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IRF7: activation, regulation, modification and function

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Abstract

Interferon regulatory factor 7 (IRF7) was originally identified in the context of Epstein–Barr virus (EBV) infection, and has since emerged as the crucial regulator of type I interferons (IFNs) against pathogenic infections, which activate IRF7 by triggering signaling cascades from pathogen recognition receptors (PRRs) that recognize pathogenic nucleic acids. Moreover, IRF7 is a multifunctional transcription factor, underscored by the fact that it is associated with EBV latency, in which IRF7 is induced as well as activated by the EBV principal oncoprotein latent membrane protein-1 (LMP1). Aberrant production of type I IFNs is associated with many types of diseases such as cancers and autoimmune disorders. Thus, tight regulation of IRF7 expression and activity is imperative in dictating appropriate type I IFN production for normal IFN-mediated physiological functions. Posttranslational modifications have important roles in regulation of IRF7 activity, exemplified by phosphorylation, which is indicative of its activation. Furthermore, mounting evidence has shed light on the importance of regulatory ubiquitination in activation of IRF7. Albeit these exciting findings have been made in the past decade since its discovery, many questions related to IRF7 remain to be addressed.

Keywords

IRF7; *IFN*; *EBV*; *LMP1*; *PRR*

Introduction

Interferon regulatory factors (IRFs) are a family of transcription factors comprised of nine members (IRF1-9) in mammalian cells. IRF10 has only been identified in avian species; its DNA homolog in humans is not expressed.[1] The first member, IRF1, was identified in 1988 (ref. 2). Genes encoding IRFs exist in all principal metazoan groups although the family numbers are different.[3] In addition, the herpesviruses Kaposi's sarcoma-associated herpesvirus and rhesus rhadinovirus encode 4 and 8 viral IRF-like proteins respectively,

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which antagonize the functions of cellular IRFs.[4] Interestingly, the IRF family has coevolved with the nuclear factor (NF)κB family, both of which share some evolutionary characteristics:[3] both families are activated by pathways signaling from the same pathogen recognition receptors (PRRs) and by the same kinase family IκB kinases (IKKs); both cooperate extensively in regulation of target cytokines such as interferon (IFN)β, and together they represent the major players in innate immune responses.[3,5–8]

The IRF family members share significant homology within the conserved N-terminal DNA-binding domain (DBD), which consists of a signature tryptophan pentad that is essential for DNA binding.[9] Crystal structure studies have shown that DBD forms a helix-turn-helix structure, which recognizes the consensus DNA sequences that generally include at least two GAAA repeats,[10–14] whereas other studies have suggested that IRFs may have broader flexible binding capacities to the consensus sequence 5′-AANNGAAA-3′ (refs 9, 13, 15, 16). The viral IRFs lack several of the tryptophan residues, thus they cannot bind to DNA and as a consequence function as dominant-negative mutants. The C-termini of IRFs are different and confer on each member distinct functions.[5,17] In general, they contain an IRF-association domain, a nuclear export sequence, an autoinhibitory domain, and a signal-responding domain that has key serine residues subjected to phosphorylation upon infection with pathogens.[9] The IRF family is the key player in multiple facets of host defense systems.[5,18,19] In addition, IRFs have pivotal roles in immune cell development and regulation of oncogenesis.[19,20]

The *Irf7* gene was originally cloned in 1997, in the context of latent Epstein–Barr virus (EBV) infection where the encoded protein binds to and regulates the EBNA1 Q promoter.[21] The human *Irf7* gene is located on chromosome 11p15.5, and encodes four isoforms, IRF7A, -B, -C and -D (-H).[22] Human IRF7A protein consists of 503 amino acids with molecular size of 55kD, and mouse IRF7 consists of 457 amino acids with molecular size of 52kD. IRF3 is the closest family member to IRF7; together they are key regulators of the type I IFN (IFNα/β) responses, which are central to both innate and adaptive immunity.[18]

This review summarizes research on IRF7 since its discovery, with emphasis on recent findings of the potential roles of posttranslational modifications (PTMs) on activation as well as regulation of IRF7. Although most studies have focused on IRF7 phosphorylation leading to its activation and on its role in IFN antiviral innate immune responses, emerging evidence supports an important role for non-degradative ubiquitination in activation of IRFs including IRF7. Induction and activation of IRF7 in the EBV context indicate that IRF7 may have an important role in EBV latency and oncogenesis. Study of IRF7 in the context of EBV is thus important not only for understanding the interaction between EBV and host IRF7/IFN signaling in EBV oncogenesis, but also will provide valuable information on IRF7-mediated immune responses triggered by a wide range of pathogens.

Activation of IRF7

Activation of IRF7 is prerequisite for its functions as a transcription factor. Inactive IRF7 resides in the cytoplasm as a `latent' form. Pathogenic infection triggers IRF7 phosphorylation and translocation into the nucleus, where with other co-activators it forms a

transcriptional complex that binds to the promoter regions of target genes to activate transcription.[23,24] Crystal structure studies for IRF3 have supported a model for its activation: the IRF-association domain of IRF3 has a hydrophobic surface that is covered by an autoinhibitory domain in the `latent' form, and phosphorylation uncovers the hydrophobic surface for dimerization and functional interactions with other co-activators.[12,25] Structural study of IRF5 has supported this model as a general mechanism for activation of IRFs.[10] In addition, in line with this model, artificial deletion of an autoinhibitory domain of IRF7 (human IRF7A aa 247–467) can generate a constitutively active form of IRF7 (ref. 26). In contrast, another crystal structure study has indicated that phosphorylation is directly involved in dimerization and other functional interactions.[11] In addition, analyses with truncated mutants have indicated that the C-terminus of IRF7 contains several other functional domains, which regulate IRF7 activity. Importantly, the virus-activation domain spanning aa 278–305 of human IRF7A is indispensable for IRF7 activation.[26]

Activation by PRRs

Pathogen-associated molecular patterns from invading pathogens launch innate immune responses by recognizing host PRRs, which include transmembrane Toll-like receptors (TLRs), and cytoplasmic nucleotide-binding oligomerization domain-like receptors, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), double-stranded RNA-dependent protein kinase,[27] DNA-dependent activator of IRFs,[28] absent in melanoma 2 (refs 29–32), and the recently identified DEAH box polypeptide 9 and −36 (ref. 33), IFN-inducible gene 16 (ref. 34) as well as RNA polymerase III;[35–37] the last transcribes dsAT-rich microbial DNA into 5′-ppp dsRNA that is recognized by RIG-I.[35–37]

Among these identified PRRs, endolysosomal TLRs (endocytic TLR3 and TLR4, −7, −8 and −9) (ref. 38), and cytosolic RLRs,[39] DNA-dependent activator of IRFs, RNA Pol III, nucleotide-binding oligomerization domain-2 (ref. 40), IFN-inducible gene 16, and DEAH box polypeptide 9 and −36, have been shown to activate IRFs for production of type I IFNs. Several recent reports have identified unexpected roles of TLR2 and −8 in activation of IRFs for production of type I IFNs in specific cell types.[41–43] TLR2 can be internalized and activate IRF1, −3 and −7 in inflammatory monocytes[41] and bone marrowderived macrophages,[43] and murine TLR8, which was thought to be non-functional, mediates production of type I IFNs in murine plasmacytoid dendritic cells (pDCs) in response to poly(A)T-rich DNA derived from vaccinia virus.[42] Core signaling components involved in signaling cascades leading to activation of IRFs include the adaptors TRIF (for TLR3 and −4) and MyD88 (for TLR2/7/8/9), IRAK1/4 (refs 44, 45), TRAF6 (for TLR7, −8 and −9 and RIG-I)[46,47] and TRAF3 (for TLR3 and −4, RIG-I and nucleotide-binding oligomerization domain-2) (refs 48–50), and the IKKs, IKKε and TBK1. Core components unique to RLR signaling cascades leading to activation of IRFs include IFNβ promoter stimulator 1 (also called MAVS/VISA/CARDIF),[51–53] stimulator of interferon genes (also called MITA/ERIS/MPYS)[54–57] and Fas-associated death domain[58] (Figure 1). Stimulator of interferon gene functions as an adaptor that links IFNβ promoter stimulator 1 to TBK1 for the activation of IRF3/7 following cytosolic non-CpG DNA-mediated signaling[59] and other viral DNAs.[34]

IRF7 is activated by pathogenic nuclei acids through pathways mediated by TLR3, −7 and −9, RIG-I and likely DNA-dependent activator of IRF and IFI16, as well as by TLR2-mediated signaling pathway.[41,43] IRF7 is predominantly activated by TLR7 in pDCs, in which both TLR7 and IRF7 are expressed at extra high levels that make these cells `professional' producers of type I IFNs. In contrast to TLR3, which requires both IRF3 and −7 for sufficient induction of type I IFNs, it is generally accepted that IRF7 is not activated by TLR4 (ref. 19). However, several reports have shown IRF7 can be activated by TLR4 under certain conditions, for example, in conventional DCs and monocytes after IFNβ priming.[60,61]

Increasing evidence supports the involvement of the phosphatidylinositol 3 kinase (PI3K) pathway in the regulation of activation of IRFs by TLRs.[62] The PI3K pathway can be activated by various TLR ligands and can negatively or positively regulate TLR responses, depending on cell types and the ligands.[63] Both TLR9 and -3 activate the PI3K/Akt/mTOR pathway leading to the activation of IRF7, -3 and -5 (refs 64–66). PI3K is critical for the nuclear translocation of IRF7 and type I IFN production by human pDCs in response to TLR7/9 activation,[66] and mTOR Ser/Thr kinase activity is required for the interaction between MyD88 and IRF7 (ref. 64). In addition, induction of some IFN-stimulated genes such as Mx1, CXCL10, TNF-related apoptosis-inducing ligand by TLR7 in pDCs is dependent on the PI3K/p38MAPK pathway.[67]

Activation by EBV LMP1

Of special interest, IRF7, and likely IRF4, are induced as well as activated by the EBV oncoprotein latent membrane protein-1 (LMP1) (refs 68–71). LMP1 is a member of the tumor necrosis factor (TNF) receptor superfamily with constitutive activity. LMP1 exerts its functions by initiating both anti-apoptotic and proliferative growth factor-like signals, which are complex, have diverse outcomes and share signaling cascades with CD40, TLRs and a combination of TNF receptor-I and -II (refs 72–75). Our recent studies have shown that RIP1 and TRAF6, two key mediators participating in TNF signaling pathway, are also required for LMP1 activation of IRF7 (refs 70, 71). However, TRAF2 and -3, two other TRAFs involved in TNF signaling, are not required.[76] Phosphorylation is believed to be the mechanism underlying IRF7 activation by LMP1 as shown by *in vivo* ^{32}P-orthophosphate labeling[68] and by the fact that the phosphorylation-deficient mutant, IRF7(S477A/479A), failed to be activated by LMP1 (ref. 71). Importantly, our recent studies has indicated that K63-linked non-degradative ubiquitination of IRF7 is indispensable for its activation by LMP1 as well as by IKKε,[71] and probably the ubiquitination event is prerequisite for its phosphorylation.[70]

Regulation of IRF7

Regulation of IRF7 expression

IRF7 is a lymphoid-specific factor, which is constitutively expressed in the cytoplasm in B cells, pDCs and monocytes in the spleen, thymus, and peripheral blood lymphocytes, and is potently inducible by type I IFNs, virus infection and other stimuli such as 12-o-tetradecanoylphonol-13-acetate, TNFα and lipopolysaccharide in various cell types.[21,77]

The positive regulatory feedback between IRF7 and type I IFNs during antiviral immune responses is the major source for IRF7 expression in the cell.[78–80] At the early `priming' stage of virus infection, the low level of endogenous IRF7 in the cell is phosphorylated and activated by signaling triggered from PRRs, and together with NFκB and IRF3, which are also activated by the same pathways, binds to the virus-responsive elements in the *Ifna* and *Ifnb* promoters and induces small amounts of type I IFNs, which secrete and bind to IFNA receptors on other cells. IRF7 has a pivotal role in the priming. Binding of IFNs to IFNA receptor results in the activation of the IFN Janus kinase-signal transducers and activator of transcription signaling cascade, leading to phosphorylation and activation of signal transducers and activator of transcription 1 and -2. The activated signal transducers and activator of transcription 1/2 then bind to IRF9 as a complex named `IFN-stimulated gene factor 3', which in turn binds to the IFN-stimulated response element on the IRF7 promoter and induces synthesis of more IRF7. Later, the newly synthesized IRF7 is activated and induces more IFNs so that more and more IRF7 and IFNs are produced, but IRF3 at late stages is degraded by virus infection.[78–80]

Induction of IRF7 by LMP1 in EBV latency is an important event as this occurs in a quite different biological context[69] and this setting implies that IRF7 has another important role in oncogenesis, as also supported by a large body of other evidence (see later). Both LMP1 C-terminal functional domains, C-terminal activator regions 1 and -2, are involved in the induction of IRF7. NFκB, which is also activated by LMP1, was shown to be required for the induction.[81] The IRF7 promoter contains at least 4 NFκB-binding sites in a 3 kb fragment starting from the translational start codon ATG.[81,82] As it is induced by LMP1, IRF7 is associated with EBV latency programs; it is expressed at a low level in type I but at a high level in type III latency. IRF4, like IRF7, is also induced by LMP1 (ref. 83). However, another family member, IRF2, is not induced by LMP1 (ref. 69), although it is also highly expressed in type III latency.[84]

In addition, IRF7 is induced by TNFα and 12-o-tetradecanoylphonol-13-acetate through NFκB activation and chromosomal accessibility,[85] and is silenced by promoter hypermethylation.[82] Thus, reagents that can loosen chromatin structure such as topoisomerase II inhibitors can also induce IRF7 (ref. 85). We have shown that autoregulation of IRF7 also contributes to IRF7 induction in response to virus infection.[86]

IRF7 mRNA encodes four natural splicing variants, IRF7A, -B, -C and -D (-H).[22] Moreover, IRF7 mRNA translation is repressed by the translational repressors, 4E-BP1/2. Production of type I IFNs is enhanced and virus infection is suppressed in 4E-BP1/2-deficient mouse embryo fibroblasts and knockout mice, correlated with upregulated IRF7 mRNA translation.[87]

Half-life of the IRF7 protein

Unlike its closest member IRF3 that is constitutively expressed and stable in most cells, IRF7 remains at low levels in most cell types, and has a very short half-life of 0.5~1 h in infected cells and approximately 5 h in uninfected cells but can be stabilized by the 26S proteasome inhibitor, MG132, or by a dominant-negative mutant of Cul1, a component of the SKP1-CUL1-F-box E3 ubiquitin ligase complex,[88,89] suggesting that its stability is

controlled by the ubiquitin–proteasome system. This claim is also supported by the fact that both murine and human IRF7, but not IRF3, contains a conserved potential prolineglutamic acid-serine-threonine sequence,[88] which is essential for the target protein for destruction.

Similar to wild-type IRF7, a phosphorylation-deficient mutant was also partially degraded in infected cells, but a phosphomimetic mutant is less stable than the wild type even in the absence of virus, suggesting that phosphorylation is not necessary for but may contribute to virus-stimulated IRF7 degradation.[89] IRF7 stability is tissue specific. Compared with that in mouse embryo fibroblasts, IRF7 half-life is longer and virus infection stabilizes rather than degrades IRF7 in thymocytes and splenocytes. Further analyses indicated that virus-induced IRF7 stability in these cells is controlled by both IFN-dependent and virus-dependent/IFN-independent mechanisms.[89] Another study has shown that, in human lymphocytes, endogenous IRF7 is very stable and the half-life is > 24 h even without virus infection, and even in EBV-transformed cells in which IRF7 is phosphorylated, which usually precedes protein degradation.[81] Thus, mouse and human IRF7 may have significant differences in stability.

IRF7 transcriptional coregulators

The transcription factors NFκB, PU.1 and SMAD have important roles in immunity and are known to directly interact with IRFs.[3] Upon activation, IRF7 forms a transcriptional complex enhanceosome together with IRF3, NFκB, c-Jun, activating transcription factor 2 and p300/CREB-binding protein on the promoter region of the *Ifnb* gene.[16,23,90] IRF7 is also able to form homodimers or heterodimers with IRF5 in regulation of target genes.[91,92] SMAD3, a key component in the transforming growth factor-β signaling, which modulates many aspects of immune functions, was identified as an IRF7-interacting protein by yeast two-hybrid screening, and cooperates with IRF7 in the induction of IFNβ.[93] In fact, the C-termini of IRFs share structural similarity with the SMAD/Forkhead-associated domain.[94] These lines of evidence strongly suggest that IRF7 does not bind to the target promoters as a sole molecule.

To our knowledge, no transcriptional corepressor has been identified for IRF7 so far. Recently, the transcription factor, MafB, which impairs the interaction of co-activators with IRF3, is reported also to inhibit IRF7-dependent transcription, probably through interfering with the binding of IRF7 to target promoters, as efficient interaction between MafB and IRF7 requires IRF7 DBD. Thus, MafB may contribute to the limitation of type I IFN production spontaneously induced by constitutive IRF7 activity under physiological conditions such as in pDCs and macrophages in which high constitutive levels of IRF7 is detected.[95]

Regulation of IRF7 activity and protein stability by viral proteins

Owing to their pivotal role in host immunity, IRF7 and -3 are counteracted by numerous viruses through different strategies.[96,97] For example, the Thogoto virus non-essential accessory protein ML strongly inhibits both IRF3 and -7 (refs 98, 99). Rotavirus nonstructural protein 1 mediates the degradation of IRF3, -5 and -7 (ref. 100). Human papillomavirus E6 oncoprotein binds to IRF3 and inhibits its transcriptional activity through

a proteasome-independent mechanism.[101] Ebola Zaire virus VP35 promotes sumoylation of both IRF3 and -7 and therefore blocks type I IFN production.[102] Hepatitis C virus NS3/4A protease cleaves IFNβ promoter stimulator 1 and TRIF and therefore inhibits activation of IRF3 and -7 during hepatitis C virus infection.[103]

As to the herpesvirus family, to ensure successful infection and establishment of latency in the host, many virus-encoded immediate-early (IE) proteins can antagonize the effect of IRFs. For Kaposi's sarcoma-associated herpesvirus, IRF7 is negatively regulated by the IE lytic transactivator RTA/ORF50, which possesses ubiquitin E3 ligase activity, through ubiquitination-mediated degradation,[104] and by another IE protein ORF45 that inhibits IRF7 phosphorylation and nuclear translocation.[105,106] In addition, the four viral IRFs function as dominant-negative mutants of cellular IRFs.[4,107–109] For example, vIRF3 inhibits cellular IRF5 (ref. 107) and −7 (refs 109, 110). For herpes simplex virus, the IE transactivator ICP0, which possesses ubiquitin E3 ligase activity, inhibits IRF3/7 activation in different ways, including induction of proteasome-dependent degradation of DNA-PK that targets IRF3 N-terminal Thr135 phosphorylation,[111] and likely recruitment of cellular USP7/HAUSP, the herpesvirus-associated ubiquitinspecific protease.[112–114]

As to EBV, the IE proteins BZLF1 (also called Zta)[115] and LF2 (also called BILF4),[116] have recently been found to bind to IRF7 and repress its activity, and another IE transactivator, BRLF1 (also called RTA), downregulates expression of multiple IRFs including IRF7 and −3 and therefore impairs IFNβ production during EBV reactivation.[117] LF2 interacts with the IRF-association domain of IRF7 and prevents its dimerization.[116] Another EBV IE protein BGLF4, the only herpesvirus protein kinase conserved in EBV,[118] has been identified as an IRF3-interacting protein by yeast two-hybrid screening.[119] BGLF4 phosphorylates IRF3 *in vitro*, does not prevent IRF3 dimerization and nuclear translocation, but prevents its DNA-binding activity in response to poly(I:C) treatment[119] (Figure 2a).

Regulation of IRFs in EBV latency

EBV latency has an intimate association with the IRF family, as manifested by several lines of evidence: (i) Several members including IRF7 (refs 69, 120), −2 (ref. 84) and −4 (refs 83, 121, 122), which have oncogenic properties, as well as IRF5 (refs 92, 121, 123), are all expressed in much higher abundance in EBV latency III; (ii) both IRF4 (refs 83, 121) and −7 (ref. 69) are induced by LMP1, and IRF5 is induced by both TLR7 and LMP1 (refs 121, 124), whereas IRF2 is induced through an unclear mechanism;[69] (iii) IRF7, and likely IRF4, are activated by LMP1 (refs 70, 71, 83) (Figure 2b).

In addition to IRF5 that negatively regulates IRF7 activity through heterodimerization with it in EBV latency,[92] we have recently identified the dual function ubiquitinediting enzyme A20, which is also induced by LMP1 (refs 125, 126), as another negative regulator, which regulates IRF7 activity through regulation of its ubiquitination,[127] indicating that IRF7 is complexly modulated in the EBV context. In addition, as IRF7 in EBV latency is constitutively phosphorylated and ubiquitinated, we believe that some other cellular proteins contribute to regulation of these important events in EBV latency through distinct signaling pathways, and we are conducting proteomic screening coupled with mass spectrometry to profile IRF7-interacting proteins from EBV-transformed cells. Further functional analyses

of these proteins in the EBV/IRF7 interface are important not only for understanding how regulation of IRF7 contributes to the delicate balance of EBV latency as well as the interaction between EBV and IFN signaling pathways, but also will expand our knowledge in regulation of IRF7-mediated innate antiviral immune responses.

Modifications of IRF7

Posttranslational modifications of IRF7

Phosphorylation—Like other transcription factors, IRF7 undergoes various PTMs, the most important of which is phosphorylation. For human IRF7A, the most convincing major phosphorylation sites, serines 477 and 479, have been identified by serine–alanine substitution, which resulted in abrogation of IRF7 ability to transactivate *Ifn* gene promoters,[26] and a phosphorylation-specific antibody has been developed which recognizes these two phosphorylation sites.[128] Other substitution studies have shown that phosphorylation of Ser471, 472, 483, 484 and 487 also contributes to its activation.[129–131] For mouse IRF7, Ser425 and 426 are considered as the critical phosphorylation/activation sites.[78]

The kinases identified for IRF7 phosphorylation include IKKε, TBK1 (refs 132–135), IRAK1 (ref. 136) and IKKα,[137] which may phosphorylate IRF7 in cell typespecific manner. Study with knockout mice has indicated that the two IκB kinases, IKKε and TBK1, are the major kinases for IRF3/7 phosphorylation and activation.[134] IRAK1 is involved in MyD88-dependent TLR7/9 signaling leading to IRF7 activation in pDCs.[136] IRAK1 phosphorylates IRF7 *in vitro*, and kinase-dead IRAK1 can inhibit MyD88-dependent production of type I IFNs. IRAK1 is autophosphorylated, dissociates from the receptor complex, and associates with and activates TRAF6, which subsequently activates TAK1. At the same time, IRAK1 autophosphorylation may lead to its inactivation and therefore inhibits IRF7 in TLR and RLR responses. So IRAK1 may not be a kinase for IRF7 *in vivo*.[138] IKKα is critical for IRF7 activation in TLR7/9 signaling cascades in pDCs.[137] A later study has shown that the NFκB-inducing kinase differentially regulates IKKα in IRF7/3 activation.[139] NFκB-inducing kinase can phosphorylate IKKα at Ser176 and Ser180. Substitution of these two residues with glutamate mimics IKKα phosphorylation. Although IKKα(S176E) activates IRF3/7, IKKα(S180E) does not.[139]

LMP1 also promotes IRF7 phosphorylation and activation,[68] and likely targets the same two major sites, Ser477/479, as the phosphorylation-deficient mutant, IRF7(S477A/479A), could not be activated by LMP1 (ref. 71). Further investigation is necessary to identify the kinases involved in LMP1 activation of IRF7.

Ubiquitination—The immune system is under stringent regulation in order to orchestrate an appropriate immune response.[140] As with its role in other biological processes, ubiquitination is one of the most important regulatory mechanisms in the immune system.[140] The well studied type of ubiquitination is K48-linked polyubiquitination, which is known as the principal process whereby proteins are targeted for proteasomal degradation through the 26S proteosome. In recent years, proteasome-independent functions for non-degradative ubiquitination, especially K63-linked polyubiquitination and monoubiquitination, have been

identified. The importance of these ubiquitination and other ubiquitination-like events such as sumoylation and acetylation in a variety of cellular processes, including receptor internalization (endocytosis), vesicle trafficking, DNA repair, stress responses and protein kinase activation, is becoming increasingly recognized.[141–143]

IRFs are also regulated by ubiquitination.[144] IRF3 (ref. 97) and IRF7 (refs 89, 104, 145) have been reported to be degraded by virus infection through the ubiquitination pathway. Ubiquitination of IRF7 and −3 by the HECT E3 ligase RAUL results in their degradation and consequently restricts type I IFN responses.[145] Ubiquitination of IRF3 by the E3 ubiquitin ligase RNF54, which is also called RBCC protein interacting with PKC1 (RBCK1) (ref. 146), or by the TRIM E3 ligase TRIM21/Ro52 (ref. 147) results in IRF3 degradation through proteosome-dependent pathway. A recent study has also shown that Ro52 interacts with IRF7 and promotes IRF7 ubiquitination and degradation.[148] IRF6 has recently been linked to degradation through the ubiquitination pathway induced by cellular proliferation signaling.[149] IRF8 is degraded by Cbl-mediated ubiquitination.[150] The cellular levels of IRF1 (ref. 151) and IRF7 (ref. 89) under normal physiological conditions are also controlled by ubiquitination.

More interesting and importantly, accumulating evidence has supported an innovative concept that ubiquitination is required for activation of IRF7 (refs 70, 71), IRF3 (refs 152, 153), IRF5 (ref. 154), IRF2 (ref. 155) and IRF8 (ref. 156). Our recent study has shown that the TRAF6 E3 ligase promotes K63-linked polyubiquitination of IRF7 (ref. 70), and this modification is required for IRF7 activation by EBV LMP1 and IKKε.[70] Similarly, TRAF6 also promotes K63-linked polyubiquitination of IRF5, and this polyubiquitination is required for IRF5 transactivation of the *Ifna* promoter and nuclear translocation.[154] Biochemical evidence from a cell-free system has shown that Ubc5-mediated K63-linked polyubiquitination has a key role in IRF3 activation.[153] Thus, K63-linked polyubiquitination may be a common mechanism for activation of IRFs, and is likely a prerequisite for their phosphorylation. We are now investigating this hypothesis using IRF7 as a model; this study may uncover the mechanism of regulatory ubiquitination as a key missing link in the activation of IRFs.

In addition to its role in activation of IRFs and regulation of their stability, ubiquitination also positively and negatively regulates the transcriptional activity of IRFs.[97] For example, ubiquitination of IRF3 by TRIM21 was recently shown to be required for sustaining IRF3 activity after viral infection.[157] The murine hepatitis virus-encoded deubiquitinase PLP2 deubiquitinates IRF3 and prevents its nuclear translocation, and therefore impairs IRF3-mediated type I IFN production.[152] In contrast to RNF54 that specifically interacts with IRF3, TRIM21 also interacts with IRF7 and −8. However, TRIM21-mediated ubiquitination of IRF8 enhances its cytokine production ability in macrophages.[156] MDM2, a ubiquitin E3 ligase targeting P53 for degradation, has been identified as E3 ligase for IRF2, and ubiquitination of IRF2 by MDM2 may attenuate the function of IRF2 as a transcriptional repressor.[155]

Sumoylation—Small ubiquitin-related modifiers (SUMOs) are a ubiquitin-like protein family, which includes SUMO1, −2 and −3 in higher eukaryotes. Protein modification

mediated by SUMOs (sumoylation) generally occurs on lysines located in the motif ψKxE where ψ is a large hydrophobic residue. Like non-degradative ubiquitination, the functions of sumoylation include but are not limited to: regulation of subcellular localization, protein–protein interaction, DNA-binding, transcription, DNA repair, chromosomal functions and signal transduction.[158,159]

Recently, mouse IRF7 was reported to be sumoylated in response to viral infection, and the authors also identified K406 as the sumoylation site,[160] a site corresponding to human IRF7 K452, which we also have shown to be likely a site for TRAF6-mediated ubiquitination.[70] IRF7 sumoylation is mediated by PIAS1 (ref. 102). However, mutation of K406 to R406 did not abolish IRF7 sumoylation promoted by Ebola Zaire virus VP35 protein, indicating that there are other potential sumoylation site(s), one of which is K43 (corresponding to human IRF7A K45),[102] and human IRF7A(K45R) can barely activate IFN promoter constructs.[161] In contrast to K63-linked ubiquitination that promotes IRF7 activation, sumoylation negatively regulates the transcriptional activity of IRF7 and -3 (ref. 160). Similarly, IRF1 (refs 162–164), IRF2 (ref. 165) and IRF3 (refs 102, 160) have been shown to be sumoylated. Sumoylated IRF1 was elevated in tumor cells,[164] and displays oncogenic potential by interfering with IRF1-mediated apoptosis,[163] as well as enhanced resistance to degradation.[163] PIAS3 has been identified as a SUMO1 ligase for IRF1, and the PIAS3-mediated sumoylation represses IRF1 transcriptional activity in reporter assays,[162] but the physiological significance has not been investigated. Sumoylation of IRF2 by PIAS4 has no significant effects on its nuclear localization and DNA-binding activity, but increases its ability to inhibit IRF1 transcriptional activity and decreases its ability to activate the IFN-stimulated response element and H4 promoters.[165]

Acetylation—In addition to phosphorylation, ubiquitination and sumoylation, IRF7 also undergoes lysine acetylation in response to Newcastle disease virus infection. IRF7 is acetylated by the histone acetyltransferases p300/CREB-binding protein-associated factor and GCN5 on the position K92, and the acetylation impairs IRF7 DNA-binding activity.[166] The mutant, IRF7(K92R) lost DNA-binding activity whereas another mutant, IRF7(G90T/T93R), which retains K92 but cannot be acetylated, showed increased DNA-binding ability compared with wild-type IRF7 (ref. 166), suggesting other modification(s) on K92 may be critical for IRF7 DNA binding. IRF1 and -2 were also shown to be acetylated by p300 and p300/CREB-binding protein-associated factor following 12-o-tetradecanoylphonol-13-acetate treatment, which induces expression of p300 and p300/CREB-binding protein-associated factor.[167,168] Under physiological conditions, acetylation of IRF2 is likely required for its transactivation of the H4 promoter, which is dependent on cell growth.[167] Besides K92, K45 and K120 of human IRF7 were also acetylated when overexpressed, as identified by mass spectrometry.[169] Other IRF family members also undergo lysine acetylation.[169] In contrast to IRF7, acetylation of IRF3 by CREB-binding protein unmasks its DBD and thus facilitates its activation.[170] Acetylation of IRF9 on K81 may be required for its DNA binding, as the mutant, IRF9(K81R) lost DNA-binding activity.[169] However, this mutant may mask other modifications on this site such as ubiquitination, which may indeed be required for IRF9 DNA binding.

Promoter methylation

The IRF7 promoter contains a putative CpG island flanking the TATA box. The CpG island is endogenously methylated in the human fibroblasts, 2fTGH. Methylation of the IRF7 promoter results in *Irf7* gene silencing in these cells, even in the presence of IFN treatment. 5-AzaC, an inhibitor of methyltransferase, can restore IRF7 expression in 2fTGH cells.[82] Methylation of the IRF7 promoter is also found in immortalized fibroblasts from Li-Fraumeni syndrome[171] and in lung cancer cell lines.[172]

Functions of IRF7

IRFs have been involved in regulation of a variety of cellular functions. Besides their roles in IFN-mediated immune responses, IRFs also have a role in leukemia and other malignancies in many cell types,[173] and in regulation of cell growth and apoptosis, and they therefore affect susceptibility to and the progression of cancer. Another important function conferred by IRFs is the regulation of immune cell differentiation and activation. In addition, IRFs, especially IRF5, has been shown to be involved in several autoimmune diseases such as systemic lupus erythematosus (SLE).[174]

IRF7 as the `master' regulator of type I IFN production

Type I IFNs, encoded by a single *Ifnb* and 13 closely related *Ifna* genes that are all clustered on human chromosome 9p22, constitute a highly pleiotropic cytokine family that participates not only in immune modulation, including pathogen-elicited innate immune and subsequent adaptive immune responses, as well as autoimmune responses, but also in oncogenesis, cellular development and homeostasis. Aberrant production of IFNs is associated with many types of diseases, such as cancers, immune disorders and multiple sclerosis.[175–179] Thus, fine regulation of type I IFN production is critical to maintain homeostasis. IFNs exert their functions through induction of >300 IFN-inducible genes such as dsRNA-dependent protein kinase, inducible nitric oxide synthase, STAT1, 2′,5′-OAS, major histocompatibility complex class I, Mx GTPase, IKKε, TRIM5α, caspase-1, melanoma differentiation associated gene 5, P53 and IRF7 (refs 175, 180).

Five IRFs, IRF1, -3, -5, -7 and -8 (ref. 181) are positive regulators of type I IFNs in different cell types,[182] but IRF1, -5 and -8 are not necessary for induction of type I IFNs. Although both IRF3 and -7 are required for efficient IFN production in most immune cells, their functions are not redundant and have distinct roles. A recent study has shown that IRF3, which is constitutively expressed in most cells, is crucial for initial induction of IFNβ and IFNα1 (ref. 183). However, the constitutive low levels of IRF7 present in most immune cells are indispensable for this priming, and more importantly, IRF7 has a major role in subsequent feedback amplification of both IFNαs and IFNβ when new IRF7 is synthesized but IRF3 is degraded, in spite of the dependence on MyD88 and in both innate and adaptive immunity.[18] In IRF7 knockout mice, MyD88-independent production of type I IFNs was severely impaired. No type I IFNs were produced in MyD88-dependent pathway in pDCs.[174] The late-phase production of IFNs greatly amplifies protective responses and is important for initiation of adaptive immunity. In addition, at specific stages, IRF3 and -7

physically bind and together with other transcription factors such as NFκB, cooperatively regulate the *Ifnb* promoter.[18,80]

pDCs are `professional' producers for type I IFNs, in which both TLR7 and IRF7 are expressed at extremely high levels even in the absence of virus infection. TLR7 recognizes single-stranded RNA released from many RNA viruses such as human immunodeficiency virus,[184] hepatitis C virus,[185] vescular stomatitis virus and influenza virus, and produce type I IFNs mainly through activation of IRF7. TLR9, which recognizes CpG DNA from DNA viruses such as herpes simplex virus 1, is also expressed at a high level in these cells and dominantly activates IRF7 for production of type I IFNs.[186]

IRF7 in regulation of oncogenesis and apoptosis

In addition to regulation of immune responses, another important function of IRFs is their role in regulation of oncogenesis and apoptosis.[5,19,182,187]

IRF1 can induce cell cycle arrest and apoptosis, has obvious tumor-suppressor function, and is a new member of the tumor susceptibility genes.[188] IRF2 and -4 have oncogenic potential.[83,189] IRF2 may execute its oncogenic function via antagonizing IRF1. IRF4 targets c-Myc and vice versa.[189] Knockdown of IRF4 by short hairpin RNA in EBV-positive lymphoblastoid cells decreases cell division and increases apoptosis,[83] and induces a rapid and profound non-apoptotic cell death in multiple myeloma cell lines.[189] Single-nucleotide polymorphisms of *Irf4* 3′-UTR are strongly associated with chronic lymphocytic leukemia susceptibility.[190] IRF4 may need additional factors to exert its oncogenic function. IRF3 can mediate virus-induced apoptosis[191–193] through activation of the Bcl2 family member Bax.[194] Aberrant expression of IRF3 and its variants have also been detected in human lung cancer.[195] IRF5 mediates stress-induced cell cycle arrest and p53-independent, TNF-related apoptosis-inducing ligand/Fas-dependent apoptosis in a cell type-dependent manner, and inhibits the growth of tumor cells both *in vitro* and *in vivo*.[196–198] TNF-related apoptosis-inducing ligand triggers a signal leading to IRF5 phosphorylation and nuclear translocation,[198] whereas activation of Fas receptor did not result in IRF5 nuclear translocation.[196] Moreover, IRF5 is a direct target of the tumor suppressor p53, and like p53, is a candidate tumor suppressor.[199] In addition, IRF4 and -8 regulate telomerase activity in immune cells.[200] IRF8 also has tumor-suppressor function and downregulates Bcl-2 expression,[201] and its mRNA expression is reduced in chronic myeloid leukemia and acute myelogenous leukemia.[202] IRF6 expression is reduced or absent in breast carcinomas, and may be a tumor suppressor.[149]

Like IRF2 and -4, IRF7 has oncogenic properties, as indicated by several lines of evidence from our studies and others: (i) IRF7 is induced and activated by EBV LMP1 in EBV latency programs, which are associated with a variety of malignancies.[203] (ii) IRF7 is over-expressed in EBV-positive central nervous system lymphomas,[204] as well as in EBV-negative acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and adult T-cell leukemia/lymphoma.[205,206] (iii) IRF7 induces expression of the EBV principal oncoprotein LMP1 so that they form a regulatory circuit that may potentiate oncogenic effects of both factors.[120] (iv) Moreover, IRF7-expressing NIH 3T3 cells induce tumor formation in nude mice.

Importantly, our data show that IRF4 upregulates expression of miR-155 in EBV latency. However, in this setting, IRF7 has little if any effect (to be published). In addition to its role in innate immunity,[207,208] miR-155 is the first oncogenic microRNA shown to have increased expression in cancers,[209] and is now believed to be critical for various types of cancers.[210,211] Like IRF7 and -4, miR-155 is also associated with EBV latency as it is induced by LMP1 (refs 212–214).

On the other hand, IRF7 has antitumor effects in macrophages,[192] partially through induction of TNF-related apoptosis-inducing ligand,[215] a TNF superfamily member that induces caspase-8-dependent apoptosis selectively in tumor cells but not in normal cells. Other experimental data supporting IRF7's antitumor effects include that IRF7 is induced by the tumor-suppressor BRCA1 in response to IFN-γ signaling in MDA-derived breast cancer cell lines and overexpressed IRF7 inhibits growth of MCF-7 breast cancer cells,[216] and that IRF7 may be potentially activated by DNA-damaging reagents as exogenously expressed IRF7 is translocated to the nucleus in response to these reagents in HeLa,[217] a cervical carcinoma cell line. In addition, IRF7 is not expressed in fibrosarcoma cells,[82] Li-Fraumeni Syndrome fibroblasts[171] and lung cancer cell lines,[172] because of promoter methylation. Thus, IRF7 regulation of oncogenesis may be cell type dependent.

Role of IRF7 in the EBV context

As stated above, the IRF family is tightly associated with EBV latency. Although IRF2, −4 and −7 are believed to be positive regulators of EBV oncogenesis, IRF5 may be a negative regulator of it. IRF5 expressed in EBV-infected cells has at least two natural variants, a truncation mutant V12 (ref. 121) and a point mutant IRF5(A68P),[123] both of which function as dominant-negative mutants. In fact, we have shown that IRF5 in EBV-infected B cells negatively regulates LMP1-promoted IRF7 activity.[92] The point mutant IRF5(A68P) also exists in adult T cell leukemia and chronic lymphocytic leukemia.[123] Both IRF5(V12) and IRF4 in the EBV context are able to neutralize TLR7 ligand-induced cell growth inhibition. Like IRF7, IRF2 is constitutively expressed at a low level in type I latency,[218,219] but at a higher level and represses Qp in type III latency.[84] In addition, as with its role in antiviral responses,[220] IRF4 may negatively regulate TLR7 activation of IRF5 in EBV latency (Figure 2).

Although along with others, we have presented overwhelming evidence that IRF7 is associated with EBV latency and has oncogenic properties, the role of IRF7 in oncogenesis remains unclear. IRF7 itself may be an oncoprotein targeted by LMP1. More likely, as a transcription factor, IRF7 may exert this function through regulation of a set of genes involved in regulation of cell growth and proliferation in EBV-transformed cells. However, until now, no such targets have been identified except the gene encoding the viral oncoprotein LMP1 (ref. 120), and *Bam*H I-A rightward transcript P1 promoter[221] (Figure 2). *Bam*H I-A rightward transcript-derived microRNAs downregulate LMP1 expression and regulate LMP1 signaling in nasopharyngeal carcinoma cells and therefore have a role in EBV oncogenesis.[222] By microarray analysis from shIRF7-expressing EBV-transformed cells, we have identified many cellular genes targeted by IRF7 such as apoptosis inhibitor 5 and c-IAP1/2 (data not shown). Some of these genes overlap with those targeted by the

LMP1/NFκB pathway. Thus, the LMP1/IRF7 pathway may cooperate with the LMP1/NFκB pathway in EBV oncogenesis.

Although IRF7 is the key regulator of type I IFNs, EBV does not induce substantial type I IFNs in latency where it activates IRF7 (ref. 22). Understanding the underlying mechanism of this paradox is of vital importance as the outcomes of the interaction between EBV and IFN signaling shape the immune response to viral infection as well as affect aspects of host cell proliferation and survival. In addition, LMP1-activated IRF7 induces TAP2, type I IFNs and other IFN-stimulated genes upon superinfection and therefore helps to establish cellular antiviral states in EBV latency[68,223,224] (Figure 2).

Besides these roles, the LMP1/IRF7 pathway also contributes to maintenance of EBV long-term latency as IRF7 inhibits activity of the EBNA1 Q promoter in type III latency.[21]

IRF7 in autoimmune diseases

Although PRR recognition of pathogenic nucleic acids orchestrates immune responses for defense, recognition of cellular `self' nucleic acids derived from tissue damage produces aberrant type I IFNs, which have received particular attention because of their role in autoimmune diseases such as SLE and rheumatoid arthritis.[225] SLE is characterized by `IFN signature' in the serum.[226] Nucleic acid-recognizing TLRs (TLR3, −7, −8 and −9) and RLRs, 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.[18,177,226] RNAs in these immune complexes have 5′-triphosphates, which are required for RIG-I recognition.[39] In addition, whether the recently identified PRR, DNA-dependent activator of IRF, is also able to recognize `self' DNA and contributes to autoimmune diseases merits study.

It is evident that single-nucleotide polymorphisms of *Irf5* are linked to lupus,[227] although the functional interaction is unclear. Recent work has shown that high levels of IRF1 are expressed in myelodysplastic syndrome patients with autoimmune disease.[228] Given that IRF7 is also activated by TLR3/7/9 and RIG-I in response to nucleic acids, and that pDCs, in which the TLR7/IRF7 pathway governs type I IFN production, secrete a large amount of IFNα in response to immune complexes and has a role in autoimmune diseases, IRF7 may also be involved in these diseases.[18,225,229] In fact, IRF7/3 recognize undegraded chromosomal DNAs released from apoptotic cells in macrophages,[230] and furthermore, a genome-wide association study has identified rs4963128, a KIAA1542 single-nucleotide polymorphism 23 kb telomeric to IRF7, in strong association with SLE.[231] A recent study of single-nucleotide polymorphisms in the *Irf7*/*Phrf1* locus also has indicated that genetic variants of *Irf7* act as risk factors for SLE, but the role needs to be further clarified.[232] Another recent study has shown that the functional IRF7 variant rs1131665 (Q412R) is associated with SLE.[233] In addition, IRF7 is implicated in the pathogenesis of type I diabetes.[234]

IRF7 in cell differentiation

The role of IRFs in regulation of the development and activation of hematopoietic cells accounts for their involvement in both innate and adaptive immune responses. IRF4, −8, −1 and −2 have been shown to have diverse roles in controlling the development, maturation and function of hematopoietic cells, including lymphoid and myeloid lineages, as well as DC subsets, which can be derived from both lymphoid and myeloid progenitors. Both IRF4 and −8 interact with PU.1, an immune cell-specific protein of the Ets family.[20,182,235] IRF5 has recently been shown to have a critical role in regulation of B-cell differentiation.[236]

Involvement of IRF7 in cell differentiation is poorly understood, and only one study has shown that IRF7 is required for monocyte differentiation to macrophages, but the mechanism remains unclear.[237] Given that virus-induced type I IFNs can drive pDC maturation from immature circulating cells to differentiated cells that contribute to adaptive immunity, IRF7 may have an indispensable role in DC differentiation. IRF7 is also involved in expression of CCL19, which has a central role in DC biology.[238] In addition, we have results showing that IRF7 regulates expression of MyD88 and macrophage colony-stimulating factor, two critical factors involved in cell differentiation (to be published).

Other functions

Compared with the closest family member IRF3 that has a strict DNA-binding specificity to GAAANNGAAANN, IRF7 binds to a wider DNA consensus sequence GAAWNYGAAANY.[239] This means IRF7 has the ability to regulate a larger range of target genes, which may be involved in diverse cellular processes. For example, IRF7, but not IRF3, is associated with EBV latency. IRF7 directly induces expression of IRF1 and LMP2, two key players in adaptive immunity.[240] IRF3 has only been found to function in antiviral innate immunity and virus-induced apoptosis.[17,192] Moreover, the consensus DNA-binding motif of IRF7 has been found in promoters of many oncogenes,[18] and microarray results from the stable cell line BJAB–IRF7 have shown that IRF7 induces a subset of pro-apoptotic proteins, as well as a group of mitochondrial genes and genes affecting the DNA structure.[241]

Questions

The importance of IRF7 in the immune system has been quickly recognized since its discovery in the EBV context. However, IRF7 has been less studied in immunity compared with IRF3, in apoptosis compared with IRF1 and −5, in oncogenesis compared with IRF2 and −4, in cell differentiation compared with IRF4 and −8, and in autoimmune diseases compared with IRF5 and −1. There are many questions to be addressed.

(1) Structural and functional domains. Crystal structure has been reported for other family members but not for IRF7. The functional domains of IRF7 have only been characterized by deletion analysis, and the underlying mechanisms are not understood. For example, why is the virus-activation domain important for its activation? Moreover, functions of isoforms other than IRF7A are not clear. Recently, IRF7C has been shown to inhibit IRF7A transcriptional activation of

Ifn genes, and like IRF7A, is associated with EBV latency and has oncogenic potential, as it produces anchorage-independent growth of NIH 3T3 cells.[242]

(2) Physiological targets. Transcriptional target genes of IRF7 in the EBV context and in the immune system have not been profiled. As a transcription factor, comprehensive profiling of IRF7 target genes is not only important for better understanding of its known roles in immune responses and EBV latency, but also important for revealing its novel functions in other biological processes. Although one report has identified genes targeted by IRF7 using BJAB cells stably expressing IRF7 (ref. 241), these identified genes may not represent those targets under physiological settings.

(3) Regulation of expression. Study of IRF7 regulation is important as its expression is lymphoid specific. Although it has been shown that pDCs express a very high level of the translational inhibitors 4E-BP1 and -2, which may account for the extremely high level of IRF7 in pDCs,[87] the molecular mechanism requires further clarification. In addition to the binding sites responsible for NFκB and IFN induction, which have been identified, other potentially functional cis-regulatory elements recognized by transcription factors such as c-myc, Sp1 and SREBP exist in the IRF7 promoter.[82] Regulation of IRF7 expression by microRNA has not been reported.

(4) Functional regulation. Deregulation of type I IFNs is associated with many types of diseases including cancers. As the `master' regulator of type I IFNs, fine regulation of IRF7 activity is thus necessary for its functions for normal immune responses as well as many other fundamental cellular processes involving IFNs. However, most studies have focused on its activation although accumulating evidence has identified viral proteins, which counteract its functions. Cellular proteins such as transcriptional co-regulators involved in regulation of IRF7 have been rarely identified.

(5) Posttranslational modifications. Accumulating evidence shows that IRF7 undergoes many types of PTMs including phosphorylation, ubiquitination, sumoylation and acetylation, which are critical for regulation of its functions. Thus, understanding these PTMs in regulation of IRF7 may have an important impact on the field of innate immunity. However, except for phosphorylation, other PTMs of IRF7 and their interplay are poorly understood; even its phosphorylation sites have not been fully profiled. Moreover, the role of ubiquitination in activating and regulating IRF7 activity is not established. In addition, all the sites undergoing modifications have been identified by amino acid substitution, which may mask other PTMs or its function. Thus, employment of contemporary approaches such as mass spectrometry, which is still under development in this field, will be important for identification of these sites.

(6) Can any signaling pathways other than those triggered by LMP1 and TLR/RLR innate immunity activate IRF7? For example, LMP1 mimics CD40, BCR, TNF receptor and TLR in many facets of signaling transduction.[73,75] Since LMP1

and TLR activate IRF7, does any other similar signaling pathway activate IRF7? Activation of IRF7 by other signaling pathways may endow IRF7 with important novel functions in the corresponding biological contexts. In fact, IRF7 is potentially activated by DNA-damaging reagents through MKK4-JNK pathway,[217] suggesting that IRF7 may have a role in DNA damage response.

(7) Key signaling intermediaries for IRF7 activation. In past years, extensive efforts have been focused on the immune signaling pathways leading to IRF3/7 activation, and an increasing list of the signaling intermediaries have been identified, including STING, TRAF3, IKKs and others. However, an entire and clear picture of the signaling cascade is still a distant prospect.

(8) All known functions for IRF7 so far are as a transcription factor in the nucleus. Does IRF7 have other functions in the cytoplasm? P53 is believed to promote apoptotic events directly in the cytoplasm, independent of its role as a transcription factor.[243]

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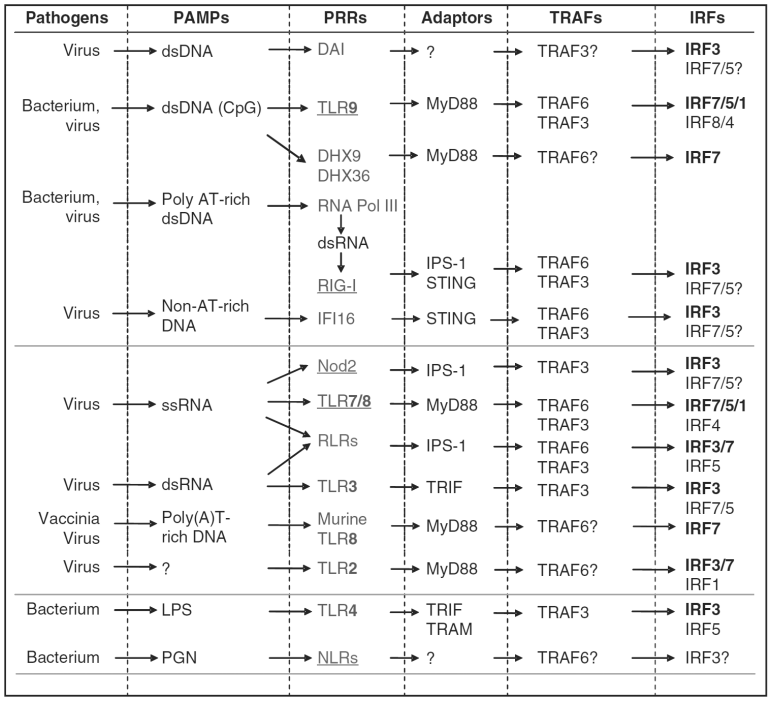

Figure 1.

Activation of IRFs through signaling pathways triggered by different PRRs. Pathogen-associated molecular patterns (PAMPs) derived from invading pathogens are recognized by distinct PRRs located on the membranes of endosomal compartments and trigger signaling cascades, which lead to activation of IRFs and type I IFN production in the host cell.

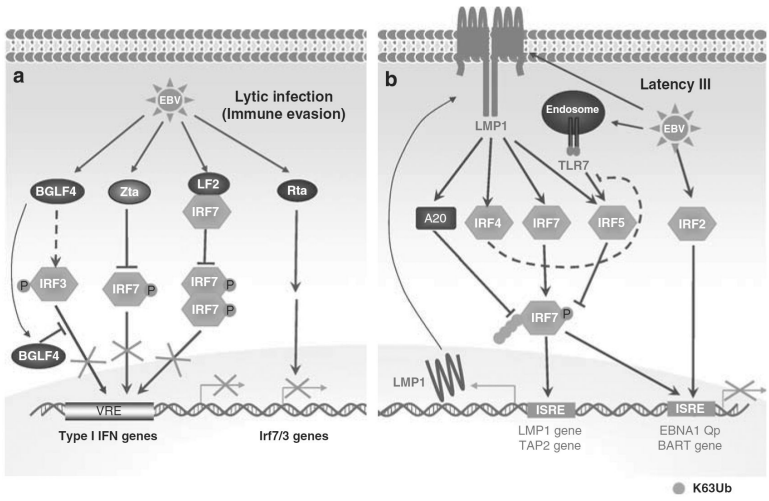

Figure 2.

Regulation of IRFs in EBV lytic and latent infections. (**a**) Lytic infection. BGLF4 phosphorylates IRF3, but blocks its DNA-binding activity. Zta inhibits IRF7 transcriptional activity and RTA downregulates expression of IRF7 and -3 through unclear mechanisms. LF2 interacts with IRF7 and therefore blocks its dimerization and transcriptional activity. (**b**) Latency 3. EBV LMP1 induces expression of IRF7, -4, -5 and A20. LMP1 also activates IRF7 through ubiquitination, but A20 inhibits LMP1-stimulated IRF7 ubiquitination and activity. IRF7 induces expression of LMP1 and TAP2, but inhibits *Bam*H I-A rightward transcript (BART) transcript. EBV also induces expression of TLR7 and its downstream target IRF5, and IRF5 inhibits IRF7 through dimerization with IRF7. EBV also induces IRF2 through unknown mechanism.