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Editor

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Interferon Omega (IFN-ω)

► Type I Interferons

Interferon Regulatory Factor

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Synonyms

IRF1: Interferon regulatory factor 1; MAR
IRF2: Interferon regulatory factor 2
IRF3: Interferon regulatory factor 3
IRF4: Interferon regulatory factor 4; Lymphocyte-specific IRF (LSIRF); PU.1-interaction partner (PIP); ICSBP in adult T-cell leukemia cell lines or activated T cells (ICSAT); Multiple myeloma oncogene 1(MUM1); SHEP8; NF-EM5
IRF5: Interferon regulatory factor 5; Systemic lupus erythematosus, susceptibility to, 10 (SLEB10)
IRF6: Interferon regulatory factor 6; Van Der Woude Syndrome (VWS1); OFC6; PPS1
IRF7: Interferon regulatory factor 7; IMD39
IRF8: Interferon regulatory factor 8; IFN-consensus-sequence-binding protein (ICSBP)
IRF9: Interferon regulatory factor 9; IFN-stimulated gene factor 3, Gamma (ISGF3G); ISGF3 P48 Subunit (P48)

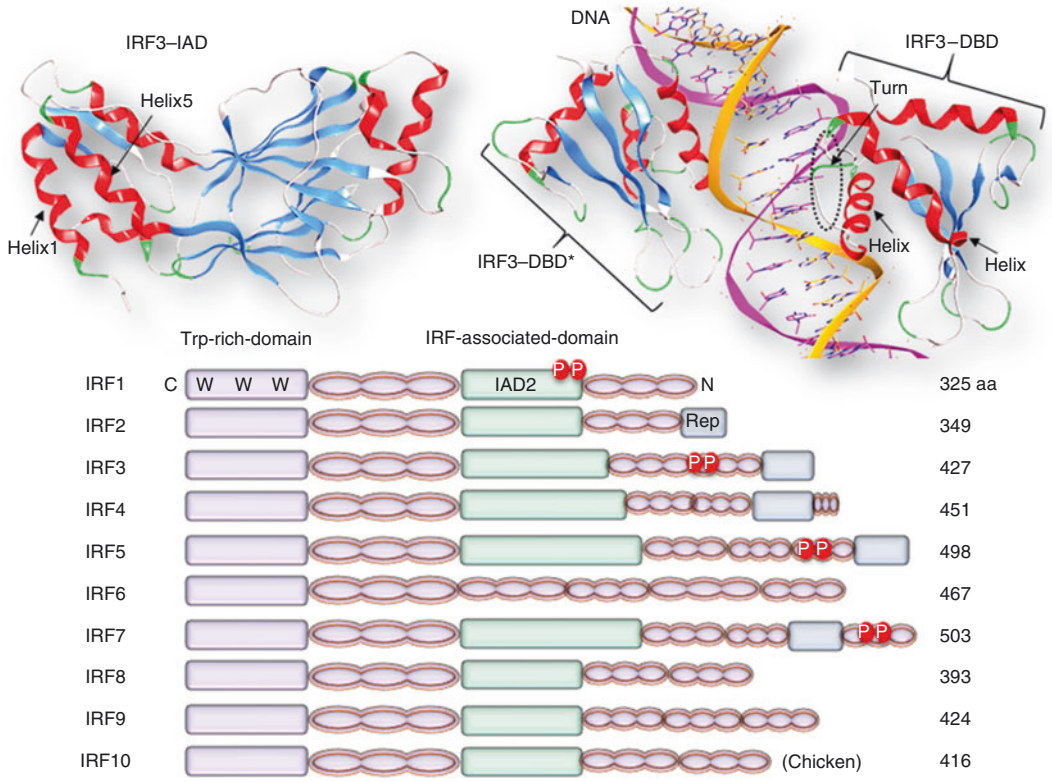
Historical Background

Interferon regulatory factors (IRFs) are a family of type-I interferon transcriptional regulators, consisting of nine members (IRF1-9). The first IRF was identified in 1998 (Miyamoto et al. 1988), and since then their role in immunity has been extensively studied. IRF1 was first identified as *IFNβ* gene-binding protein, which is induced by viruses (Miyamoto et al. 1988). The following year, IRF2 was identified through cross-hybridization with *IRF1* cDNA (Harada et al. 1989). After the identification of IRF1 and IRF2, numerous experimental approaches were adopted to explore this family and additional members were identified, including IRF3, IRF4 (also known as ICSAT, LSIRF, MUMI, or PIP), IRF5, IRF6, IRF7, IRF8 (also known as ICSBP), and IRF9 (also known as p48 or ISGF3γ) (Honda and Taniguchi 2006).

Structure, Mechanism, and Function of Interferon Regulatory Factors (IRFs)

Depending on the type of IRF, protein length ranges from 300 to 450 amino acids (Chen et al. 2013). The tertiary structure of a typical IRF protein contains a well-defined DNA-binding domain (DBD) that contains a series of conserved tryptophan (Trp)-rich repeats (Fig. 1). The Trp-rich DBD has a typical helix-turn-helix pattern and binds to a consensus DNA sequence GAAA, known as the IRF-element (IRF-E). The IRF-E lies in the promoter region of interferons (IFN) and is similar to the IFN-stimulated response element (ISRE) (Fujii et al. 1999). In addition to the DBD, most IRFs contain two distinct types of IRF-association domain (IAD), IAD1 and IAD2 (Fig. 1). The IADs of all IRFs (except IRF1 and IRF2) share sequence homology with the SMAD (Mothers against decapentaplegic) family (Yanai et al. 2012). Within the IRF family, IRF1 and IRF2 share 62% homology in their DBD-containing termini (Harada et al. 1989).

A full-length crystal structure has not yet been resolved for any IRF; however, many partial structures have been submitted to the Protein Data Bank (PDB). From the known crystal structures of IRFs bound to DNA, the IRF protein is composed of four β-sheets, three helices, and a loop, bound to the ISRE in the promoter region, with a GAAA consensus motif (Escalante et al. 1998; Panne et al. 2004). The IAD containing the C-terminal domain is composed of a β-sandwich core flanked by loops and helices (Takahasi et al. 2003) (Fig. 1). After their activation and subsequent translocation to the nucleus, IRFs bind to the enhancer region of IFNs and aid in



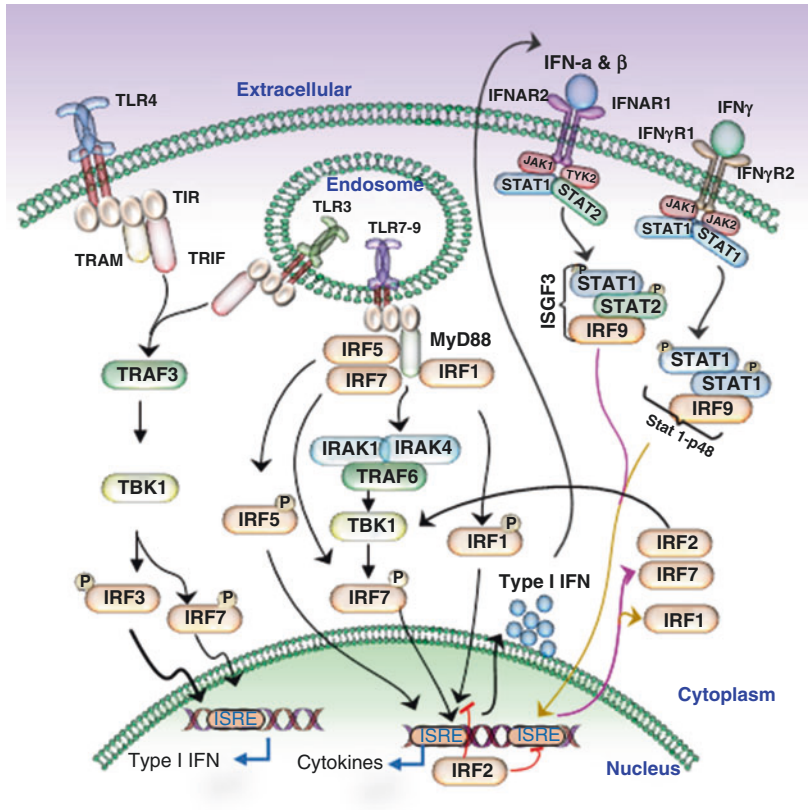
Interferon Regulatory Factor, Fig. 1 Schematic illustration and domain organization of interferon regulatory factor (IRF) protein sequences. All IRFs contain a conserved homologous tryptophan-rich DNA-binding domain (DBD) at their C-terminus (*transparent purple*). IRF1 and IRF2 share homology in the IAD domain and make IAD2, while the other family members share IAD1 (*transparent green*). Some IRFs contain a repression (Rep) domain at their C-terminus (*transparent blue*). IRFs that depend on phosphorylation for function are labeled "P" in a red sphere. In 2002, a novel IRF, IRF10, was reported in chicken that shares homology with mammalian IRF4

transcription. The IAD domain plays a defined role in the regulation of IRFs. However, the H1 and H5 helices present in the IAD domain of IRF3 and IRF7 are involved in an autoinhibitory mechanism (Fig. 1) (Takahasi et al. 2003). Kinase-dependent phosphorylation dislocates this autoinhibitory domain, leading to dimerization and nuclear translocation. The IAD domain is conserved in all IRFs, except IRF1 and IRF2, but the autoinhibition mechanism has only been reported in IRF3 and IRF7 (Qin et al. 2003).

Role of IRFs in IFN Signaling

Interferons (IFNs) are the central mediators of the innate immune system and can be grouped into two categories: type I (IFNα and β) and type II (IFNγ). Type I IFNs are primarily regulated by IRFs in the host after pathogen invasion and are considered the crucial mediators of an antiviral response. Type II IFNs are regulated and produced by other immune cell types, including NK cells and T-cells (Honda and Taniguchi 2006).

The ubiquitously expressed IRF1 and IRF2 are dramatically upregulated during viral infection or in cells stimulated by immune factors, interleukin (IL) 1β, IL6, and tumor necrosis factor-α. This activation is also associated with posttranslational modification of IRFs, such as phosphorylation. Phosphorylated IRF1 is associated with activation of type I IFN promoters, leading to the induction of *IFNα* and *IFNβ* genes via transcription factors nuclear factor kappa-light-chain-enhancer of



Interferon Regulatory Factor, Fig. 2 TLR-dependent activation of IRFs and their role in IFN production. Several interferon regulatory factors (IRFs) are activated in MyD88-dependent and/or independent pathways after activation of respective TLRs. Among the TLRs located on the plasma membrane, only TLR4 is involved in IRF signaling and activates IRF3 and IRF7 in a MyD88-independent manner. This involves activation of TRAF3 through association of the TIR-domain containing adaptor protein inducing IFNβ (TRIF) and TRIF-related adaptor molecule (TRAM), which then activate TANK-binding kinase 1 (TBK1). TBK1 then phosphorylates IRF3 (majorly; *thick black arrows*) and IRF7 (scarcely; *thin black arrows*), leading to their dimerization and nuclear translocation. A similar signaling mechanism is adopted by the endosome-expressed TLR3. Other TLRs expressed in endosomes activate multiple IRFs in a MyD88-dependent manner. Activated TLR7 and TLR9 phosphorylate MyD88-bound IRF7 (bound to the death domain of MyD88) through interleukin-1-receptor-associated kinase 4 (IRAK4), IRAK1, and inhibitor of NF-κB (IκB) kinase α (IKKα). All proteins shown in this figure are essential to the pathway, as suggested by gene-knockout studies. Like IRF7, IRF5 interacts with MyD88 (death domain-independent interaction) and undergoes phosphorylation. Activated IRF5 translocates to the nucleus and aids in pro-inflammatory cytokine production. IRF4 competes with the IRF5-binding domain of MyD88 and negatively regulates IRF5 activation. Secreted type I and type II IFNs bind to cell surface IFN receptors in an autocrine or paracrine manner and activate the JAK/STAT pathway. Activation of type I IFN receptors leads to the induction of IFN-stimulated gene factor 3 (ISGF3, a heterotrimer of STAT1, STAT2, and IRF9), which induces transcription of IRF2 and IRF7 after nuclear translocation (*pink arrow*). Activation of type II IFN receptors helps in the transcription of IRF1 (*yellow arrow*), which promotes T_H1 differentiation. Abbreviations: ISRE, IFN-stimulated response element; LPS, lipopolysaccharide; STAT, signal transducer and activator of transcription

activated B cells (NF-κB) and signal transducer and activator of transcription (STAT) (Honda and Taniguchi 2006). Unlike IRF1, IRF2 contains a repressor region that downregulates expression of type I IFNs. Phosphorylated IRF2 binds to DNA and represses ISRE and IRF-E controlled transcription, thereby halting the IRF1-dependent induction of type I IFNs (Jia and Guo 2008) (Fig. 2). IRF3 and IRF7 are also ubiquitously expressed in cells and share relatively similar

structures. These IRFs contain phosphorylation sites in their C-terminal region and rely on kinase-dependent activation before entry into nucleus. After phosphorylation, these IRFs dimerize (hetero- or homodimerization) and translocate to the nucleus where they bind to ISRE and IRF-E motifs and activate type I IFNs (Holland et al. 2008). Like IRF1, IRF3 and IRF7 are also upregulated in virally infected cells (Taniguchi et al. 2001). The transcriptional activity of IRF3 and IRF7 has been reported to be mutually dependent (Murphy et al. 2013). For example, the absence of both IRF3 and IRF7 in $IRF3^{-/-}$/$IRF7^{-/-}$ double knockout mice leads to uncontrolled viral infection and rapid death. However, in single knockout mice, either $IRF3^{-/-}$ or $IRF7^{-/-}$, viral growth as well as cell death rate were less severe (Murphy et al. 2013).

IRF4 and IRF8 are expressed in cells that play a key role in immune responses (Kanno et al. 2005). Levels of IRF4 have been shown to be increased with elevated levels of IFNα, whereas IRF8 expression is mainly regulated by IFNγ (Wang and Morse 2009). IRF4 and IRF8 directly bind to IRF-E and ISRE motifs and regulate cellular immunity (Lu 2008). This interaction between IRF4/IRF8 and the ISRE motif is mediated by the synergistic effect of the PU.1 transcription factor. In addition, Spi-B and several other factors have been reported to regulate IRF4 and IRF8 function during IFN signaling (Escalante et al. 2002).

The precise mechanism of IRF5 activation is not yet fully understood. However, it has been suggested that TRAF6-mediated ubiquitination is required for IRF5 nuclear translocation, following toll-like receptor (TLR)7 and TLR9 activation (Balkhi et al. 2008). Like IRF3 and IRF7, the C-terminus of IRF5 also contains a phosphorylation site, which helps to dislocate the auto-inhibitory region in the IAD domain, leading to homodimerization and subsequent nuclear translocation of IRF5 (Chen and Royer 2010). IRF9 was identified as a DNA-binding subunit of the interferon-stimulated gene factor 3 (ISGF3) and can induce many IFN-inducible genes. Induction of IRF9 is triggered by activation of the IFNα/β receptors (Chen et al. 2014). After binding to IFNAR or IFNϒR receptors, type I and type II IFNs induce phosphorylation of STAT proteins through JAK1/TYK2 and JAK1/JAK2, respectively (Fig. 2). The phosphorylated STAT factor then binds to IRF9, which translocates to the nucleus and induces expression of IFN-inducible genes through ISRE-containing promoters (Dussurget et al. 2014).

Role of IRFs in TLR Signaling

TLR signaling can be divided into two types, depending on the type of TLR and the adaptor protein involved: myeloid differentiation primary-response protein 88 (MyD88)-dependent and MyD88-independent (TRIF-dependent). The MyD88-dependent pathway is shared by almost all TLRs, whereas the TRIF-dependent pathway is limited to TLR3 and TLR4 (Tamura et al. 2008). IRF-related molecular events are mainly activated through TLR3, TLR4, TLR7, and TLR9 in MyD88-dependent and/or TRIF-dependent pathways. In response to invading pathogens, a stimulus, such as dsRNA or the pathogen itself, initiates the TLR pathways and activates the IRF kinase, such as TANK-binding kinase 1 (TBK1), through MyD88- and TRIF-dependent pathways (Fig. 2). This activated kinase then phosphorylates IRF3 and IRF7, leading to their dimerization and nuclear translocation (Sasai and Yamamoto 2013).

A substantial amount of evidence exists regarding the induction and activation of IRF4 (Banerjee et al. 2013; Wang and Ning 2013). It was recently reported that IRF4 is activated through c-Src-mediated phosphorylation; however, this kinase-dependent activation has not been fully investigated. Furthermore, the latent membrane protein 1 (LMP1) pathway induced by the Epstein-Barr (EBV) virus leads to activation of IRF4 (Wang and Ning 2013). Upon activation, the IRF4 protein localizes mainly to the nucleus; however, a considerable amount also resides in the cytoplasm. Cytoplasmic IRF4 binds to the IRF5 binding region on MyD88 and inhibits the sustained activity of IRF5 but not IRF7 (Negishi et al. 2005). Expression of

pro-inflammatory cytokines was markedly enhanced in peritoneal macrophages derived from IRF4$^{-/-}$ mice, which was inhibited by ectopic expression of IRF4 in these cells (Negishi et al. 2005). IRF4 has also been reported as a negative regulator of TLR-induced NF-κB (Honma et al. 2005).

Unlike TLR3 and endosomal TLR4, TLR7 and TLR9 regulate IFN signaling via the MyD88 adaptor protein. Following the activation of TLR7 or TLR9, IRF7 is activated either through the kinase cascade or directly through the death domain of MyD88 (Fig. 2) (O'Neill and Bowie 2007). A robust production of type I IFN signaling can be achieved via a positive feedback loop during TLR7-MyD88-IRF7 pathway activation (Colonna 2007). Like IRF7, IRF5 is also activated by direct binding to MyD88 and TRAF6; activated IRF5 then dimerizes, translocates to the nucleus, and participates in pro-inflammatory cytokine induction (Brown et al. 2011).

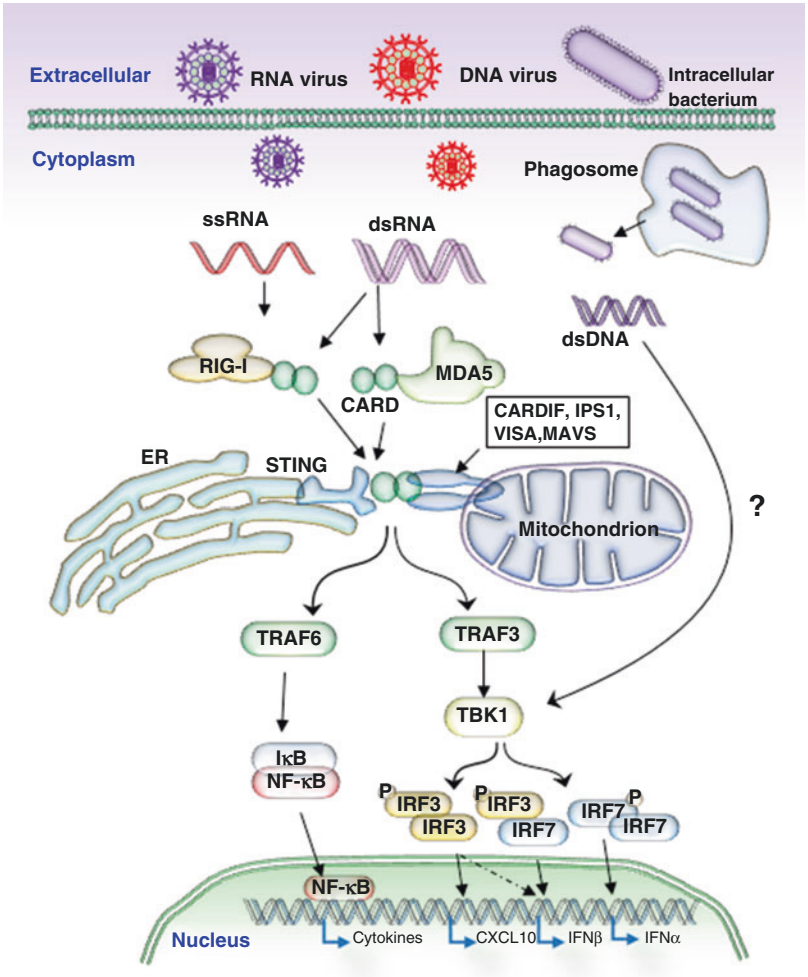
IRF8 has been reported to be involved in TLR9 signaling and augmenting the type I IFN response. Direct activation of pro-inflammatory cytokines has also been attributed to TLR9-dependent activation of IRF8 (Lande and Gilliet 2010). In addition to being a key regulator of TLR signaling, IRF8 has been shown to suppress TLR3 expression by suppressing IRF1 and also by inhibiting polyinosinic-polycytidylic acid (poly(I:C))-mediated TLR3 signaling in human monocyte-derived DCs (Fragale et al. 2011).

Role of IRFs in Cytosolic PRR Signaling

Pathogen recognition receptors (PRRs) can be broadly divided into membrane-associated TLRs and cytosolic PRRs. Cytosolic PPRs include the IFN-inducible dsRNA-dependent PKR, retinoic acid-inducible gene I (RIG-I) receptors, and nucleotide-binding oligomerization domain (NOD) proteins (Akira et al. 2006). Among these, RIG-I and melanoma differentiation-associated gene 5 (MDA5) are the most extensively studied receptors that recognize viral dsRNA and activate the underlying pathways (Takeuchi and Akira 2010). Signals from activated PPRs are relayed to TBK1 and induce kinase-dependent dimerization of IRF3 and IRF7 (Fig. 3). Activated dimerized IRF3 and IRF7 then bind to the ISRE or IRF-E, leading to transcription of type 1 IFNs and chemokines. Likewise, IRF5 is also phosphorylated by TBK1 and induces IFN activation during viral infection (Savitsky et al. 2010). Mitochondrial antiviral-signaling protein (MAVS), a RIG-I-like receptor adaptor protein, is also reported to induce IFN-stimulated genes (ISGs) through an IRF5-dependent pathway (Lazear et al. 2013).

Regulation of IRFs During Viral Infection

Viruses have evolved defense mechanisms to escape the host immune system and utilize proteins to engage, degrade, or modulate the normal immune system and find a way to replicate themselves (Bowie and Unterholzner 2008). The V protein of the mumps virus and parainfluenza virus 5 mimics cellular IRF3 and hinders its phosphorylation through host kinases. Similarly, the IRF protein from Kaposi's sarcoma-associated herpesvirus (KSHV) binds to cellular IRF7 and inhibits its DNA binding. The transcription factor K-bZIP in KSHV mimics host IRF3 and binds to IRF-E, thereby blocking the transcriptional activation of IFNβ. Furthermore, some viruses degrade host IRFs through their expressed proteins and evade the host immune system (Bowie and Unterholzner 2008). For example, infected cell protein 0 (ICP0) in bovine herpesvirus degrades IRF3 to overcome the host immune response. The NSP1 protein found in rotavirus binds to IRF3, causing its degradation (Barro and Patton 2005). The HIV-1 proteins, Vpr and Vif, have also been reported to degrade IRF3 during their replication (Fig. 4). In addition to mimicking, degrading, or modulating the effect of IRFs to disguise the host immune response, some viruses utilize IRFs during their replication cycle. For example, IRF1 and IRF8 have been reported to participate in HIV-1 transcription (Sgarbanti et al. 2002). Furthermore, IRF4

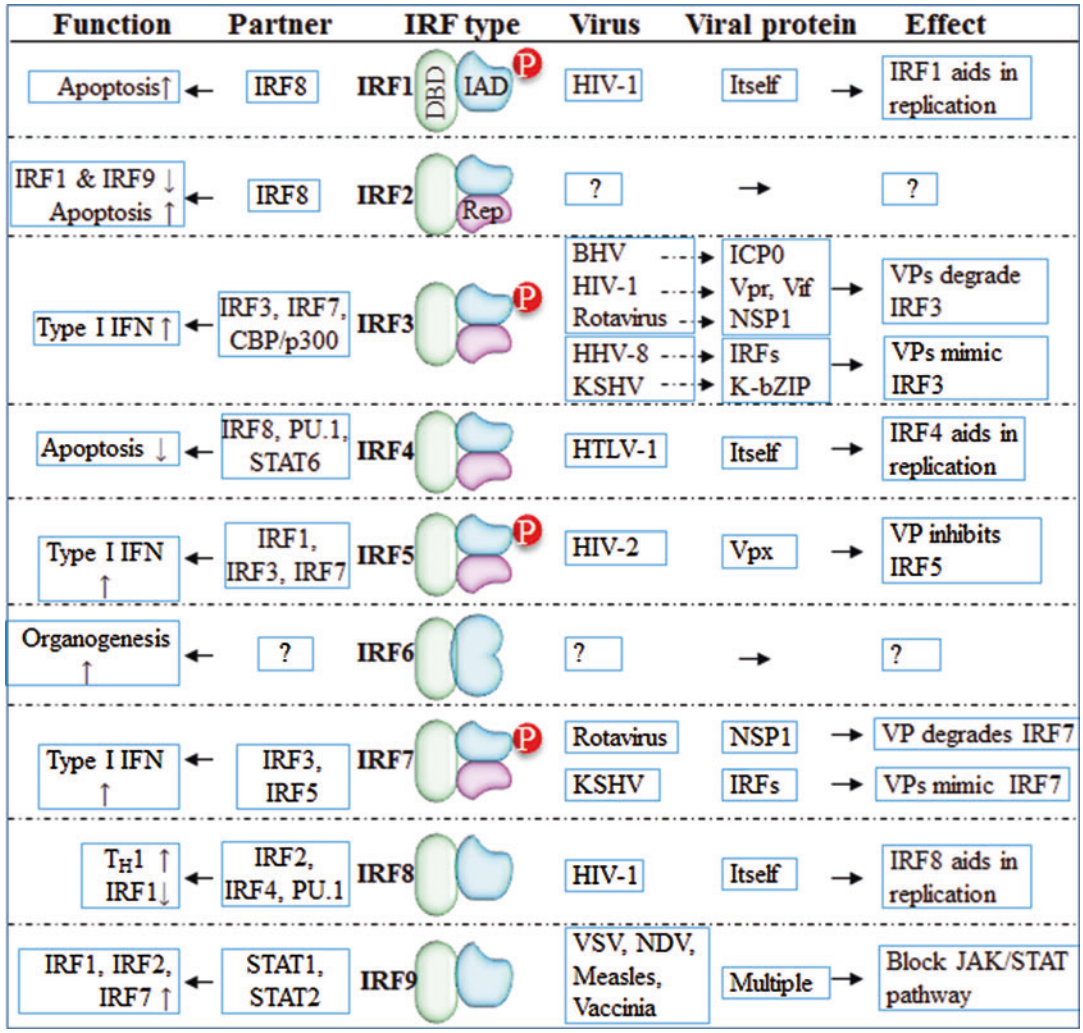


Interferon Regulatory Factor, Fig. 3 Role of cytosolic PRRs in IRFs signaling. After entering the host cellular system, viruses and intracellular bacteria undergo replication by hijacking the host protein machinery. The invading pathogens trigger the host immune system through the cytosolic pattern recognition receptors (PRRs) that recognize their nucleic acids (NA i.e., dsDNA, ssRNA, or dsRNA). Of the cytosolic PRRs, retinoic-acid-inducible gene 1 (RIG1) and melanoma-differentiation-associated gene 5 (MDA5) identify these NA and establish an interaction with their caspase-recruitment domain (CARD) and the CARD-like adaptor protein (also known as CARDIF, MAVS, VISA, or IPS1) located on mitochondria. These interactions result in NF-κB activation via tumor-necrosis-factor-receptor-associated factor 6 (TRAF6) and TANK-binding kinase 1 (TBK1) via TRAF3, respectively. Activated TBK1 phosphorylates IFN-regulatory factor 3 (IRF3) and IRF7, leading to their homo- or hetrodimerization. After activation, the dimers translocate to the nucleus and preferentially transcribe IFNα (by IRF7 homodimer) or IFNβ (by IRF3-IRF7 heterodimer or IRF3-IRF3 homodimer). Abbreviations: CARDIF, CARD adaptor inducing interferon-β; CXCL10, chemokine CXC-chemokine ligand 10; ER, endoplasmic reticulum; IPS1, IFNβ-promoter stimulator 1; MAVS, mitochondrial antiviral signaling protein; STING, stimulator of interferon genes; VISA, virus-induced signaling adaptor

expression in human T-lymphotropic virus 1 (HTLV-1)-infected cells downregulates the expression of cyclin B1 by binding to its promoter region, thereby decreasing CDC2 kinase activity (Mamane et al. 2002).

Role of IRFs in Disease

IRFs are critical regulators of the immune system, and therefore any abnormality in their expression or function can predispose the host to numerous



Interferon Regulatory Factor, Fig. 4 Illustration of cellular functions governed by IRFs and viral subversion of the IRF-mediated immune response. After activation, mammalian interferon regulatory factors (IRFs) induce hundreds of other proteins to combat invading pathogens. Activated IRFs either translocate to the nucleus alone or recruit a partner protein to accomplish transcription and modulate cellular homeostasis accordingly. Invading pathogens (viruses) have also evolved defensive strategies to evade the host immune system and in some cases utilize host immune regulators to assist their replication. Abbreviations: ?, function not known; ↓ downregulation; ↑ upregulation; BHV, bovine herpes virus; DBD, DNA-binding domain; HHV-8, human herpesvirus-8; HIV, human immune deficiency virus; HPV, human papillomavirus; HTLV, human T-lymphotropic virus; IAD, IRF-association domain; KSHV, Kaposi's sarcoma-associated herpes virus; NDV, Newcastle disease virus; NSP1, non-structural protein 1; Rep, repressor domain; VP, viral protein; VSV, vesicular stomatitis virus

diseases. There is much evidence to indicate that IRFs have key functions in the regulation of cellular responses linked to oncogenesis (Tamura et al. 2005). Moreover, IRFs have been reported to be involved in the pathogenesis of cardiovascular, neurological, and metabolic diseases (Zhao et al. 2015). Chronic and inappropriate production of type I IFN has been linked to a predisposition to many neurological diseases (Zhao et al. 2015). New discoveries have shown that IRFs can function alone, independent of their immune-related effects, suggesting that IRF-related diseases could be due to their role in immune system as well as their autonomous functions. The involvement of multiple IRFs can lead to

the progression of a single pathophysiological condition. As discussed above, IRFs share a high degree of sequence and functional homology. Therefore, when investigating a disease or immune disorder it is important to consider the possibility of cross talk between multiple activated IRFs.

Summary

The IRF family of proteins plays diverse roles in immunity, both innate and adaptive, and provides vital mechanisms to defend the host against pathogens. In addition, IRFs also play a critical role in the development of immune cells. Accumulating evidence indicates that IRFs undergo posttranslational modification to activate or attenuate the transcriptional process, and any abnormality in IRF expression or function could predispose the host to numerous diseases. Future studies will elucidate the active, genome-wide behavior of individual IRFs before, during, and after transcription, which could uncover new ways to overcome IRF-related immune disorders.

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Interferon Regulatory Factor 5

► IRF5

Interferon-Gamma

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Synonyms

IFNG; IFN-gamma; IFN-γ; Immune IFN; Type II interferon

Historical Background

Interferons (IFNs) were first described in 1957 by Issacs and Lindenmann as substances that restrict viral replication (Isaacs and Lindernmann 1957). In mid-1960, Wheelock reported that human