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The interferon-α signature of systemic lupus erythematosus

G Obermoser[1,2] and **V Pascual**[1]

[1]Baylor Institute for Immunology Research, Dallas, TX, USA

[2]Department of Dermatology, University Hospital Innsbruck, Innsbruck Medical University, Austria

Abstract

Systemic lupus erythematosus (SLE) is a prototypic multisystem autoimmune disorder where interplay of environmental and genetic risk factors leads to progressive loss of tolerance to nuclear antigens over time, finally culminating in clinical disease. The heterogeneity of clinical manifestations and the disease's unpredictable course characterized by flares and remissions are very likely a reflection of heterogeneity at the origin of disease, with a final common pathway leading to loss of tolerance to nuclear antigens. Impaired clearance of immune complexes and apoptotic material and production of autoantibodies have long been recognized as major pathogenic events in this disease. Over the past decade the type I interferon cytokine family has been postulated to play a central role in SLE pathogenesis, by promoting feedback loops progressively disrupting peripheral immune tolerance and driving disease activity. The identification of key molecules involved in the pathogenesis of SLE will not only improve our understanding of this complex disease, but also help to identify novel targets for biological intervention.

Keywords

autoantibody; autoantigen; B cells; complement; dendritic cells; genetics; immune complex; interferon; pathogenesis; systemic lupus erythematosus; Toll-like receptor

Introduction

The pathogenesis of systemic lupus erythematosus (SLE) is incompletely understood. Even though the hallmark of the disease is a loss of tolerance to nuclear antigens, clinical manifestations as well as disease severity and course vary from patient to patient. This most likely reflects the heterogeneous genetic background that underlies disease susceptibility. The past few years have witnessed an explosion of SLE genomic studies. Here we summarize recent genetic and transcriptome data that are helping to reconstruct the puzzle of SLE pathogenesis. However, many questions remain to be addressed, including the factors governing disease expression in specific organs, which, with the exception of congenital heart block, remain largely unknown.

SLE has a complex genetic basis

A genetic contribution is important to cause disease even though the concordance rate for SLE is only 25% among monozygotic twins.[1] More than 25 genetic risk loci have been

Correspondence to: Virginia Pascual, MD, and Gerlinde Obermoser, MD, Baylor Institute for Immunology Research, 3434 Live Oak, Dallas, TX, USA. virginip@baylorhealth.edu and gerlinde.obermoser@i-med.ac.at.

identified in recent genome-wide association scans. Despite this impressive progress, it is estimated that less than 10% of the total genomic susceptibility to SLE has been characterized to date.[2] The genetic risk for lupus is likely derived from variation in many (perhaps as many as 100) genes, each of modest effect size with odds ratios between 1.15 and 2.0.[3]

HLA-DRB1, signal transducer and activator of transcription 4 (STAT4) and interferon regulatory factor 5 (IRF5) are the three most frequently observed alleles accounting each for a little more than 1% of the variance in genome-wide association scans.[4] Together they point towards an interplay of alterations in the innate and adaptive immune systems: IRF5 is involved in the transcription of type I interferon and pro-inflammatory cytokines triggered by TLR signaling and STAT4 plays a key role in type I and type II IFN signaling. Presentation of epitopes within the grooves of MHC-I or MHC-II defines the choice of targets for the adaptive immune system and thereby explains the towering dominance of MHC in determining genetic susceptibility, not only in SLE but also in many other autoimmune disorders.[5]

Summarizing current knowledge, genes associated with SLE are involved in the following pathways[2–4,6–16] (Figure 1):

- **A.** Antigen presentation to the T-cell receptor of CD4+ T cells via HLA-DR (which is expressed primarily on dendritic cells, monocytes and B cells): HLA-DR2, HLA-DR3.
- **B.** Components of pathways upstream and downstream of type I IFN: (i) components of Toll-like receptor (TLR) signaling pathways (IRAK1, IRF5, IRF7, IRF8, SPP1 and TNFAIP3), (ii) IFN signaling (STAT4), (iii) intracellular DNA degradation (TREX1), (iv) autophagy-related genes (ATG5) which might contribute to IFN production by plasmacytoid dendritic cells.
- **C.** Signaling molecules activated after engagement of the T-cell receptor (TCR; such as TNFSF4/OX40L, PDCD1, PTPN22, STAT4).
- **D.** Signaling molecules activated after engagement of the B-cell receptor (BCR; such as BANK1, BLK, LYN, PTPN22).[17,18]
- **E.** Molecules involved in the clearance of apoptotic debris and of immune complexes such as FCGR2A/CD32 and FCGR3A/CD16, ITGAM/CD11b, an integrin which functions as complement receptor 3 but is also involved in the extravasation of leukocytes into tissues and in neutrophil phagocytosis and apoptosis; [19] CRP, C4A, C4B, C2 and C1Q, which are important in opsonization.
- **F.** Other molecules involved in ubiquitination (UBE2L3, TNFAIP3), DNA methylation (MECP2) and other yet undefined pathways such as PXK, XKR6, KIAA1542 or SCUBE1.

Potentially most informative results are to be expected from functional and immunological characterization of the latter group of genes. This will undoubtedly lead to the identification of novel pathogenetic pathways in SLE.

The serologic hallmark of SLE is the production of antinuclear antibodies

Autoantibodies are present many years before the onset of clinical symptoms in SLE. Antinuclear antibodies (ANA), anti-Ro, anti-La and antiphospholipid antibodies appear first (mean 3.4 years), followed by anti-dsDNA antibodies (mean 2 years) and anti-Sm and anti-RNP autoantibodies, which appear around 1 year before diagnosis of SLE and often coincide with the first clinical symptoms.[20] Most of these autoantibodies have not been

shown to play a pathogenetic role, correlate with disease activity or decrease following high-dose immunosuppressive treatment.

The most common lupus autoantibodies recognize double-stranded DNA (dsDNA) and small nuclear ribonucleoproteins (snRNPs), which are macromolecular complexes of small nuclear RNA (snRNA) and associated proteins. Anti-histone antibodies are frequently found in drug-induced SLE as well as in naturally occurring SLE.

Some of the nuclear autoantigens targeted in SLE have been described clustered in cell-surface blebs during keratinocyte apoptosis.[21] These autoantigens can be cleaved by granzyme B, a serine protease present in natural killer and cytotoxic T cells, leading to the generation of unique antigenic fragments not observed during other forms of cell death.[22] Other forms of cell death besides apoptosis might contribute to make nuclear antigens accessible to antibodies and cells of the adaptive immune system. In particular, neutrophils release DNA and histones as part of a unique type of cell death characterized by the extrusion of chromatin and proteins from neutrophilic granules into the extracellular space. This novel type of death, which aims at killing bacteria, is known as ‘netosis’ based on the formation of neutrophil extracellular traps (NETs).[23,24] In fact, histones have been shown already in the late 1950s to have bactericidal activity when released into the extracellular space.[25]

Broadening of the antigenic repertoire (‘epitope spreading’) is a characteristic of the SLE immune response. There is evidence supporting that this is an antigen-driven and T-cell-dependent process. Thus, autoreactive B cells require (similarly self-reactive) CD4 T-cell help for autoantibody production. Of note, only little is known about the epitope specificity of autoreactive T cells in SLE.[26,27]

Impaired clearance of immune complexes in SLE

A characteristic feature of SLE is an impaired clearance and accumulation of autoantigen–autoantibody complexes in tissues such as the kidney glomeruli or the dermo-epidermal junction of the skin in variants of cutaneous lupus erythematosus (‘lupus band’; see the article on ‘Pathogenesis of cutaneous lupus erythematosus’ in this issue). Deficiencies of early components of the classical pathway of complement such as C1q, C2 or C4 are rare, but they confer the strongest genetic susceptibility to an SLE-like disease in humans, with a penetrance rate from 30% (C4 deficiency) to over 90% (C1q deficiency).[28–30] Although homozygous mutations are exceedingly rare, nevertheless these ‘experiments of nature’ unequivocally demonstrate the functional consequences of impaired clearance on self-tolerance. Recently, Lood *et al.* reported that C1q inhibits immune-complex triggered IFN-α production by plasmacytoid dendritic cells (pDC), providing a novel link between complement deficiency and the activation of the type I IFN pathway in SLE as further discussed below.[31]

The IFN family of cytokines was discovered by its ability to interfere with viral replication,[32] although the antiviral potency of individual IFNs varies considerably. IFNs are classified based upon amino acid sequence and recognition of specific receptors into three families.[33] Type I IFN comprise IFN-α (which includes 13 subspecies), IFN-β, IFN-ε (expressed in the placenta), IFN-κ (expressed in keratinocytes), and IFN-ω in humans.[34,35] Type II IFN consist of a single member, IFN-γ, which has weak antiviral, but potent immunomodulatory functions. Type III IFN, IFN-λ1 (IL-29), IFN-λ2 (IL-28A) and IFN-λ3 (IL-28B), exert antiviral properties.

The IFN-α signature of SLE

Several observations led to the identification of IFN-α as a central player in SLE pathogenesis: IFN-α was found to be elevated in lupus sera,[36] most notably during disease flares, and anecdotal reports described the induction of a lupus-like syndrome following treatment with IFN-α for melanoma or hepatitis C.[37] The ability of DNA-containing immune complexes from lupus sera to induce IFN-α production by a novel cell type [38–41] later identified as the pDC was described in the late 1990s.[42] Furthermore IFN-α regulated gene transcripts were shown to be significantly upregulated in peripheral blood of pediatric and adult SLE patients upon gene expression profiling.[43,44] As described above, a genetic association with pathways related to type I IFN transcription and or signaling has been confirmed in SLE (for example, IRF5, STAT4, TNFAIP3 or TREX1).[2–4,7,9–13,15,16,45,46] Indeed, an excessive production and/or response to type I IFN explains many of the immune alterations observed in the disease.[47,48] Consequently, IFN-α is a logical therapeutic target, a hypothesis that has been tested in a phase I clinical trial as reported recently.[49] Moreover, the IFN-α signature is being assessed as a new biomarker for SLE disease activity.[49,50]

Immature pDC are the main source of type I IFN following endosomal TLR7 or TLR9 ligation

Many cells can produce IFN-α in response to viral infection in small quantities. pDC, previously called ‘naturally interferon-producing cells’, are unique in their capacity to produce vast amounts of IFN-α capable of generating systemic effects.[42,51] A single pDC, for example, can synthesize up to one billion IFN-α molecules within 12 hours (or 3–10 pg per cell), which is 200–1000 times more than the amount produced by any other cell type.[42,52] This unique ability of pDC can in part be explained by the constitutive expression or TLR7, TLR9 and IRF7.[53–57] Upon pDC maturation, IFN-α secretion is switched off, the cell acquires a dendritic morphology and assumes a ‘professional’ antigen-presenting function.[52,58]

pDC have been described by pathologists as early as the 1970s as an unusual cell with morphological and immunohistochemical features reminiscent of plasma cells, T lymphocytes and monocytes (‘plasmacytoid T cells’ or ‘plasmacytoidmonocytes’). pDC are Lin-BDCA-2+CD123+HLA-DR+ILT7+ and constitute less than 1% of circulating white blood cells.[51,52,59] Their frequency is decreased up to 100-fold in the peripheral blood of SLE patients[42,60,61] due to increased exodus into inflamed tissue like the kidney and skin[62–64]. Interestingly, phototesting can reproduce clinically and histologically photosensitive variants of cutaneous lupus erythematosus, including an influx of pDC following UV irradiation[65] (see also the review on ‘Photosensitivity, phototesting, and photoprotection in cutaneous lupus erythematosus’ in this issue).

The innate immune system contributes to the loss of tolerance to nucleic acids in SLE

The endosomal localization of TLR7 and TLR9, their inability to recognize endogenous DNA and RNA sequences and the rapid extracellular degradation of free nucleic acids by ubiquitous DNAses and RNAses are assumed to function as physiological protective barriers against ‘accidental’ activation of these potent receptors by self-nucleic acids.

There is experimental evidence that all of these protective mechanisms can be circumvented in SLE: DNAse1 knock-out mice develop a lupuslike disease;[66] moreover, DNAse1 deficiency was also observed in some lupus patients.[67] Molecules such as LL37, produced by neutrophils or damaged keratinocytes,[68] or the ubiquitous HMGB1 not only protect self-

nucleic acids from extracellular degradation but are also involved in their uptake through lipid rafts and/or receptors such as RAGE into endosomal TLR7/9 compartments.[69,70] Moreover, immune complexes can bind to FcgRIIa (CD32) on pDC and thereby gain access to endosomes by receptor-mediated endocytosis. [71,72] Hypomethylated DNA rich in linear cytosine– guanosine (CpG) sequences and uracil-rich small nuclear RNA (particularly U1 snRNA tightly bound to Sm and other small ribonucloproteins) are infrequent in the human genome; interestingly such unusual sequences are enriched in immune complexes in SLE [73] and are preferentially recognized by endosomal TLRs.[74–78]

pDCs sense aggregated DNA structures in early endosomes through TLR9. This leads to signaling through a TRAF3-IRAK1-OPN complex, leading to IRF-7 nuclear translocation and induction of type I IFN gene transcription. Linear (monomeric) DNA structures (or their synthetic correlate type B ODN) traffic through early endosomes into more acidic late endolysosomes where TLR7/9 activation recruits a different set of signaling molecules (i.e. NF-kB and IRF5) leading to transcription of inflammatory cytokines (IL-6, TNF-α) and costimulatory molecules (CD80, CD86 and CD40), DC maturation and diminished IFN-α secretion.[79] Synthetic compounds specifically targeting TLR9 and TLR7 to prevent immune complex stimulated IFN-α production in pDC promise new therapeutic avenues in the treatment of SLE.[80,81] In fact, an ‘old’ drug in the treatment of SLE already targets TLR9: chloroquine directly inhibits CpG-driven activation of TLR9, which might explain one of the actions of this antimalarial at the molecular level in autoimmune diseases.[82,83]

pDC and type I IFN at the center of lupus pathogenesis

Under steady-state conditions, immature mDC capture antigen and migrate, without maturing, to draining lymph nodes where they present self-peptide MHC complexes in the absence of costimulatory signals to self-reactive T cells, which leads to anergy and deletion.[84] Furthermore, immature DC may contribute to peripheral tolerance through the induction and maintenance of regulatory CD4+ T cells. Thus, autoreactive T cells escaping negative selection in the thymus are kept in check by peripheral immune tolerance. IFN-α contributes to disrupting peripheral immune tolerance by promoting mDC maturation.[61,85] Moreover, defects in Treg cell activity[86] and functional impairment of a novel subset of CD19+CD24hiCD38hi B cells with IL-10/B7 (B7=CD80/CD86) mediated suppressor activity on CD4+ T cells have been recently described as contributing to impaired immune tolerance in SLE.[87]

IFN-α-induced upregulation of costimulatory molecules such as CD80 and CD86 contributes to the survival, expansion and differentiation of self-reactive T cells. Autoreactive CD4+ T cells provide help to autoreactive CD8+ T cells. Furthermore IFN-α enhances a cytotoxic program of CD8+ T cell maturation characterized by an increased expression of perforin and granzymes.[88] These autoreactive CD8+ T cells contribute to tissue damage and to the generation of novel granzyme B dependent autoantigens,[22] further fueling immune complex driven production of IFN-α (Figure 1).

Importantly, IFNα upregulates the expression of TLR7 and IRF7 in pDC, mDC and monocytes, thereby increasing the responsiveness to nucleic-acid-containing immune complexes with further augmentation of IFN-α synthesis.[89]

IFN-α has myelosuppressive effects explaining in part the B-cell and T-cell lymphopenia observed in the peripheral blood of lupus patients. At the same time BLyS/BAFF is induced by IFN-α and contributes to the survival of mature, peripheral B cells. IFN-α promotes the differentiation of activated B cells into plasmablasts and, together with IL-6, permits plasmablasts to develop into antibody-secreting plasma cells.[90] Autoreactive B cells generate autoantibodies and thereby provide, through the formation of nucleic-acid-

containing immune complexes, a positive feedback loop for enhanced TLR7/9 activation and even more increased IFN-α production. Since B cells express TLR7 and TLR9 similarly to pDC, they too can be targeted by nucleic-acid-containing immune complexes.[48,90,91]

These effects explain the dramatic upregulation of type I IFN-inducible genes (the so-called 'IFN signature') described in the majority of SLE patient's blood.

Our understanding of the pathogenetic pathways involved in SLE has greatly expanded over the past decade. Defects in the clearance of immune complexes and apoptotic cells, altered B- and T-cell signaling, the production of autoantibodies and the link of all of the above with unabated IFN-α production provide a comprehensive picture of the pathogenic immune alterations taking place in SLE. Targeting B-cell hyperactivity by monoclonal antibodies directed against IFN-inducible proteins such as BAFF/BlyS or its receptor TACI as well as against type I IFN are already being tested in clinical trials in SLE patients. A number of new promising compounds that inhibit TLR7 and TLR9 show promising results in animal studies.[80] Despite the incredible progress made in the last few years, we probably have only discovered some islands of fact in a sea of uncertainty.[92] We therefore impatiently await the discovery of novel pathways leading to the identification of novel targets for biological intervention and successful treatment of this devastating disease.

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List of abbreviations

SLE	Systemic lupus erythematosus
ANA	Antinuclear antibodies
IFN	Interferon
IFN-α	Interferon alpha
DC	Dendritic cell
mDC	Myeloid dendritic cell
pDC	Plasmacytoid dendritic cell
TLR	Toll-like receptor
IRF7	Interferon regulatory factor 7
IRAK1	Interleukin-1 receptor-associated kinase 1
TNFAIP3	Tumor necrosis factor alpha-induced protein 3
TREX1	Three prime repair exonuclease 1
STAT4	Signal transducer and activator of transcription 4
ATG5	Autophagy protein 5
TCR	T-cell receptor
TNFSF4	Tumor necrosis factor (ligand) superfamily member 4 (=OX40L)

PDCD1	Programmed cell death 1
PTPN22	Protein tyrosine phosphatase non-receptor type 22
BCR	B-cell receptor
BANK1	B-cell scaffold protein with ankyrin repeats 1
BLK	B lymphoid tyrosine kinase
LYN	v-yes-1 Yamaguchi sarcoma viral-related oncogene homolog
FcGR2A	Low-affinity IIa receptor for Fc fragment of IgG (CD32)
FcGR3A	Low-affinity IIIa receptor for Fc fragment of IgG (CD16)
ITGAM	Integrin alpha M (complement component 3 receptor 3, CD11b)
CRP	C-reactive protein
C4A	Complement component 4A
C4B	Complement component 4B
C2	Complement component 2
C1Q	Complement component 1q
UBE2L3	Ubiquitin-conjugating enzyme E2L 3
MECP2	methyl CpG binding protein 2
PXK	PX domain containing serine/threonine kinase
XKR6	X Kell blood group precursor-related family member 6
SCUBE1	Signal peptide-CUB domain-EGF-related
TRAF3	TNF receptor-associated factor 3
OPN	Osteopontin
ODN	Oligodeoxynucleotides
NFkB	Nuclear factor kappa-light-chain-enhancer of activated B cells
TNF-α	Tumor necrosis factor alpha
BAFF/BlyS	B-cell activating factor/B lymphocyte stimulator
TACI	Transmembrane activator and calcium modulator and cyclophilin ligand interactor

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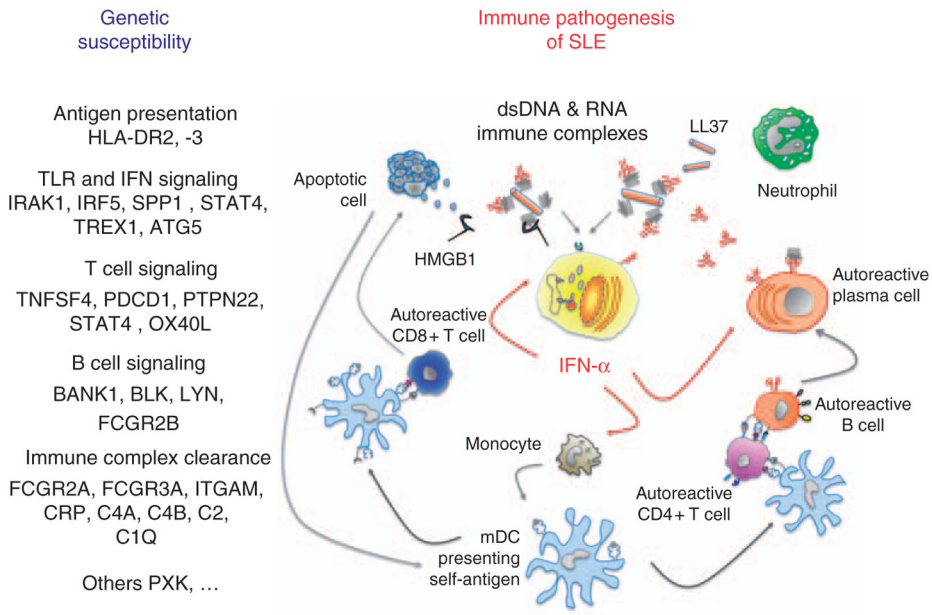

Figure 1.

The IFN-α signature of systemic lupus erythematosus (SLE). Genetic susceptibility to SLE includes genes involved in immune complex clearance, the stimulation of IFN-α production and IFN-α signaling as well as antigen presentation and B- and T-cell signaling contributing to immune pathogenesis of SLE as shown in the right part of this figure. Nucleic acids can act as endogenous triggers of IFN-α production in pDC. Molecules such as LL37 and HMGB1 not only protect self-nucleic acids from extracellular degradation, but are also involved in their uptake through lipid rafts and/or receptors such as RAGE into endosomal TLR7/9 compartments to stimulate IFN-α production. Moreover, immune complexes can bind to FcgRIIa (CD32) on pDC and thereby gain access to endosomes by receptor-mediated endocytosis. IFN-α induces and maintains the generation of mature DCs, which expand and activate rather than delete autoreactive T cells. The latter contribute to tissue damage yielding large numbers of nucleosomes, which can be captured by mature DCs, further amplifying the autoreactive process. Together with IL-6 IFN-α promotes plasmablasts to develop into antibody-secreting plasma cells. Also BLyS/BAFF is induced by IFN-α and contributes to the survival of mature, peripheral B cells. Moreover, IFNα upregulates the expression of IRF7 in pDC, and of TLR7 and IRF7 in mDC and monocytes, thereby increasing the responsiveness to DNA and/or RNA-containing immune complexes with further augmentation of IFN-α synthesis. For a color version of this figure, see online version of this article.