Interferon Regulatory Factors and Autoimmune Diseases

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Interferon (IFN) Regulatory Factors (IRFs) are a small family of transcription factors, which are significantly conserved within their N-terminal DNA-Binding Domain (DBD) [1]. As shown in their names, IRFs are key regulators of the production of type I IFNs in response to pathogen attacks, but only IRF3 and -7 are indispensable.

IRFs are phosphorylated and activated through the signaling pathways triggered by invading pathogens, which release Pathogen-Associated Molecular Patterns (PAMPs) that are recognized by host Pathogen Recognition Receptors (PRRs). A pool of PRRs have been identified, among which endolysosomal Toll-Like Receptors (TLR3 and -4, -7, -8 and -9), and those located at other different cellular compartments including RIG-I-Like Receptors (RLRs), RNA Polymerase III, NOD2, IFI16, MITA/STING, MRE11, and DHX9 and DHX36, have been shown to activate IRFs for production of type I IFNs [2].

A large body of autoimmune diseases (up to 80 different types), such as Systemic Lupus Erythematosus (SLE), Sjogren’s syndrome, and Rheumatoid Arthritis (RA), have been identified. SLE is a systemic autoimmune disease (Type III hypersensitivity reaction) that can affect any part of the body, and occurs nine times more often in women than in men, especially in women in child-bearing years. SLE is characterized by “IFN signature” in the serum [3,4]. The inappropriate induction of IFNs leads to auto-antibody production, and finally tissue and organ damage [5].

Activation of IRFs by PRR-mediated pathways triggered by pathogenic nucleic acids elicits immune responses for defense. However, activation of IRFs by PRR-mediated pathways triggered by cellular “self” nucleic acids derived from tissue damages, such as apoptotic cells defective in being removed and mislocated small nuclear Ribonucleoprotein Particles (snRNPs), produces aberrant type I IFNs that play a key role in autoimmune diseases (Figure 1) [3,6,7]. Consistently, nucleic acid-recognizing TLRs (TLR3, -7, -8, and -9), RLRs, MITA/STING and HIN200, have been implicated in autoimmune diseases orchestrated by autoantibodies which recognize DNA or RNA-containing immune complexes such as snRNPs and debris of apoptotic cells [3,4,8,9,10]. For example, up to 29% SLE and 70% Sjogren’s syndrome patients develop autoantibodies to IFI16 [11] (Figure 1).

Among IRFs, IRF5 and also IRF7, -1, and -8, have been implicated in autoimmune diseases including SLE [5,12]. Genetic variants in the genes Irf5 and Irf7 are associated with the increased levels of IFNs in SLE patients [12,13]. Irf5 SNPs confer either susceptibility to, or protection from, SLE, depending on different genetic variants which include at least nine types of SNPs associated with SLE susceptibility and corresponding SNPs associated with protection [5]. The Irf5 SNPs associated with SLE susceptibility contribute to the heritability of serum IFNα activity in SLE patients.

A genome-wide study has revealed that rs4963128, a KIAA1542 SNP 23kb telomeric to Irf7, is strongly associated with SLE [14]. The IRF7 variant rs1131665 (Q412R), which is functional, is associated with SLE [15]. Another study on SNPs in the Irf7/Phrl1 locus has also indicated that genetic variants of Irf7 act as risk factors for SLE [16]. Moreover, IRF7 is implicated in the pathogenesis of metabolic autoimmune disorders including diabetes and obesity[17,18].

The overwhelming evidence for the engagement of type I IFNs, which are strictly transcribed by a few specific IRFs, in SLE susceptibility and for their implications in other autoimmune diseases...
provides great insight into the etiology of these disorders. Elucidation of the underlying molecular mechanisms will shed light on type I IFNs for therapeutic interventions.

**Competing Interests**
The author declares no conflict interest.

**Acknowledgements**
This work is supported by American Society of Hematology Scholarship Award to S. N.

**References**