Interferon regulatory factors: critical mediators of human lupus

MARK A. JENSEN, and TIMOTHY B. NIEWOLD

ROCHESTER, MINN

The pathogenesis of systemic lupus erythematosus (SLE) is multifactorial, and the interferon regulatory factors (IRFs) play an important role. Autoantibodies formed in SLE target nuclear antigens, and immune complexes formed by these antibodies contain nucleic acid. These immune complexes can activate antiviral pattern recognition receptors (PRRs), resulting in the downstream activation of IRFs, which can induce type I interferon (IFN-I) and other inflammatory mediators. Genetic variations in IRFs have been associated with susceptibility to SLE, and current evidence supports the idea that these polymorphisms are gain of function in humans. Recent studies suggest that these genetic variations contribute to the break in humoral tolerance that allows for nucleic acid binding autoantibodies, and that the same polymorphisms also augment IFN-I production in the presence of these autoantibody immune complexes, forming a feed-forward loop. In this review, we will outline major features of the PRR/IRF systems and describe the role of the IRFs in human SLE pathogenesis. (Translational Research 2015;165:283–295)

Abbreviations: A = adenosine; AMP = adenosine monophosphate; AP1 = activator protein 1; Blys = B lymphocyte stimulator; C = cytosine; Cardif = Caspase activation and recruitment domain containing adaptor inducing IFN-β; cGAMP = cyclic AMP-GMP; cGAS = cyclic guanosine monophosphate-adenosine monophosphate synthase; CREB1 = cyclic AMP responsive element binding protein 1; DDX41 = DEAD box polypeptide 41; DEAD box = conserved motif sequence aspartic acid-glutamic acid-alanine-aspartic acid; dsDNA = double-stranded DNA; ETS = E26 transformation-specific; G = guanosine; GMP = guanosine monophosphate; IBD = inflammatory bowel disease; IC = immune complex; IFI16 = interferon-γ–inducible protein 16; IFIH1 = IFN induced with helicase C domain 1; IFN-I = type I interferon; IFNAR = Interferon alpha/beta receptor; IL = interleukin; IL-1R = interleukin 1 receptor; IPS-1 = interferon-β promoter stimulator 1; IRF = interferon regulatory factor; ISGF3 = ISG factor 3; ISGs = IFN-stimulated genes; IκB = inhibitor of kappa B; LD = linkage disequilibrium; MAVS = mitochondrial antiviral signaling; MDA5 = melanoma differentiation factor 5; MECP2 = methyl CpG binding protein 2; MHC = major histocompatibility complex; MRE11 = meiotic recombination homolog 11a; MyD88 = Myeloid differentiation primary response gene 88; NEMO = NF-κB Essential Modifier; NOD-like receptors = nucleotide-binding oligomerization domain receptors; PBMC = peripheral blood mononuclear cells; PDC = plasmacytoid dendritic cell; PEST = Proline (P) Glutamic acid (E) serine (S) Threonine (T); PRR = pattern recognition receptors; Rag2 = Recombination activating gene 2; RLR = retinoic acid–inducible gene 1 (RIG-I)-like receptors; SLE = systemic lupus erythematosus; SNP = single nucleotide polymorphism; ssRNA = single strand RNA; STAT = signal transducer and activator of transcription; STING = stimulator of IFN genes; T = thymidine; TANK = TRAF family member-associated nuclear factor kappa B activator; TLR = toll-like receptor; TNF-α = tumor necrosis factor α; TNIP1 = TNFAIP3 interacting protein 1; TRAF = Tumor necrosis factor receptor

From the Division of Rheumatology, Department of Immunology, Mayo Clinic, Rochester, Minn.

Submitted for publication August 8, 2014; revision submitted October 1, 2014; accepted for publication October 2, 2014.

Reprint requests: Timothy B. Niewold, Division of Rheumatology, Department of Immunology, Mayo Clinic, 200 1st Street SW, Guggenheim Building 3-42, Rochester, MN 55905; e-mail: Niewold.Timothy@mayo.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2014.10.002

associated factor; TREX1 = three prime repair exonuclease 1; TRIF = Toll/IL-1 receptor-domain-containing adapter-inducing interferon-β; U = uridine; UTR = untranslated region; VISA = Virus-induced signaling adapter; ZBP-1 = Z-DNA-binding protein 1

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic complex multisystem autoimmune disease that often arises during early adulthood, resulting in great morbidity. Clinical symptomology varies between individuals and within individuals over time, as inflammation often affects multiple organs and tissues. Almost any organ system can be involved, and sites commonly impacted by disease include the joints, skin, lungs, neurologic system, kidneys, and hematological systems.[1] Antibodies reactive to nucleic acids and nuclear proteins are prominent in lupus subjects and most individuals have circulating antibodies to numerous autoantigens. Antinuclear antibodies found in the disease can be reactive to nucleosomes, double-stranded DNA (dsDNA), Ro (Sjogren's syndrome A), Smith, small nuclear ribonucleoproteins, and La (Sjogren's syndrome B), with up to 90% of patients having reactivity against nucleosomes.[1] Disease is thought to result from a break in immune tolerance to self-proteins, including DNA and other nuclear proteins, with both genetic and environmental factors contributing to disease susceptibility and symptomology.

Although the etiology of SLE is unknown, many individuals with SLE show defects in their ability to clear apoptotic cells and cellular debris, suggesting that an excess of nucleic material contributes to autoreactivity to nuclear antigens.[2-10] Reactivity to nuclear material leads to the formation of circulating immune complexes that serve as a stimulus for the production of type I interferon (IFN-I) by plasmacytoid dendritic cells (PDCs).[11-14] Immune complexes are internalized in PDCs via surface-expressed Fc receptors and traffic to endosomal compartments, where the nucleic acid contained within them binds to toll-like receptors (TLRs) that recognize RNA (TLR7, TLR8) and DNA (TLR9). TLR7, TLR8, and TLR9 triggering activates members of interferon regulatory factor (IRFs) family of transcription factors including IRF1, IRF3, IRF5, IRF7, and IRF9, which are positive regulators of IFN-Is.[15-21] Uptake of immune complexes is thought to trigger IFN-I production by PDCs, and increased levels of IFN-Is are detectable in the blood of roughly half of SLE individuals.[22-26] This concept is supported by the fact that the strongest predictor of high IFN-I levels in human SLE patients is the presence of antibodies targeting DNA- and RNA-binding proteins.[27] Interestingly, these autoantibodies are not sufficient for high serum IFN-I,[28] suggesting that there are also disease-associated factors that modify the association between nucleic acid immune complexes and high IFN in SLE. One likely factor is intrinsic overactivity within the TLR signaling system. Human genetic variants in IRF5, IRF7, and IRF8 have been implicated in SLE susceptibility,[29-36] suggesting that gain-of-function polymorphisms in these molecules augment TLR signaling. Many studies have placed the IRF family as central mediators in human SLE.[37] In this review, we will summarize the TLR/IRF/IFN-I pathways and the role of this system in human SLE pathogenesis.

IFN-I IN SLE

IFN-Is are classically involved in viral defense and induce activation of antigen presenting cells and increased expression of major histocompatibility complex and costimulatory molecules. IFN-I has been implicated as a primary pathogenic factor in human SLE by various lines of evidence.[38] Increased IFN-I levels are clustered in SLE families as a heritable trait,[26,39] and this clustering supporting heritability is not observed with other SLE-associated cytokines such as tumor necrosis factor α.[40,41] Many of the genetic factors associated with SLE function within the IFN-I pathway,[42] with clear overrepresentation of the IRF family as noted previously (3 of the 9 IRF family members have genetic variants associated with SLE). When SLE-risk polymorphisms in IFN pathway genes have been investigated functionally in humans, they have been associated with increased IFN-I pathway signaling,[43-45] supporting the idea that gain-of-function variants in the IFN-I pathway underlie human SLE.[46,47] Additionally, human subjects given recombinant human IFN-I in the form of IFN-α2 as a treatment for malignancy or chronic viral infection have developed de novo SLE,[48] which has generally resolved when the IFN-α was discontinued.[49] These data all support a causal role for IFN-I in human SLE. There are two major categories of IFN-I in SLE, IFN-alpha and IFN-β, and the majority of the IFN-I detectable in the circulation of SLE patients is IFN-alpha.[26,50,51] A prominent IFN gene signature, comprising genes strongly activated by IFN-Is (IFN-stimulated genes [ISGs]), is present in circulating peripheral blood mononuclear cells (PBMCs) in a subgroup of patients with SLE and is associated with the presence of anti-dsDNA antibodies, increased IFN levels, and worse disease