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Mini review

The emerging role of interferon regulatory factor 9 in the antiviral host response and beyond

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ABSTRACT

The host response to viral infections relies on tightly regulated and intricate signaling pathways involving type I interferons (IFN-Is). The IFN-Is mediate their antiviral effects predominantly through a signaling factor complex that comprises the transcription factors, interferon regulatory factor 9 (IRF9) and the signal transducers and activators of transcription (STAT) 1 and STAT2. While STAT1 and STAT2 have been studied extensively, the biological significance of IRF9 is only beginning to emerge. Recent studies have revealed a unique role for IRF9 as a conductor of the cellular responses to IFN-Is. Intriguingly, novel roles for IRF9 outside of the antiviral response are also being identified. Thus IRF9 may have a more extensive influence on cellular processes than previously recognized, ranging from antiviral immune responses to oncogenesis and gut homeostasis. In this review, we will focus on the distinct and emerging roles of IRF9 in the antiviral host response and beyond.

1. Introduction

The interferon regulatory factor 9 (IRF9) plays an integral role in the antiviral immune response, contributing to the intracellular signaling of all three classes of interferons (IFNs). In particular, type I IFNs mediate their antiviral effects predominantly through a signaling factor complex that comprises IRF9 and the signal transducers and activators of transcription (STAT) 1 and STAT2. Studies into IRF9 deficiency have revealed roles for IRF9 that are distinct from those of STAT1 and STAT2. During inflammation, IRF9 steers signaling towards a type I IFN response and prevents the emergence of a potentially harmful IFN-γ-like response. IRF9 also participates in non-canonical IFN signaling and thus contributes to the pleotropic effects of IFNs. Several studies have suggested that IRF9 may have a more extensive influence on cellular processes than previously recognized, ranging from antiviral immune responses to oncogenesis and gut homeostasis. In this review, we will focus on the distinct and emerging roles of IRF9 in the antiviral host response and beyond.

2. IRF9 is an essential part of the interferon regulatory response

IRF9 plays an integral role in interferon signaling and contributes to the intracellular signaling of all three classes of interferons. Namely, type I interferons (IFN-Is) which include the IFN-α's and IFN-β amongst others, type II interferon with IFN-γ being the only member, and the type III interferons (IFN-IIIs), consisting of the IFN-λs (reviewed in [1–3]). IFNs regulate the intensity and duration of innate and adaptive immune reactions as well as govern the survival, proliferation, and differentiation of responding cells [2–5]. However, IFNs are also instigators of several serious neuroinflammatory disorders [6]. This dual nature of IFNs requires that their expression and signaling be tightly regulated. Key to this regulation is a family of transcription factors called IFN regulatory factors (IRFs), of which IRF9 is a member.

The IRF family consists of nine members, which despite being structurally related, have a diverse range of functions. Common to all IRFs is a conserved N-terminal DNA binding domain containing

Abbreviations: OASL, 2'-5'-oligoadenylate synthetase; PKR, double-stranded RNA-dependent protein kinase; GAS, gamma-activated site; HCMV, human cytomegalovirus; ISG, IFN-I-stimulated genes; IFNAR, interferon alpha receptor; IFNGR, interferon gamma receptor; IRF, interferon regulatory factor; IRF9, interferon regulatory factor 9; ISGF3, interferon stimulated gene factor 3; ISRE, interferon stimulated response element; IFN, interferon; JAK1, janus kinase 1; LCMV, lymphocytic choriomeningitis virus; MS, multiple sclerosis; MEFs, murine embryonic fibroblasts; STAT, signal transducers and activators of transcription; TAD, transcriptional activation domain; IFN-I, type I interferon; IFN-III, type III interferon; TYK2, tyrosine kinase 2; VSV, vesicular stomatitis virus.

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five tryptophan repeats. The DNA binding domains of all IRFs recognize and bind similar DNA motifs. These motifs include the interferon stimulated response element (ISRE) found in the promoter region of most IFN-inducible genes, the IFN consensus sequence and the IFN regulatory factor element [7]. With the exception of IRF6, all members of the IRF family have been shown to contribute to the host antimicrobial and antiviral response and are important in immune cell development and homeostasis [8]. Their specific functions are attributed to a number of factors including cellular localization, inherent structural properties and importantly the ability to interact with co-factors. Of the nine members, IRFs 1, 2, 3, 5, 7 and 9 have been implicated as regulators of IFN-I production and IFN effector functions [9]. Their biology has been reviewed extensively elsewhere [8,10,11] and we will only summarize it briefly below.

Following a viral infection, both IRF3 and IRF7 induce and amplify the expression of IFN-Is (reviewed in [12]). IRF3 is constitutively expressed and is therefore an immediate responder to viral infection [13]. Upon recognition of a virus by pathogen recognition receptors, IRF3 becomes activated and induces the initial expression of IFN-β [14] and IFN-α_4 [15]. This first wave of IFN-Is initiates an autocrine positive feedback mechanism, leading to the induction of the expression of the *Irf7* gene [15,16]. Subsequently, IRF7 induces the expression of IFN-β and other IFN-α subtypes to amplify the IFN-I response and to upregulate expression of several hundred IFN-I-stimulated genes (ISGs) [15,17].

As will be discussed in detail below, IRF9 is critical for the increased expression of most ISGs by mediating the intracellular effects of all IFN-Is [18–22]. By contrast, IRF1 augments the expression of a subset of ISGs, including double-stranded RNA-dependent protein kinase (*Pkr*, also known as *Eif2ak2*) and 2′-5′-oligoadenylate synthetase (*Oasl*) [23–26]. Importantly, while IRF1 enhances the expression of some IFN-I stimulated genes, their expression is not dependent on IRF1 [19,27]. IRF2 on the other hand is a functional antagonist of IRF1 and acts as a repressor of IRF1-stimulated transcription [28]. In addition to this repressive role, a recent study has discovered a novel function for IRF2 [29]. In the unstimulated state, IRF2 binds to the promoters of IFN-inducible genes to maintain an active chromatin structure. Subsequently, upon viral infection, IRF1 is able to rapidly activate transcription at these promoters [29]. This suggests that IRF2 has positive as well as negative effects on IFN-stimulated gene expression. Similar to IRF1, IRF5 is also a positive regulator of the IFN-response. IRF5 was shown to induce the production of IFN-Is in a human fibrosarcoma cell line (2fTGH) in response to

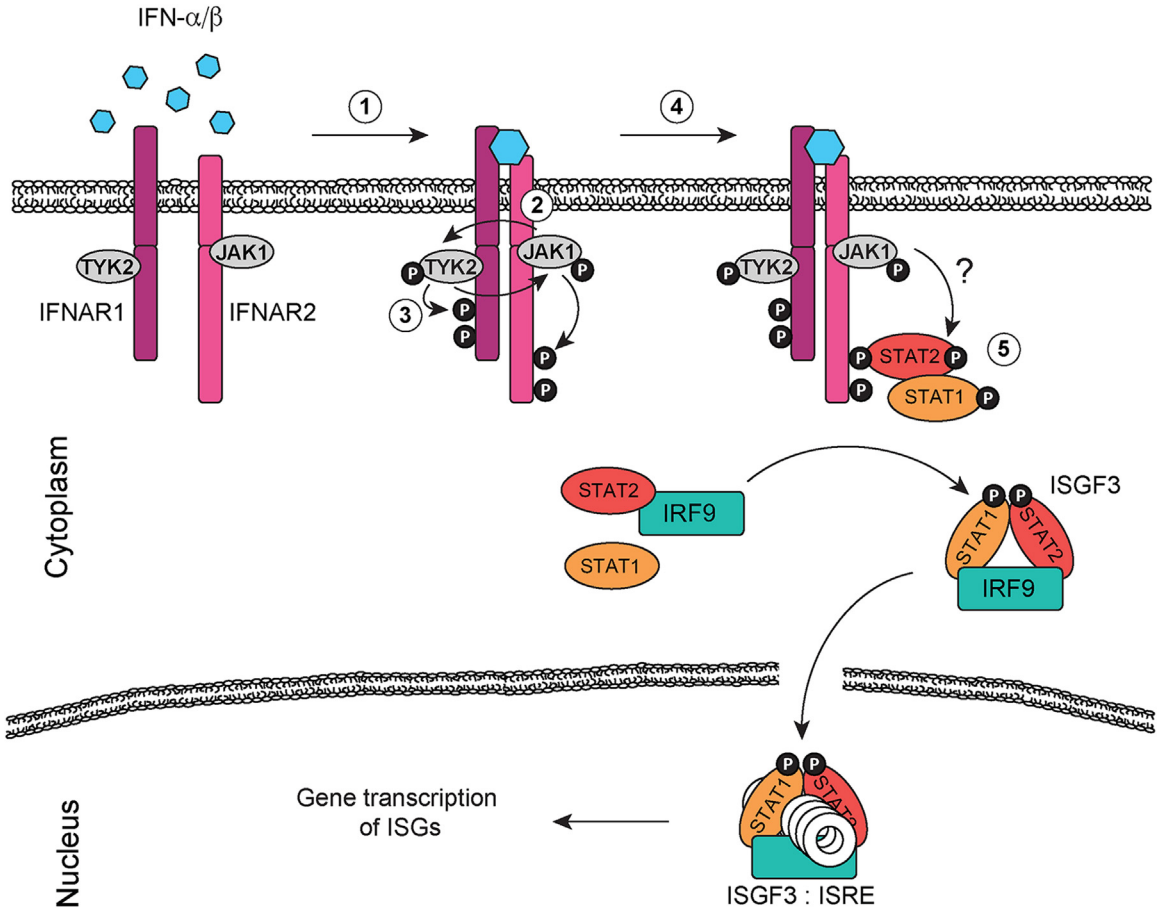

Fig. 1. Canonical IFN-I signalling.
Ligation of the IFNAR receptor by IFN-I causes the two chains IFNAR1 and IFNAR2 to dimerise (1). Dimerization activates the tyrosine kinases JAK1 and TYK2 via transphosphorylation (2). JAK1 and TYK2 then phosphorylate multiple tyrosine residues in the receptor chains (3), which allow docking of the signalling factors STAT1 and STAT2 (4). Unphosphorylated STAT2 is constitutively associated with IRF9 in the cytoplasm [47,48], however it is unknown what happens to this association when STAT2 is recruited to the receptor complex. STAT2 binds IFNAR2 while STAT1 may be recruited by STAT2 [106] (5). Following phosphorylation of the STAT proteins, they dissociate from the receptor complex and form a trimolecular complex with IRF9, termed ISGF3. ISGF3 translocates to the nucleus where it binds to ISREs in the promoter region of target genes resulting in transcription of ISGs. Ⓟ = Phosphorylation.

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