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Interferon Regulatory Factors in Human Lupus Pathogenesis

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Abstract

Systemic lupus erythematosus (SLE) is a severe multi-system autoimmune disease which results from both genetic predisposition and environmental factors. Many lines of investigation support interferon alpha (IFN-α) as a causal agent in human lupus, and high levels of serum IFN-α are a heritable risk factor for SLE. Interferon regulatory factors (IRFs) are a family of transcription factors involved in host defense, which can induce transcription of IFN-α and other immune response genes following activation. In SLE, circulating immune complexes which contain nucleic acid are prevalent. These complexes are recognized by endosomal Toll-like receptors, resulting in activation of downstream IRF proteins. Genetic variants in the IRF5 and IRF7 genes have been associated with SLE susceptibility, and these same variants are associated with increased serum IFN-α in SLE patients. The increase in serum IFN-α related to IRF5 and 7 genotypes is observed only in patients with particular antibody specificities. This suggests that chronic stimulation of the endosomal Toll-like receptors by autoantibody immune complexes is required for IRF SLE-risk variants to cause elevation of circulating IFN-α and subsequent risk of SLE. Recently, genetic variation in the IRF8 gene has been associated with SLE and multiple sclerosis, and studies support an impact of IRF8 genotype on the IFN-α pathway. In summary, the SLE-associated polymorphisms in the IRF family of proteins appear to be gain-of-function variants, and understanding the impact of these variants upon the IFN-α pathway in vivo may guide therapeutic strategies directed at the Toll-like receptor/IRF/IFN-α pathway in SLE.

Keywords

Interferon Alpha; Genetics; Systemic Lupus Erythematosus; Interferon Regulatory Factor; Autoantibodies; Autoimmunity

Introduction

Since the 1970's, high levels of type I interferon have been observed in serum of SLE patients (1). Type I interferons include interferon alpha (IFN-α) and interferon beta (IFN-β), and both of these molecules signal through the same type I interferon receptor (2). IFN-α normally functions in viral defense, and forms a bridge between the innate and adaptive immune systems (3). In this way, IFN-α is also important in setting thresholds for self-reactivity and autoimmunity. In recent microarray studies comparing SLE patients to healthy controls, over-expression of IFN-α-induced genes was one of the most dominant findings in

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the peripheral blood mononuclear cells of SLE patients (4,5). While the finding of overactive IFN-α pathway signaling in SLE patients does not allow us to infer whether IFN-α is causal or a secondary reactive finding, a number of lines of evidence suggest that this relationship between IFN-α and SLE is primary and causal.

Strikingly, some individuals who have received recombinant human IFN-α injections to treat chronic viral infections or malignancy have developed de novo SLE (6,7). IFN-α-induced SLE frequently resolves with discontinuation of IFN-α therapy (7). This human experience provides some "proof-of-principal" that IFN-α can break tolerance (8), and that this IFN-α-induced tolerance break in some individuals results in the very specific autoimmune phenotype of SLE.

Additionally, abnormally high levels of IFN-α are present in healthy first degree relatives of SLE patients as compared to healthy unrelated subjects (9,10), suggesting that high serum IFN-α is an inherited risk factor for SLE. High levels of IFN-α were not observed in spouses of SLE patients (Niewold TB et al, unpublished data), suggesting that genetic and not environmental influences are the cause of this familial clustering. A number of genetic variants have now been associated with increased IFN-α in SLE (11–15), outlining some of the genetic architecture of this SLE-associated trait. The high IFN-α trait is common across SLE patients of all ancestral backgrounds (16), however the particular genetic variants which underlie this SLE-associated trait sometimes differ between ancestral backgrounds (11,17–20).

A number of genetic polymorphisms in genes directly within the IFN-α pathway have been associated with susceptibility to SLE, including IRF5 and IRF7 (21,22). Consistent with the above data, these SLE-associated polymorphisms in IRF5 and IRF7 are gain-of-function variants, which are associated with higher serum IFN-α than the non-risk variants of the gene (19,23–25). As their name would suggest, interferon regulatory factors (IRFs) play a crucial role in the induction of IFN-α, and thus occupy an essential position in this pathogenic mechanism in SLE. In this review we will synthesize some recent work examining the unique role that IRFs play in human lupus pathogenesis.

Toll-like Receptor System of IFN-α Generation in SLE

Toll-like receptors (TLRs) are pattern recognition receptors which are capable of responding to a number of microbe-associated molecular patterns. Ligation of TLRs in cells of the innate immune system results in cell activation and secretion of cytokines and chemokines, in an effort to activate the immune system against pathogens. TLR3, TLR7, and TLR9 physiologically respond to viral RNA and DNA, and these TLRs are located in the endosomal compartment within the cell (26). Activation of these endosomal TLRs results in the production of IFN-α, which normally functions in viral defense. In SLE, autoantibodies are present which can bind either double-stranded native DNA (dsDNA antibodies) or small nuclear RNA-binding proteins such as Ro, La, Sm, and RNP. Immune complexes formed by these autoantibodies contain DNA or RNA respectively. Self-derived nucleic acid contained within these immune complexes is delivered in an abnormal way to the endosomal TLRs after they are taken up by cells via Fc receptors. This abnormal delivery may then pathologically activate normal anti-viral immunity, amplifying an autoimmune response. Experiments examining SLE-associated immune complexes in vitro provide strong support for this model, demonstrating that these immune complexes can stimulate cells via the endosomal TLR system resulting in IFN-α production (27,28) (Figure 1).

In support of this model, autoantibody traits provide the strongest association we have observed between serum IFN-α and clinical features in SLE, and this association extends to SLE patients of all ancestral backgrounds (9,16). While this clinical association is strong and

in vitro models suggest a causal relationship between autoantibodies and IFN-α via the endosomal TLR system, the presence of these autoantibodies is not completely predictive of high IFN-α in patients in vivo (29). This suggests that other host factors influence the relationship between autoantibodies and serum IFN-α in humans. An interplay between SLE-associated autoantibodies and high- vs. low-functioning genetic variants in the TLR system is an attractive hypothesis to explain some of the variability in the relationship between autoantibodies and serum IFN-α in SLE patients in vivo.

Interferon Regulatory Factors

There are nine members of the IRF family in humans, numbered from IRF1 to IRF9 (30,31). This transcription factor family shares a helix-turn-helix DNA binding motif, and IRFs are classically involved in type I interferon signaling (31). In addition to roles within the type I interferon pathway, IRFs have also been implicated in immune cell development and tumor suppression (30,32,33). In particular, IRF4 has been implicated in lymphoid malignancies by a number of different groups (34). Strikingly, genetic variations in three of the nine IRFs have been linked to SLE susceptibility, supporting a major role for this family of proteins in SLE pathogenesis.

The three IRF family members in which genetic variation has been linked to SLE susceptibility are IRF5, IRF7, and IRF8 (22,35,36). IRF5 and IRF7 interact with the MyD88 adaptor protein downstream of Toll-like receptor signaling, and are phosphorylated and activated following Toll-like receptor engagement (30). IRF8 has not been shown to directly interact with MyD88, but does seem to play a role in the Toll-like receptor pathway as dendritic cells lacking IRF8 do not produce inflammatory cytokines in response to Toll-like receptor 9 ligand (37). In addition to direct roles inducing IFN-α and IFN-induced genes downstream of Toll-like receptor activation, the SLE-associated IRFs may also play a role in tumor suppression and immune cell development (33,38).

IRF5 in SLE

IRF5 was an ideal candidate gene to study for an impact upon serum IFN-α levels in SLE patients. IRF5 can induce transcription of IFN-α mRNA (39), and strong genetic associations between IRF5 gene variants and SLE were discovered long before large-scale GWAS screening studies (21). A robust body of work supports genetic variation in the IRF5 gene as a risk factor for human SLE across multiple global populations (21,35,40–44). In Europeans, a risk haplotype containing multiple functional genetic elements has been defined, including a promoter insertion deletion, a splice site variation, a 30 base pair in-frame insertion/deletion, and an alternate polyadenlyation site in the 3’ UTR region (35,45,46). Due to high linkage-disequilibrium between these variants, it is not currently clear which functional element or minimum combination of elements is required for SLE susceptibility. We have shown that this IRF5 SLE-risk haplotype is associated with increased serum IFN-α in SLE patients (23), and subsequent studies have supported this concept by showing that SLE-associated IRF5 variants are associated with increased activation of the IFN-α pathway (24,25).

Interestingly, in our study the association between IRF5 SLE-risk genotype and increased serum IFN-α was completely dependent upon autoantibodies (23). Thus, in SLE patients who lacked anti-dsDNA and anti-RNA-binding protein autoantibodies, there was no relationship between IRF5 and serum IFN-α levels. These data were striking, and suggest that the autoantibodies represent a chronic stimulus to the endosomal TLR system which is required for the IRF5 SLE-risk haplotype to result in dysregulation of circulating IFN-α levels (Figure 2). Thus, these data support a “gene + antibody = high IFN-α” model, which we would explore further in the context of IRF7 genetic variants in SLE patients. It is also

possible that IRF5 SLE-risk genotype may predispose to the production of autoantibodies in the first place, as IRF5 deficient lupus model mice show a major defect in autoantibody generation (47). If this is the case in human SLE, then a feed-forward model would be supported, in which IRF5 genotype predisposes to autoantibody formation, and then subsequently also predisposes to greater IFN-α production in the setting of those same autoantibodies.

IRF7 in SLE

IRF7 is another IRF family member which functions downstream of the endosomal TLRs which can induce transcription of IFN-α mRNA (48). A genome-wide association scan in European ancestry SLE patients detected a significant association near the IRF7 gene (22). To date, the causal functional genetic elements are not well described in the IRF7 locus, which also includes another gene named PHD and ring finger domains 1 (PHRF1). IRF7 seems like the more plausible candidate in this region given the potential biological relevance of the IRF family of genes in SLE pathogenesis, and upcoming fine-mapping and resquencing efforts will likely improve our ability to localize the genetic association with SLE in this locus.

We have recently explored the IRF7/PHRF1 locus in SLE patients, examining the relationship between genotype, autoantibodies, and serum IFN-α (19). We found a very similar model as that described above for IRF5, in which an impact of IRF7 genotype upon IFN-α was only observed in the presence of particular autoantibodies (19). Interestingly, the particular genetic variants and the particular associated autoantibodies differed somewhat between ancestral backgrounds, but the overall “gene + antibody = high IFN-α” model was conserved between different backgrounds. A direct genetic association between these particular autoantibodies and the respective IRF7 genotypes was also observed. In this case, SLE patients with the particular IRF7 genotypes were more likely to have the autoantibodies which cooperated with that genotype to result in higher serum IFN-α. It seems likely that this represents a gene-microenvironment interaction, in which the effect of the risk genotype is brought out by the microenvironmental stimulus. When IRF5 and IRF7 genotypes were considered jointly in the same patients, there was an additive effect observed between the risk genotypes of these two polymorphisms upon serum IFN-α in the autoantibody positive group, which was not present in the autoantibody negative group (19). The data above support the idea that this autoantibody-IRF7 interaction is important to disease susceptibility and pathogenesis in this subset of SLE patients, and provide a strategy for molecular stratification of the SLE population that will be useful in future studies of this locus in SLE patients.

IRF8 in SLE and Multiple Sclerosis

A recent genetic association study has strongly implicated a variant near the IRF8 gene in SLE susceptibility in Europeans (36). Interestingly, a different genetic variation in the IRF8 gene has been implicated in multiple sclerosis (49). Multiple sclerosis is treated effectively with recombinant human IFN-β (50), a type I interferon which signals through the same receptor as IFN-α (2). Paradoxically, the genetic variation in IRF8 which was associated with multiple sclerosis was also associated with increased type I IFN-induced gene expression in a human cell line, despite the therapeutic benefit of recombinant type I IFN in the treatment of the disease (49). We are currently performing studies of this locus in relation to serum IFN-α levels in SLE, as it is striking that different genetic variations in the same IRF gene are associated with two autoimmune syndromes which demonstrate an opposite relationship with type I IFN (causal in SLE, and therapeutic in multiple sclerosis). Similar to IRF7, the discovery of genetic associations between IRF8 variants in both SLE

and multiple sclerosis are recent, and further fine-mapping and sequencing of this region will likely be required to understand the functional genetic variations underlying these associations. Given the association of the IRF8 locus with two disparate autoimmune diseases, we expect that further study of this locus will broadly impact our understanding of the ways in which IRFs can impact human autoimmunity.

Conclusions

A variety of study techniques including gene expression, familial cytokine analysis, and genetic association studies all strongly support the importance of over-activity in the IFN-α pathway as a causal factor in human SLE (3,4,9,14,51). IRFs are important mediators of IFN-α and IFN-α-induced gene expression, playing a critical role in viral defense downstream of endosomal TLR activation. These endosomal TLRs are pathogenically activated by SLE-associated autoantibody immune complexes (27), which likely provide a chronic endogenous stimulus to the IFN-α pathway in SLE patients. Detailed investigations of the SLE-associated genetic polymorphisms in IRF5 and IRF7 support the idea that these polymorphisms are gain-of-function in humans in vivo (19,23), resulting in some of the IFN-α pathway activation observed in the disease. The impact of both of these polymorphisms upon serum IFN-α in SLE patients is dependent upon particular autoantibodies, providing evidence for a gene-microenvironment interaction (gene + autoantibody = high IFN-α, as shown in Figure 2).

It is not currently clear whether the observed gene-autoantibody interaction upon IFN-α is dependent upon other parts of the SLE phenotype. This is difficult to test in humans, as healthy subjects typically do not have SLE-associated autoantibodies. The genetic associations between gain-of-function variants in IRF genes and SLE susceptibility may also be relevant in SLE patients who lack the particular associated autoantibodies. It is possible that nucleic acid containing immune complexes represent one of many TLR stimuli which could interact pathologically with SLE-associated IRF variants. For example, Epstein-Barr virus infections have been implicated in SLE pathogenesis (52), and viral infection would provide a strong stimulus to the TLR/IRF system. In this case, a similar “gene + microenvironmental stimulus = high IFN-α” model may still apply, although potentially in a more self-limited manner than the consistent production of nucleic acid-containing immune complexes that is frequently observed in SLE patients.

Genetic studies support the relevance of IRF8 in both SLE and multiple sclerosis (36,49). The type I IFN system is of critical importance in both of these conditions, although in multiple sclerosis type I IFN is therapeutic while it is thought to be pathogenic in SLE. These studies all support the importance of the IRF family of proteins in human SLE, and further work in human disease may provide improved methods for diagnosis, classification, and possibly novel therapeutic strategies. While the IRF proteins have not been directly targeted by therapeutics to date, agents directed at upstream targets such as endosomal TLRs (53) and downstream targets such as IFN-α (54) are in early stage clinical trials in SLE patients. We expect that an improved understanding of the role of IRFs in human SLE will inform these therapeutic efforts and help to enable personalized medicine in SLE.

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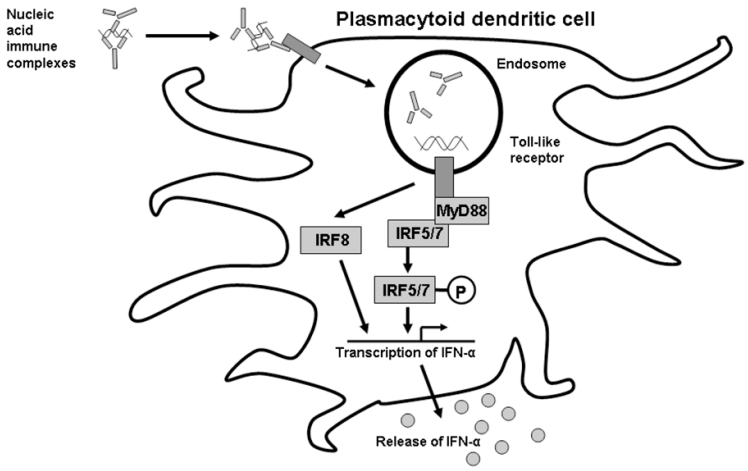

Figure 1.

Proposed relationship between SLE immune complexes, endosomal TLRs, and downstream IRF proteins with respect to IFN-α production in SLE patients. A plasmacytoid dendritic cell is shown, as these cells are thought to be the major IFN-α producing cells.

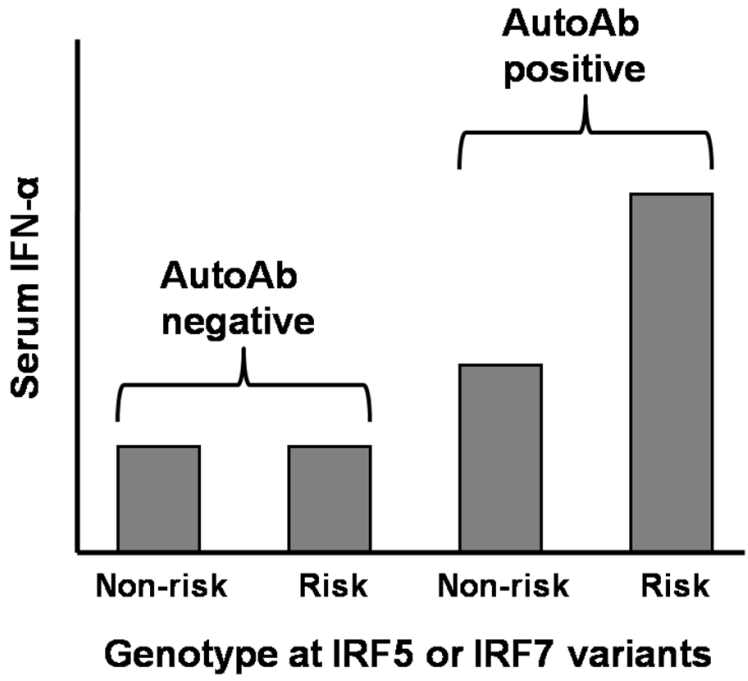

Figure 2.
Representation of the interaction between autoantibodies and IRF5 and IRF7 genotype upon serum IFN-α levels in SLE patients. Bars on the graph represent median serum IFN-α levels in a group of SLE patients defined by the labels on the graph. “Risk” refers to subjects who carry IRF5 or IRF7 polymorphisms associated with SLE susceptibility in case-control studies, and “non-risk” refers to subjects who lack these variants.