addition to the innate nucleic-acid sensors, self-DNA can be recognized by auto-reactive B-cells which may amplify autoreactivity. DNases, particularly the extracellular DNASE1L3, are critical to preserve self-tolerance and development of SLE (reviewed in [30]). Homozygous deletions of DNASE1L3 and coding polymorphisms in humans are associated with SLE [30]. Recently, a *Dnase1l3*$^{-/-}$ murine model of lupus illustrated the facilitating effect of type I IFN signaling and pDCs to maintaining and amplifying self-reactivity in a TLR-dependent manner [31].

Another example of abnormal handling of nucleic acids was demonstrated by the finding that loss of sumoylation, conjugation of small ubiquitin-like modifiers (SUMOs) to lysines, by SUMO2 and SUMO3 leads to a potent type I IFN response. This is independent of the classic IFN-inducing sensors and transcription factors [32, 33].

The cytosolic nucleic acid sensors are also thought to play critical roles in SLE (reviewed in [24, 33]). Activation of the cGAS-STING pathway is crucial for antiviral immunity and plays an important role in autoimmunity [33]. In this sense, UVB light exposure has been shown to increase type I IFN response both locally and systemically in a c-GAS-dependent manner in mice and humans [34]. Recently, a STING-independent DNA sensing pathway was identified in human cells but not in laboratory mice [35]. The sensor of the STING-independent DNA sensing pathway corresponds to the damage response protein DNA-PK, with the heat shock protein HSPA8 is a downstream target [35]. These data support the idea that cGAS-STING independent pathways could be important in SLE, as does human genetic data which implicates both MDA5 [10] and MAVS [36].

Type I IFNs in the Initiation of SLE

Type I IFNs are implicated in SLE susceptibility by multiple lines of investigation, including genetics, family studies, and induction of SLE by type I IFN treatment [37]. Chronic elevation of type I IFN predisposing to SLE is thought to be due to overproduction,

increased sensitivity, and impaired negative regulation (Figure 1). For example, genetic polymorphisms in the interferon regulatory factor (*IRF*)5 and *IRF7* genes are associated with increased type I IFN in circulation [38, 39]. Genes downstream of the type I IFN receptor (IFNAR) have also been implicated in SLE, including the Signal Transducer and Activator Of Transcription 4 (*STAT4*) [40]. In human studies, SLE patients carrying the *STAT4* risk allele have greater type I IFN-induced gene expression for a given amount of IFN compared to patients with the non-risk allele, suggesting that this allele confers increased sensitivity to type I IFN [8]. Supporting this idea, a recent study showed that rs7574865, the most significantly associated SNP in *STAT4*, is associated with an augmented T-cell response to IFN-α in patients with SLE [41]. Lastly, deficiency in negative regulators of type I IFN has also been suggested by polymorphisms in the suppressive inhibitory molecules immunoglobulin-like transcript 3 (*ILT3*) receptor expressed on dendritic cells (DCs). Gene variants that reduce expression of the ILT3 receptor are associated with increased circulating type I IFN in patients with SLE [42].

Endogenous stimuli, such as immune complexes involving SLE-associated autoantibodies, act upon a susceptible genetic background to result in type I IFN production. Neutrophils may also provide endogenous type I IFN pathway stimulation via neutrophil extracellular traps (NETs), which can increase IFN-α production by pDCs in a toll-like receptor TLR9-dependent manner [43]. Endogenous retro-elements such as LINE-1 could also activate the type I IFN system in SLE [44] as an additional nucleic acid stimulus.

It seems likely that a feed-forward loop occurs in which type I IFN may participate in the initial breaks in tolerance [17]. Both type I IFN and SLE-associated autoantibodies are elevated in the pre-disease state [45], supporting their role in disease susceptibility and initiation. In the years before diagnosis of SLE, autoantibody specificities increase in number up to the point of diagnosis, suggesting a diversification of the anti-self response in the pre-disease state [46]. These autoantibodies can form nucleic acid immune complexes that stimulate type I IFN production (Figure 1). Type I IFN increases in the pre-disease state, most dramatically beginning approximately 2 years prior to the diagnosis of SLE [45]. The pre-disease studies indicate that many of the cardinal features of the dysregulated immune response in SLE begin years before patients develop clinical manifestations and present for medical care.

Common and Rare Genetic influences on Type I IFN in SLE

SLE has been associated with over 100 genetic risk loci and many of these risk genes encode proteins with functions linked to type I IFN response [47]. Family members of patients with SLE are at higher risk of developing autoimmune diseases [48, 49]. Type I IFN levels are heritable within SLE families [17], suggesting that genetic overactivity in this pathway predisposes to SLE and other IFN-related autoimmune conditions [49]. Polymorphisms in the type I IFN gene locus itself have not been associated with either SLE or higher type I IFN levels, but a diversity of type I IFN pathway and pattern recognition pathway genes pathways have been linked to SLE susceptibility [50]. These SLE-risk polymorphisms fit with an expected gain-of-function model, as they are associated with greater type I IFN pathway activation. In addition to these known SLE susceptibility genes, genome screens

have been performed with the goal of identifying new loci associated with elevated type I IFN in SLE patients [51–54]. A genome-wide association study (GWAS) of patients with high versus low levels of type I IFN discovered a distinct panel of genes from those identified in case-control SLE GWAS [52]. One such gene, purine nucleotide phosphatase (*PNP*), encodes for an enzyme involved in the nucleotide salvage pathway. The polymorphism related to type I IFN in SLE is a coding-change polymorphism that reduces PNP enzymatic function and is also associated with decreased expression of the enzyme. These changes result in an increased propensity to S-phase block, and an increase in type I IFN-induced gene expression [9]. The exact mechanism by which the cell cycle abnormalities result in increased IFN-induced gene expression have not been fully elucidated.

Other rare and low frequency gene variants have also been recently shown to contribute to human SLE via increasing type I IFN production [55]. A recent study demonstrated that *BLK* regulates type I IFN downstream of TLR7/8 signaling possibly via regulation of *BANK1*, and variants in both genes can impair their normal function of inhibiting IRF5-mediated type I IFN production. *CXorf21* is an IFN-inducible gene associated with SLE in a sex-specific manner, as it escapes X-chromosome inactivation [56]. The *CXorf21* function was unknown until recently, when its link to IFN production via endolysosomal TLR signaling was demonstrated [57]. The *CXorf21* gene product, TLR adaptor interacting with SLC15A4 on the lysosome (TASL), interacts specifically with SLC15A4 and is necessary to activate IRF5.

In addition to the above evidence for genetic influence on type I IFN in SLE, monogenic disorders, the so-called interferonopathies, also demonstrate high type I IFN and share some molecular and clinical features of SLE [58, 59]. The gene mutations that give rise to these syndromes include *TREX1*, *SAMHD1*, *ADAR1*, *IFIH1*, among others, and have a function in nucleic acid handling [58]. The clinical syndromes vary somewhat based upon the specific gene involved, but typical manifestations include central nervous inflammation and calcification, vasculitis, and lupus-like features [58]. Considering the rare single gene interferonopathies with the common alleles that impact type I IFN in SLE, model as outlined in Figure 2 emerges. This model is similar to that observed in complex disease susceptibility. Some polymorphisms are present at a high rate in the general population that individually do not result in a large impact on type I IFN levels. It is possible that these alleles are helpful in our normal immunity and defense against viruses. Some of these alleles will form combinations in gene-gene or gene-environment interactions. Despite these combinations being less common, they may exert a greater influence on IFN levels and consequently associate with increased risk of autoimmunity. An example of such gene-environment interaction in SLE is the IRF5 and IRF7 polymorphisms, which result in much greater type I IFN in patients with SLE-associated autoantibodies [39, 60]. These gene-microenvironment interactions support the idea that the immune complex is needed as the upstream stimulus to observe the full effect of the genotype upon type I IFN.

A recent multi-ancestral SLE case-control study using Immunochip genotype data suggested that in European ancestry genetic risk for SLE manifests as a nonlinear function of the cumulative risk allele load, with a greater effect of some of the alleles when the overall

genetic load is high [61]. Younger onset SLE patients had a higher genetic load when considering non-HLA alleles [61], as might be expected. This supports the idea that genetic interactions play a role in SLE, and it is likely that these play out in pathways like the IFN pathway. A recent large family-based inheritance study found similar results, that the inheritance of SLE in childhood onset patients fit better to a more epistatic or interactive model than did adult onset SLE [48].

Epigenetic changes have been reported in SLE, and typically these have been hypomethylation at type I IFN-induced genes [62]. A recent study suggests that this finding is common across a number of other autoimmune diseases as well, including rheumatoid arthritis and Grave's disease [63]. Whether these epigenetic changes are a cause or a result of type I IFN signaling is not clear, as many of the transcripts are those typical of a type I IFN signature. It is possible that an intrinsic epigenetic sensitivity to type I IFN exists in SLE as well, and this could relate to previous stimulation by IFNs, other cytokines, or other factors.

Clinical associations with high serum IFN levels in SLE patients

There is substantial evidence that type I IFNs are important in propagating ongoing disease activity in SLE, and not just an initial susceptibility factor. Previous studies have demonstrated that elevated type I IFN in blood is associated with increased disease activity in cross-sectional studies [5, 6, 64]. Despite this robust association, longitudinal studies generally do not support the idea that IFN levels fluctuate predictably with changes in SLE disease activity [65, 66]. These findings suggest that type I IFN levels demarcate groups of patients that are more or less likely on average to have higher disease activity and flares at any given time, but that type I IFN may not be highly informative as a longitudinal biomarker. This is supported by a recent study in which elevations of type I IFN in patients who are in remission was associated with a higher risk of relapse [67].

A recent study has shown that pregnancy is associated with downregulation of the type I IFN signature in both healthy and uncomplicated SLE pregnancies; these changes typically persist through late pregnancy and the post-partum period. In complicated SLE pregnancies, the IFN signature frequently remains elevated [68], suggesting that persistent activation of the type I IFN pathway in pregnancy may contribute to adverse pregnancy outcomes [68].

It is clear that ongoing chronic type I IFN stimulation shapes the clinical phenotype and overall disease activity in SLE patients. Increased type I IFN in circulation is associated with the presence of lupus nephritis, mucocutaneous manifestations, arthritis, and autoantibodies including anti-Ro, anti-Sm, anti-ribunucleoprotein (RNP), and anti-double-stranded (anti-dsDNA) antibodies [12, 69, 70]. High IFN signature has been associated with mucocutaneous disease activity, possibly mediated by UVB-induced keratinocyte apoptosis. A recent study showed that acute exposure to UVB light stimulates a robust local and systemic type I IFN response in humans and mice, in a cGAS-dependent manner [34].

As previously mentioned, neutrophils may mediate type I IFN production via release of NETs with interferogenic properties. In particular, the low-density granulocyte (LDGs)

subset of neutrophils are elevated in SLE patients and have the greatest type I IFN signature among neutrophils, suggesting that LDGs are highly responsive to IFN [71]. Moreover, subsets with the LDG population may correlate with specific clinical features of lupus and atherosclerotic disease [71].

Non-α/β type I IFNs in SLE

Although much of the research on IFNs in SLE has focused on IFN-α and IFN-β, recent studies have shown a role for IFN-κ, another member of the type I IFN family. IFN-κ is mainly expressed in keratinocytes after exposure to UV light, hence, it has been suggested as a key mediator involved in photosensitivity and other cutaneous manifestations of SLE in humans and murine models [72, 73]. Additionally, the presence of genetic associations between IFNK gene variants and cutaneous phenotypes in SLE have been described [74]. Overall, these findings support a role for IFN-κ in the pathogenesis of cutaneous lupus mediating UV light toxicity. IFN-κ could be a potential therapeutic target to modulate type I IFN response in SLE, particularly in patients with predominantly cutaneous manifestations. A direct role of other type I IFNs in SLE is less clear.

Therapeutic strategies targeting type I IFN

Current standard of care treatment of SLE involves the use of corticosteroids and immunosuppressive agents that are associated with a wide range of potential adverse effects [75]. Type I IFN has been considered as a potential target to reduce chronic inflammation and end-organ damage in SLE [75]. Various therapeutics agents which target specific aspects of the type I interferon pathway are currently in different phases of clinical development [76]. For instance, IFN-α kinoid, a vaccine designed to induce neutralizing antibodies against IFN-α, was shown to reduce the IFN gene signature with a satisfactory safety profile in a recent phase IIb study [77]. Phase III studies are being planned. A phase I study evaluating a promising monoclonal antibody against a pDC-specific receptor that inhibits type I IFN production (blood DC antigen 2, BDCA2) was also recently published and further trials are ongoing [78]. Inhibitors of the Janus Kinases (JAK) have recently shown efficacy in cutaneous and articular manifestations of SLE. While these kinase inhibitors block multiple cytokine signals, it is likely that the efficacy of JAK inhibition in SLE relates at least in part to an impact on type I IFN signaling [79, 80].

Anifrolumab is a monoclonal antibody that blocks both IFN-α and IFN-β signal by binding to the type I IFN receptor. Interestingly, previous anti-IFN-α antibodies had not shown sufficient efficacy in phase II trials to be further developed [81, 82], while anifrolumab was taken forward to phase III trials. This could be partially due to the difference in mechanism of action, as the anti-IFN-α antibodies would not interrupt IFN-β signaling, in contrast to the complete type I IFN blockade achieved by anifrolumab. IFN-α predominates in the blood in SLE [17], but IFN-β could still play important roles in the tissue [83]. This year, results from the second of two phase III Anifrolumab clinical trials showed a statistically significant reduction in disease activity and corticosteroid use at week 52 compared with placebo in SLE patients with moderate-to-severe disease activity [84]. The first phase III trial of this agent met several secondary endpoints but failed to meet its primary endpoint

[85]. Taken together, the data from all of the phase II and phase III studies support efficacy of this agent in SLE [86]. The fact that only one of the two anifrolumab phase III studies met the primary endpoint, along with many other failed SLE trials in the recent past, underscores the difficulty in SLE trial design and conduct in general [75].

Conclusion

As our understanding of SLE pathogenesis grows, our ability to directly target the underlying pathogenic mechanisms in clinical practice continues to improve. Ideally, our enhanced understanding of human disease biology and pathogenesis, including genetic susceptibility, clinical symptoms, and immunological dysfunction will allow for more specific and effective therapy, and eventually a personalized medicine approach in SLE [87].

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Highlights:

- Type I IFN is implicated in SLE pathogenesis by multiple lines of evidence, including genetics, gene expression, and induction of SLE by IFN treatment.
- Nucleic-acid sensing pathways influence the threshold of activation and triggering of type I IFN production. Genetic mutations and molecules targeting these pathways have been used in the development of animal models of lupus.
- Abnormalities in extracellular processing of DNA can enhance type I IFN production, with a potential key role of DNASE1L3 as demonstrated by the development of lupus-like disease in the Dnase1l3$^{-/-}$ mice.
- High type I IFN levels are associated with active nephritis, mucocutaneous involvement, hematological manifestations, low complement levels and the presence of autoantibodies.
- Anifrolumab, a monoclonal antibody that blocks the type I IFN receptor, has shown therapeutic benefit in SLE. Multiple studies on other promising therapeutic agents directly or indirectly targeting the type I IFN pathway are underway.

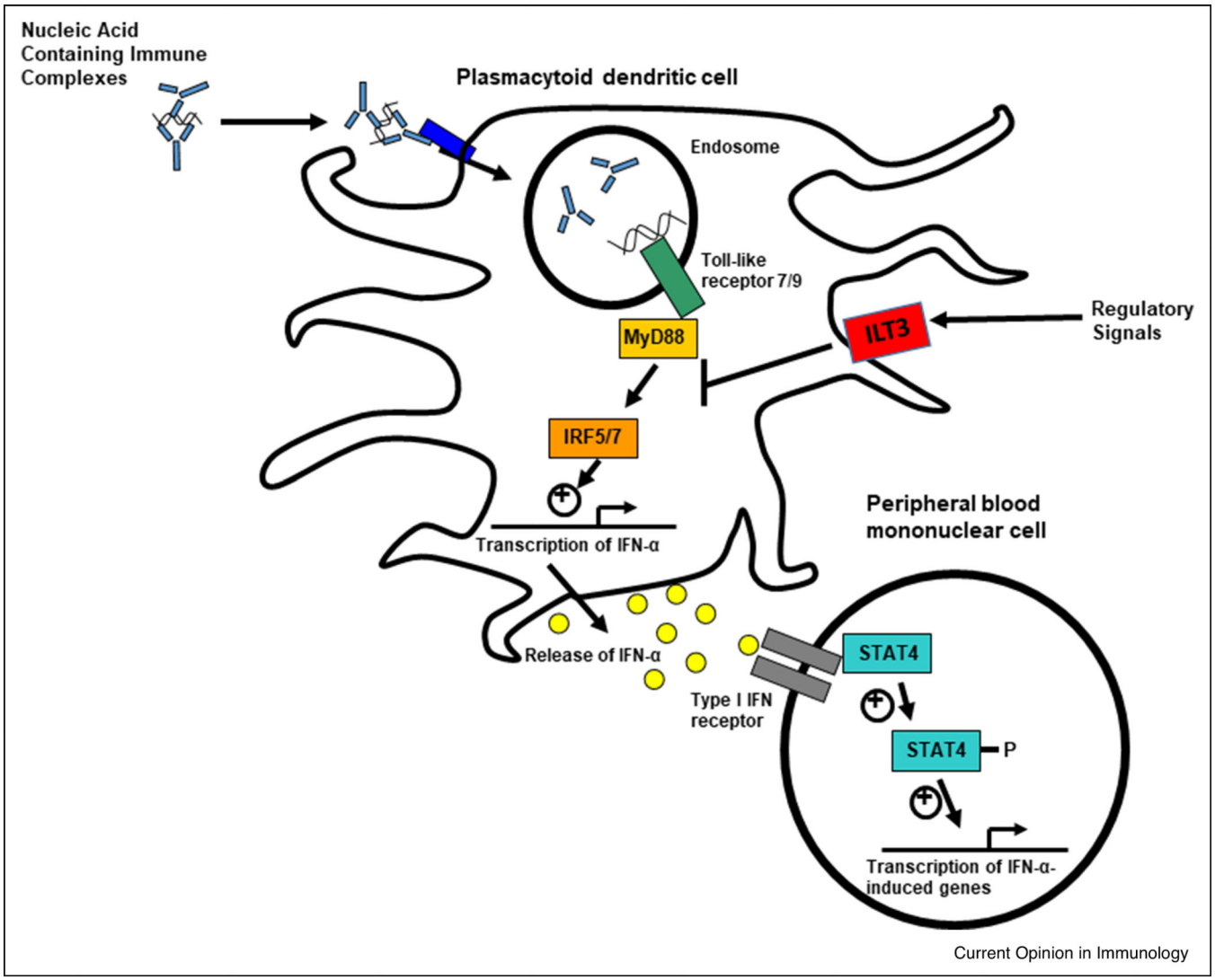

Figure 1.

Schematic diagram of various ways the type I IFN pathway is modulated in SLE. Nucleic acid containing immune complexes formed by SLE-associated autoantibodies are taken up by plasmacytoid dendritic cells. Genetic variants in IRF5 and IRF7 can result in greater type I IFN production, particularly in those patients with autoantibodies. Type I IFN then signals through the IFNAR receptor, and polymorphisms such as the SLE-associated STAT4 allele result in augmented signaling downstream of the receptor. Polymorphisms in regulatory molecules, such as ILT3, can result in defective function and decreased ability to negatively regulate inflammatory pathways. In many patients, this multifactorial process leads to persistent dysregulation of the IFN pathway at multiple locations.

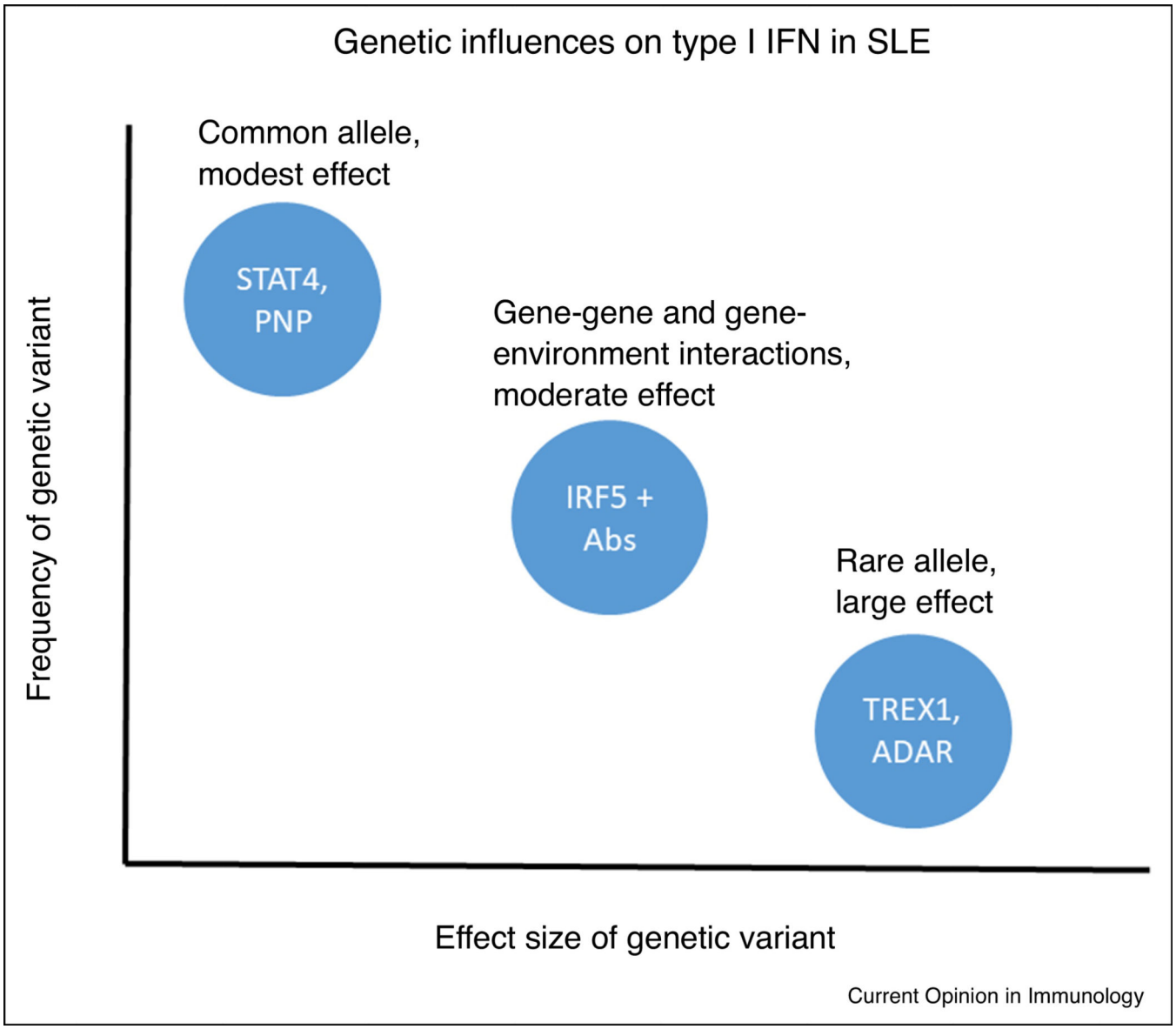

Figure 2.

Diagram of genetic influences on type I IFN in SLE patients. The X and Y axes represent relative values for effect size and frequency in the population respectively. Common polymorphisms individually exert a modest influence on type I IFN, but when paired with the appropriate gene-gene or gene-environment interaction, would exert a moderate effect on type I IFN. The need for additional factors that assort independently de facto decreases the frequency in the general population. Lastly, some extremely rare monogenic variations have been reported that have a large effect upon the type I IFN pathway and typically lead to the interferonopathy category of diseases, which share some features with SLE.