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Review article

Interferon regulatory factor signaling in autoimmune disease

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ABSTRACT

Interferon regulatory factors (IRFs) play critical roles in pathogen-induced innate immune responses and the subsequent induction of adaptive immune response. Dysregulation of IRF signaling is therefore thought to contribute to autoimmune disease pathogenesis. Indeed, numerous murine *in vivo* studies have documented protection from or enhanced susceptibility to particular autoimmune diseases in *Irf*-deficient mice. What has been lacking, however, is replication of these *in vivo* observations in primary immune cells from patients with autoimmune disease. These types of studies are essential as the majority of *in vivo* data support a protective role for IRFs in *Irf*-deficient mice, yet IRFs are often found to be over-expressed in patient immune cells. A significant body of work is beginning to emerge from both of these areas of study – mouse and human.

Contents

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1. Introduction

Interferon regulatory factors (IRFs) are a family of transcription factors that were first identified as regulators of virus-induced type I interferon (*IFNA* and *B*) gene expression [1]. With the later discovery of other IFN families (type II and III), most of the IRFs, with the exception of IRF6, have been implicated in their regulation [2]. Subsequent findings revealed that IRFs play important roles in the regulation of both innate and adaptive immune responses. In particular, IRFs have been shown to be involved in the activation and differentiation of distinct immune cell populations [3,4]. To date, ten IRFs have been discovered (IRF1-10) in vertebrates; however, some are rendered inactive or eliminated in mice and humans, such as IRF10 [5]. A number of structural features within IRFs are well conserved. All IRF family members share a highly conserved N-terminal DNA-binding domain of approximately 120 amino acids, which binds to the core recognition sequence, GAAANNGAAAG/CT/C, termed the IFN stimulated response element (ISRE) [6]. With the exception of IRF1 and IRF2 that contain a PEST (proline-, glutamic acid-, serine-, and threonine-rich) domain for protein-protein interactions, all other family members contain a non-homologous C-terminal IRF association domain (IAD) for interaction with other family members and/or protein interacting partners [7,8].

In order to initiate signaling through the IRFs, many of them need to be "activated" by a signal that leads to post-translational modification, followed by altered cellular localization. The types of modifications shown to alter IRF activation/function include phosphorylation, acetylation, ubiquitination, and sumoylation [9]. The signaling cascades that lead to IRF activation are generally downstream of pathogen recognition receptors (PRRs). Identification of PRRs that lead to *IFN* gene expression has been the subject of intense research in the past decade. Notably, many of the cellular sensors shown to be responsible for pathogen recognition require IRF activation and downstream signaling. Cellular sensors shown to be involved in IRF signaling are: membrane bound Toll-like receptors (TLR), cytoplasmic RIG-like receptors (RLR), nucleotide binding oligomerization domain (NOD)-like receptors, and a disparate family of cytoplasmic and possibly nuclear DNA sensors [1,10–12]. Activation of IRFs through many of these pathways lead to the expression of IFNs, as well as other inflammation-associated cytokines [13].

The most studied pathway(s) that leads to IRF activation is through the TLRs. TLR signaling can be divided into two pathways: one that is dependent on the adapter protein MyD88 (myeloid differentiation primary response), and the other that is MYD88-independent and requires the adapter protein TRIF (Toll/IL-1 receptor domain-containing adaptor inducing IFN-B). Depending on the IRF, one or both pathways may lead to activation, resulting in its binding to the promoters of target genes and modulation of immune responses [1,3,10]. The steps leading to IRF activation and function can be broadly summarized into five major stages: (1) signal, (2) post-translational modification, (3) dimer formation, (4) nuclear translocation, (5) regulation of target gene expression.

With ongoing advances in the field of genome-wide association studies (GWAS), genetic variations in *IRF*s have been identified and associated with numerous autoimmune diseases. These genetic associations have opened up an expansive field of research focused on determining the role of IRFs in autoimmune disease pathogenesis. Autoimmune diseases are characterized by an attack on one's "self". The attack can be either specific to a particular organ, as is the case in inflammatory bowel disease (IBD), or systemic, as seen in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's Syndrome (SS). A number of genetic variants or single nucleotide polymorphisms (SNPs) within *IRF* genes have been detected at higher rates in patients with autoimmune diseases than matched healthy controls that enable an association with risk or protection from disease. Although this review will not cover the in-depth details from GWAS since a number of excellent reviews already exist [14–18], findings from GWAS are what initiated this new field of study - IRFs in autoimmunity. We instead provide a concise summary of *in vivo* and *in vitro* data that implicate dysregulated IRF signaling in autoimmune disease pathogenesis with a specific focus on the common and/or distinct pathways leading to and from the IRFs. Given the critical role of IRFs in IFN gene regulation, it was first postulated that genetic variants would contribute to elevated type I IFN expression that is now detected in multiple autoimmune diseases [19]. Based on emerging data, however, we propose that IRF function (or dysfunction) in autoimmune diseases is more robust than just as regulators of the IFNs.

2. IRF genetic association with human autoimmune diseases

Below we summarize findings from GWAS that identified genetic variation within the *IRF*s that associate with either susceptibility to or protection from a particular autoimmune disease. Only IRFs in which genetic variation has been associated with autoimmune diseases are detailed here. It is this body of work that initiated a new field of research focused on understanding the pathogenic role of IRFs in autoimmunity.

2.1. IRF1

IRF1 regulates the transcription of genes that play essential roles in viral infection, tumor immune surveillance, pro-inflammatory injury, and immunity system development [20]. With regard to GWAS, little is currently known of *IRF1* polymorphisms and risk of autoimmune diseases. Initial data found differences in *IRF1* polymorphisms between healthy controls and patients with juvenile idiopathic arthritis (JIA) [21] and Behcet's disease (BD) [22]. In BD, *IRF1* polymorphisms associated with risk in women and patients with thrombosis [22]. In JIA, however, a subsequent study examining a larger cohort of patients with different control subjects contradicted the early associations [23]. *IRF1* polymorphisms have been identified in multiple sclerosis (MS), yet more replicative studies are needed [24]. In RA, SNPs within the introns and untranslated regions (UTRs) of *IRF1* were found to associate with risk in black South African patients [25]. Copy number variations were also identified in *IRF1* that associated with RA [26]. Continued replication of GWAS in multiple ethnicities and cohorts will be required to confirm associations of *IRF1* genetic variants in JIA, BD, MS and RA.

2.2. IRF2

IRF2 negatively regulates type I IFN responses and plays a role in the induction of Th1 differentiation [8,27]. While not well replicated, association of *IRF2* genetic variants with susceptibility to SLE has been shown, and the risk haplotype was suggested to be associated with transcriptional activation of *IRF2* [28,29].

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