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REVIEW

Regulation of immunity and oncogenesis by the IRF transcription factor family

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Abstract Nine interferon regulatory factors (IRFs) compose a family of transcription factors in mammals. Although this family was originally identified in the context of the type I interferon system, subsequent studies have revealed much broader functions performed by IRF members in host defense. In this review, we provide an update on the current knowledge of their roles in immune responses, immune cell development, and regulation of oncogenesis.

Keywords Interferon regulatory factor · Host defense · Transcriptional regulation · Immunity · Oncogenesis

Introduction

The mammalian interferon regulatory factor (IRF) family of transcription factors comprises nine members: IRF1, IRF2, IRF3, IRF4/PIP/LSIRF/ICSAT, IRF5, IRF6, IRF7, IRF8/ICSBP, and IRF9/ISGF3γ (Table 1) [1, 2]. IRFs were first characterized as transcriptional regulators of type I interferon (IFN) and IFN-inducible genes, but recent studies have revealed that this family plays a pivotal role in the regulation of host defense beyond its function in the IFN system.

All IRF proteins possess an amino (N)-terminal DNA binding domain (DBD) that is characterized by a series of five well-conserved tryptophan-rich repeats [1, 2]. The DBD forms a helix-turn-helix domain and recognizes DNA similar in sequence to the IFN-stimulated response element (ISRE, $^{A}/_{G}$NGAAANNGAAACT). 5′-GAAA-3′ is the core sequence shown to be recognized by the helix-turn-helix of IRF1 bound to the PRDI of the IFN-β enhancer. Moreover, a subsequent crystal structure analysis between the IRF2 DBD bound to a tandem repeat of GAAA revealed that 5′-AANNGAAA-3′ is the consensus IRF recognition sequence [3].

The carboxy (C)-terminal regions of IRFs are less well conserved and mediate interactions with other IRF members, other transcriptional factors, or cofactors, thereby conferring specific activities upon each IRF. Even so, two types of association modules have been identified within the C-terminal region of certain IRFs [4]: IRF-associated domain 1 (IAD1) [1], which is conserved in all IRFs except IRF1 and IRF2 and possesses structural similarities with the Mad-homology 2 (MH2) domains of the Smad family of transcription factors; and IAD2 [2], which is shared by IRF1 and IRF2 only. The nature of the protein–protein interaction dictated by these domains may determine whether the protein complex functions as a transcriptional activator or repressor, and define the nucleotide sequences adjacent to the core IRF binding motif to which the protein complex binds. For example, IRF9 acts as a DNA-binding subunit in association with signal transducer and activator of transcription 1 (STAT1) and STAT2 forming the ISGF3 heterotrimeric complex in response to type I IFN, which activates transcription through binding to ISREs [1, 2]. IRF8 can only bind to DNA in association with a partner protein, where IRF8-IRF1 complex generally acts as a transcriptional repressor on ISREs, and IRF8-PU.1 complex an activator on DNA elements composed of core IRF- and Ets-binding sites (also see below). IRF1, IRF3, and IRF7 participate in the formation of a large protein complex called an IFN-β enhanceosome/DRAF1 that also includes nuclear

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Table 1 Basic features of IRF members

IRF	Chromosome (human)	Amino acids		Expression	Localization and modification
		Human	Mouse		
IRF1	5q31.1	325	329	Constitutive and IFN-inducible in various cell types Inducible by DNA damage at transcriptional and posttranslational levels	Mainly in the nucleus and partially in the cytoplasm Modified by TLR signaling to efficiently translocate to the nucleus
IRF2	4q34.1-q35.1	349	349	Constitutive and IFN-inducible in various cell types	Mainly in the nucleus
IRF3	19q13.3-q13.4	427	419	Constitutive in various cell types	Mainly in the cytoplasm Phosphorylated upon virus infection, TRIF-dependent signaling, cytosolic PRR signaling and DNA damage and then translocates to the nucleus
IRF4	6p25-p23	451	450	Constitutive in B cells, MΦs, $CD11b^+$ DCs and pDCs Inducible by antigen stimulation in T cells and by TLR signaling in MΦs	Mainly in the nucleus and partially in the cytoplasm
IRF5	7q32	488	497	Constitutive in B cells and DCs Inducible by type I IFNs, TLR signaling and DNA damage in various cells	Mainly in the cytoplasm Phosphorylated upon virus infection, TLR signaling and DNA damage, and then translocates to the nucleus
IRF6	1q32.3-q41	467	467	Constitutive in skin	Mainly in the cytoplasm Phosphorylated and ubiquitinated when stimulated to enter cell cycle Translocates from the cytoplasm to the nucleus upon poly(rI:rC) treatment
IRF7	11p15.5	503	457	Constitutive in B cells, pDCs and monocytes Inducible by type I IFNs in various cell types	Mainly in the cytoplasm Phosphorylated upon virus infection and MyD88-dependent signaling, and then translocates to the nucleus
IRF8	16q24.1	426	424	Constitutive in B cells, MΦs, $CD8\alpha^+$ DCs and pDCs Inducible by IFN-γ in MΦs and by antigen stimulation in T cells	Mainly in the nucleus and partially in the cytoplasm
IRF9	14q11.2	393	399	Constitutive and inducible by IFN-γ in various cell types	Mainly in the nucleus

factor-κB (NF-κB), activator protein 1 (AP1), and co-activators CREB binding protein (CBP)/p300 to activate transcription of the IFN-β gene [5, 6].

In this review, we summarize the current knowledge of how IRFs contribute to the host defense, namely innate immune responses, immune cell development, and tumor suppression. Related review articles on IRFs published elsewhere are cited here [6–10].

Regulation of innate immune responses by IRFs

Detection of invading pathogens is a cardinal function of the host immune system. A limited repertoire of germline-encoded receptors called pattern recognition receptors (PRRs) is utilized by the innate immune system to recognize invariant pathogen-associated molecular patterns (PAMPs) present on potential pathogens such as bacteria and viruses [11]. Thus far, two broad classes of PRRs, cytosolic PRRs and membrane-bound Toll-like receptors (TLRs), have been identified [7, 11, 12]. Though dependent on the nature of the pathogen and host cell type, engagement of PRRs by PAMP typically results in the expression of type I IFNs, proinflammatory cytokines and chemokines. Of the cellular signaling pathways that link receptor activation and gene induction, nuclear factor-κB (NF-κB) is the best characterized and one of the most important given that is activated by almost all PRRs. In recent years,

Table 2 A summary of the role for IRFs in immune responses

IRF	Roles in immune responses	Proteins encoded by target genes
IRF1	Stimulates expression of IFN-inducible gene	GBP, iNOS, Caspase-1, Cox-2, CIITA, TAP1, and LMP2
	Binds to MyD88 and enhances TLR-dependent gene induction in IFN-γ-treated cells	IFN-β, iNOS, IL-12p35 and IL-12p40
IRF2	Attenuates type I IFN responses by antagonizing IRF1 and IRF9	Represses many IFN-inducible genes IL-12p40 and Cox-2
	In some cases, cooperates with IRF1 to activate transcription	
IRF3	Induces type I IFNs and chemokines upon virus infection, TLR stimulation and cytosolic DNA stimulation	IFN-α4, IFN-β, and CXCL10
IRF4	Binds to MyD88 and negatively regulates TLR-dependent induction of proinflammatory cytokine genes	Indirectly represses induction of cytokine genes, such as IL-12p40, IL-6, and TNF-α
IRF5	Binds to MyD88 and positively regulates TLR-dependent induction of proinflammatory cytokine genes	IL-12p40, IL-6, and TNF-α
	Induces type I IFNs and proinflammatory cytokines upon virus infection	Type I IFNs, IL-6, and TNF-α
IRF6	Unknown, but translocates from the cytoplasm to the nucleus upon poly(rI:rC) treatment	
IRF7	Binds to MyD88 and induces type I IFNs upon TLR signaling	Type I IFNs
	Induces type I IFNs upon virus infection	
IRF8	Binds to TRAF6 and is required for TLR9-signaling in DCs	
	Stimulates IFN-γ- and PAMP-inducible genes	IL-12p40, iNOS, FcγRI, PML and others
	Promotes type I IFN production in DCs	Type I IFNs
IRF9	Binds to STAT1 and STAT2 to form ISGF3 and stimulates type I IFN-inducible genes	OAS, PKR, IRF7, and many others

an extensive number of studies have revealed important and interesting functions for IRFs in most PRR signaling events (Table 2).

IRFs in cytosolic PRR signaling

IRF3, IRF7, and other IRFs in RIG-I/MDA5 signaling

Two RNA helicase enzymes, retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5), are essential cytosolic receptors for the detection of RNA, in particular uncapped 5′-triphosphate RNA and double stranded (ds)RNA including poly(rI:rC) [13–16]. Both helicases contain a C-terminal DExD/H box RNA helicase domain, responsible for the detection of viral RNA, as well as two N-terminal caspase-recruitment and activation domains (CARDs) which activate downstream signaling pathways. The adaptor molecule that links the sensing of viral RNA by RIG-I or MDA5 to downstream signaling is IFNB-promoter stimulator 1 (IPS-1, also known as VISA, MAVS or Cardif) [12]. IPS-1 contains an N-terminal CARD domain that mediates CARD–CARD interactions with the CARDs of RIG-I and MDA5 to transmit downstream signaling. IPS-1 relays signals from RIG-I and MDA5 to TANK-binding kinase 1 (TBK1) and inhibitor of NF-κB kinase ε (IKKε) that are known to phosphorylate IRF3 and IRF7 [17, 18].

IRF3 and IRF7, the two IRFs with the greatest sequence homology to one another, are essential for the RIG-I/MDA5-mediated type I IFN gene induction pathway. IRF3 and IRF7 initially reside in latent form in the cytosol of uninfected cells. Upon virus infection, RIG-I- or MDA5-activated TBK1 phosphorylates IRF3 at Ser396, 398, 402, 404, and 405 in site 2 of the carboxy (C)-terminal regulatory region, which alleviates auto-inhibition and permits IRF3 nuclear translocation and interaction with the coactivator CBP. CBP then facilitates phosphorylation of Ser385 or Ser386 at site 1 within the regulatory region, permitting IRF dimerization [19, 20]. A similar mechanism involving IRF7 is presumed to occur. As a result, a holocomplex containing dimerized IRF3 and IRF7, either as a homodimer or heterodimer, and coactivators such as CBP or p300 is formed in the nucleus [6]. This holocomplex binds to target ISRE DNA sequences within the promoters of type I IFN genes.

In addition, IRF5 is also involved in the RIG-I signaling pathway [21, 22]. IRF5 translocates from the cytoplasm to

the nucleus upon infection by vesicular stomatitis virus (VSV) or Newcastle disease virus (NDV) [21, 23]. Indeed, *Irf5*$^{-/-}$ mice show a reduction in the serum levels of type I IFN when challenged with these RNA viruses [21, 22]. Moreover, *Irf5*$^{-/-}$ mice are highly vulnerable to VSV infection [21]. However, because *Irf5*$^{-/-}$ macrophages (MΦs) are defective in the production of type I IFNs by VSV while *Irf5*$^{-/-}$ MEFs are not (possibly due to a higher expression of IRF5 in hematopoietic cells), there is a cell type-specific requirement for IRF5. In addition, *Irf5*$^{-/-}$ mice show reduced levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) upon virus infection [21, 22]. The precise mechanism by which IRF5 is activated by RIG-I and the nature of IRF5's contribution to the transcriptional regulation of type I IFN and proinflammatory genes remains poorly understood. Nevertheless, like IRF3 and IRF7, IRF5 can be phosphorylated by TBK1 [24].

IRF8 is also required for type I IFN induction in virus-stimulated DCs [25]. IRF8 appears to be involved in the transcriptional regulation of type I IFN genes; IRF8 binds to the promoters of IFN-α/β genes and is required for the second, amplifying phase of IFN transcription.

IRF3 and IRF7 in cytosolic DNA-mediated signaling

In addition to the cytosolic RNA-sensing mechanisms, recent attention has been focused on characterizing cytosolic DNA-sensing systems as they can also evoke protective and pathological immune responses. Indeed, cytoplasmic recognition of bacterial genomic DNA from *Listeria monocytogenes* results in IFN-β induction through the TBK1-IRF3 pathway [26]. Moreover, the transfection of cells with synthetic dsDNA, such as poly(dA-dT)·poly(dT-dA) (termed B-DNA hereafter), results in the induction of type I IFN in the absence of all TLR signaling [26, 27]. These observations indicate the presence of a cytosolic DNA sensor(s) that can independently initiate innate immune responses, including the induction of type I IFN genes. B-DNA stimulation results in the activation of IRF3 and NF-κB signaling pathways [27]. A required role for IRF3 is demonstrated by the observation that the B-DNA induction of IFN-β was abolished in *Irf3*$^{-/-}$ MEFs, but was normal in *Irf7*$^{-/-}$ or *Irf5*$^{-/-}$ MEFs [28]. The induction of IFN-α, however, requires both IRF3 and IRF7, since both *Irf3*$^{-/-}$ and *Irf7*$^{-/-}$ MEFs showed an impairment in its induction.

A candidate DNA sensor called DNA-dependent activator of IRFs (DAI), also known as DLM-1 or Z-DNA binding protein 1 (ZBP1), has been identified and characterized [28]. More recent studies indicate the presence of additional DNA sensors that either positively or negatively regulate cytosolic DNA-mediated innate immune responses [29, 30]. In addition, a new adaptor protein termed stimulator of interferon genes (STING)/mediator of IRF3 activation (MITA) has been reported [31, 32]. STING/MITA forms a complex with IPS-1, TBK1 [31, 32], and IRF3 [32]. The induction of dsDNA-mediated type I IFN gene expression is markedly impaired in STING/MITA-deficient MEFs [31]. These observations indicate that STING/MITA functions as an adaptor that links IPS-1 to TBK1 and the activation of IRF3 following cytosolic DNA-mediated signaling.

IRFs in TLR signaling

TLRs and their adaptors

To date, 13 different TLRs (10 in human and 12 in mice) have been identified which recognize a variety of PAMPs derived from bacteria, virus, fungi, and/or protozoa and trigger immune responses including the induction of proinflammatory and type I IFN genes [12, 33, 34]. Distinct from cytosolic receptors, TLRs are membrane-bound type receptors that utilize adaptor proteins TRIF (TIR-domain-containing adaptor protein inducing IFN and also called TICAM1) or MyD88 (myeloid differentiation primary-response protein 88) to activate NF-κB and IRF transcription factors.

IRF3 and IRF7 in the TRIF-dependent pathway

Both TLR4 and TLR3 utilize the TRIF adaptor protein to activate IRF3 to induce type I IFN [6, 12]. TLR4 is a cell surface receptor that recognizes LPS from gram-negative bacteria, and F (fusion) protein of the respiratory syncytial and Moloney murine leukemia viruses [12]. Albeit weakly, TLR4 signaling results in the induction of the genes encoding IFN-β and IFN-α4 but not other IFN-α genes [35, 36]. Upon stimulation with LPS, IFN-β expression is absent in *Irf3*$^{-/-}$ DCs, but is nearly normal in *Irf7*$^{-/-}$ cells [37, 38]. These findings are consistent with the observation that *Irf3*$^{-/-}$ mice are resistant to LPS-induced endotoxic shock [36]. Thus, in a mechanism similar to the RIG-I pathway, TLR4-induced expression of IFN-β is primarily mediated by TBK1-activated IRF3, rather than by IRF7.

TLR3 is located within the membranes of endosomes and phagosomes, and in addition to the synthetic dsRNA analog poly(rI:rC) likely recognizes viral dsRNA derived from either dsRNA viruses or as replication intermediates from ssRNA viruses [7, 12]. TLR3 is also involved in the defense against infection by some DNA viruses (such as murine cytomegalovirus and herpes simplex virus) or parasites [39–42], suggesting that ligands other than dsRNA might also be recognized by TLR3. The activation of TLR3, like TLR4, can induce type I IFN expression via a TRIF- and TBK1-dependent signaling pathway [12]. IRF3

plays an essential role in this induction [43, 44]. However, a weak induction of type I IFN mRNAs by poly(rI:rC) was still observed in *Irf3*$^{-/-}$ DCs. This residual induction was completely abolished in IRF3 and IRF7 doubly deficient DCs (T. Taniguchi, unpublished observation). Therefore, in contrast to TLR4, IRF3 and IRF7 are both required for the maximal induction of TLR3-TRIF-mediated I IFN gene expression.

IRF7 in the MyD88-dependent signaling pathway

Plasmacytoid dendritic cells (pDCs) are defined by their massive expression of IFN-α/β and, unlike conventional DCs and MEFs, express high amounts of TLR7 and TLR9 in endosomes. In response to ligands for TLR7 and TLR9, pDCs release large amounts type I IFNs. TLR7 is activated upon binding to genomic ssRNA of ssRNA viruses, while TLR9 responds to unmethylated CpG DNA motifs present in bacteria and DNA viruses [12]. TLR9 and TLR7 exclusively utilize MyD88 as its signaling adaptor [12].

IRF7, but not IRF3, directly interacts with the death domain of MyD88 [45, 46] and is essential for the robust MyD88-dependent IFN gene induction in pDCs. Upon infection by DNA and RNA viruses (HSV and VSV, respectively) or treatment with synthetic TLR ligands (CpG-A and ssRNA), splenic pDCs derived from *Irf7*$^{-/-}$ mice exhibit a profound defect in type I IFN gene induction while the induction is normal in *Irf3*$^{-/-}$ pDCs [37]. IRF7 also interacts with TRAF6 whose overexpression induces type I IFN genes through the activation of IRF7 [45]. IRAK1 and IRAK4, the signal transducers between MyD88 and TRAF6, are required for TLR9-mediated IFN-α induction in pDCs, and IKKα is essential for the phosphorylation of IRF7 [47]. Therefore, it is likely that the IRAK4-IRAK1-IKKα kinase cascade, known to be operational in the NF-κB activation pathway, also leads to IRF7 activation.

IRF5 in TLR signaling

In addition to IRF7, IRF5 also interacts with MyD88 and TRAF6 [48]. Unlike IRF7, which binds to the death domain of MyD88, IRF5 interacts with the central region (the intermediary domain and part of the TIR domain) of MyD88. In response to TLR9 activation, IRF5 translocates from the cytoplasm to the nucleus where it binds to ISREs within promoters of target genes. In particular, the expression of proinflammatory cytokines is impaired in *Irf5*$^{-/-}$ MΦs and conventional DCs following stimulation with various TLR stimuli. This is consistent with the observation that *Irf5*$^{-/-}$ mice show resistance to lethal endotoxin shock induced by CpG-B or LPS [48]. Furthermore, IRF5 is required for the full induction of type I IFN genes in pDCs when stimulated with relatively low doses of TLR7 and TLR9 ligands [49].

The detailed mechanism for the activation of IRF5 is still not well understood, but a recent study suggests that TRAF6-mediated K63-linked ubiquitination is important for IRF5 nuclear translocation in TLR7/9-MyD88-dependent signaling [50]. Moreover, phosphorylation of serine/threonine residues in a C-terminal autoinhibitory region is shown to be important for dimer formation of IRF5 and interaction with CBP/p300 in the nucleus [51]. Recent studies suggest an association between polymorphisms of the human *IRF5* gene and autoimmune diseases, especially systemic lupus erythematosus (SLE) [52], although further studies are needed to fully address if and how IRF5 contributes to the development of the disease in the context of TLR signaling.

IRF1 in the MyD88 signaling pathway

IRF1 also directly interacts with the central region (the intermediary domain and part of the TIR domain) of MyD88 [53]. Although type II IFN (IFN-γ) strongly induces IRF1 transcription, it is insufficient to fully activate IRF1. Rather, TLR9 engagement causes a MyD88-dependent "IRF1 licensing" event to occur in which IRF1 is post-translationally modified to migrate into the nucleus more efficiently than non-MyD88-associated IRF1. IRF1 is critical for the IFN-γ enhancement of a TLR-dependent gene induction program. This is underscored by the observation that *Irf1*$^{-/-}$ conventional DCs and MΦs stimulated with IFN-γ plus CpG are impaired in their induction of genes encoding IFN-β, inducible NO synthase (iNOS), and IL-12p35 [53]. IRF1 was also recently found to be required for TNF-α-mediated IFN-β gene induction in MΦs [54].

IRF4, IRF8, and IRF6 in TLR signaling

Studies have demonstrated a role for IRF4 in the negative feedback regulation of TLR signaling. Upon TLR activation, *Irf4* mRNA is induced, and IRF4 protein principally localizes in the nucleus. However, a significant fraction also exists in the cytoplasm where it co-localizes with MyD88 [55]. Since IRF4 binds to the same region of MyD88 that IRF5 binds, TLR-induced IRF4 can compete with and inhibit the sustained activity of IRF5. Consistent with its role as a negative regulator of TLR signaling, TLR-induced proinflammatory cytokines are enhanced in *Irf4*$^{-/-}$ cells and *Irf4*$^{-/-}$ mice are highly sensitive to endotoxic shock induced by CpG-B [55, 56]. As the expression of IRF4 is restricted to immune cells, particularly B cells, T cells, MΦs, and DCs, IRF4 may selectively control MyD88-dependent gene regulation in a cell type-specific manner. A recent report has suggested a regulatory role for IRF4 in inflammatory bowel diseases (IBD). Activation of nucleotide-binding oligomerization domain 2 (NOD2)

signaling by its ligand muramyl dipeptide protects mice from dextran sodium sulfate-induced experimental colitis via the upregulation of IRF4 which then inhibits TLR2 and subsequent Th1 responses [57]. It should be noted, however, that IRF4 appears to have a dual function. In a mouse model of IBD whereby colitis is induced in RAG-deficient mice by transplantation of $CD4^{+}CD45RB^{hi}$ T cells, IRF4 in T cells is required for the production of IL-6 in gut mucosa and the induction of severe colitis [58]. IRF4 is also required for trinitrobenzene sulfonic acid- and oxazolone-induced experimental colitis in mice, and IBD patients display increased IRF4 expression levels in lamina propria T cells [58].

IRF8 is also an immune cell-specific IRF family member. Although IRF8 does bind to TRAF6 [59], it has not been shown to bind to MyD88 [55]. Its interaction with TRAF6 suggests that IRF8 functions in the cytosol. In DCs, IRF8 participates in the TLR9-MyD88-dependent signaling pathway; *Irf8*$^{-/-}$ DCs fail to produce proinflammatory cytokines such as TNF-α and IL-6 upon stimulation with CpG DNA. Interestingly, data in which *Irf8*$^{-/-}$ DCs do not activate NF-κB in response to TLR9 stimulation suggest that IRF8 acts upstream of NF-κB [60]. In the nucleus, IRF8 is required for the expression of the gene encoding IL-12p40 upon various PAMP stimuli in MΦs and DCs [9, 61–63], and for the induction of type I IFN genes by viruses and TLR ligands in DCs [25].

Although the precise role of IRF6 in immune responses is still largely unknown, it does translocates from the cytoplasm to the nucleus upon poly(rI:rC) treatment [64].

Viral factors affecting IRFs

Many viruses have evolved mechanisms to counteract the activity of the host immune response. Given the diverse and potent effects of IRFs on the immune system, it is not surprising that these transcription factors and their activation pathways are the target of viral immune disturbance.

Vaccinia virus-encoded proteins N1L and K7 antagonize TLR signaling at the level of IKKs and TBK1, and DEAD box protein 3 (Ddx3), respectively [65, 66]. Hepatitis C virus (HCV) encodes nonstructural proteins 3 and 4A (NS3/4A) protease that cleave IPS-1 and TRIF, thereby inhibiting the activation of IRF3 and/or IRF7 during HCV infection [67, 68]. Rotavirus nonstructural protein 1 (NSP1) mediates the degradation of IRF3, IRF5 and IRF7 [69, 70]. Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpes virus 8 (HHV8) encodes replication and transcription activator (RTA), an ubiquitin E3 ligase that promotes IRF7 ubiquitination and proteasome-mediated degradation [71]. Furthermore, KSHV encodes a cluster of three viral IRFs (vIRFs), vIRF1, vIRF2, and vIRF3/latency-associated nuclear antigen 2 (LANA2) [72, 73]. All vIRFs show homology in their N-terminal regions to the DNA binding domain of IRFs but lack several of the tryptophan residues that are essential for DNA binding and thus, in contrast to cellular host IRFs, are presumed to be unable to directly bind to DNA. Although its precise mechanism has not been elucidated, vIRF1 is known to function as a repressor of virus-mediated induction of type-I IFN genes in a transient transfection assay [74–76]. Additionally, vIRF2 and vIRF3/LANA2 inhibit the activation of promoters of IFN genes, which may involve interference with host IRFs. Indeed, vIRF3/LANA2 binds to and inhibits the DNA binding activity of IRF7 and IRF5 [77–79].

While these viral proteins are presumed to contribute to the persistence of viral infections, they are also risk factors for virus-induced carcinogenesis. The regulation of oncogenesis by IRFs is discussed in more detail in a latter section. Epstein-Barr virus (EBV) latency has been associated with various human cancers [80]. EBV-encoded latent membrane protein (LMP)-1 is a viral protein that transforms B lymphocytes into a proliferating lymphoblastoid cell line. LMP-1 is demonstrated to induce the expression of IRF7 and activate IRF7 through receptor-interacting protein (RIP)-1 and TRAF6 [81–83]. Since IRF7 has been shown to promote the anchorage-independent growth of NIH3T3 cells and LMP-1 has an additive effect on the growth of these cells, LMP-1-mediated activation of IRF7 is thought to potentiate the EBV transformation process [83].

Human papilloma virus (HPV) is a causative agent in the etiology of cervical dysplasia and cervical cancer [84]. The high-risk types of HPV (HPV-16 and HPV-18) encode two viral oncogenes, E6 and E7, which inactivate cellular tumor suppressor proteins. E6 protein binds to p53 and promotes its proteolysis, whereas E7 protein binds to the hypophosphorylated form of Rb and interferes with its binding to E2F [84]. Furthermore, these HPV oncoproteins also target IRF family members and inhibit their activities. E6 and E7 oncoproteins interfere with IRF3-mediated type I IFN gene induction and IRF1-mediated antioncogenic activity, respectively, thereby overcoming host immunity against cervical tumor development [85, 86].

Regulation of immune cell development by IRFs

In addition to the functions assigned to IRFs in differentiated immune cells, studies have revealed pivotal roles for multiple IRFs in the development of various immune cells (Table 3).

Table 3 A summary of the role for IRFs in immune cell development

IRF	Roles in immune cell development	Proteins encoded by target genes
IRF1	Required for NK cell development	IL-15 in bone marrow stromal cells
	Required for differentiation of CD8$^+$ T cells	
	Promotes Th1 differentiation	IL-12 receptor β1 subunit in T cells, and IL-12p35 and p40 in MΦs/DCs
	Suppresses Th2 differentiation	Represses IL-4
IRF2	Required for differentiation of CD4$^+$ DCs	
	Required for NK cell development	
	Suppresses basophil expansion	
	Promotes Th1 differentiation	IL-12p40 in MΦs
	Suppresses Th2 differentiation	Represses IL-4
IRF4	Required for differentiation of CD4$^+$ DCs	
	Supports B cell development	Ig light chains
	Required for plasma cell differentiation and germinal center formation	AID and Blimp-1
	Required for Th2 differentiation	IL-4
	Required for Th17 differentiation	IL-17 and IL-21
IRF6	Required for keratinocyte differentiation	
IRF8	Required for differentiation of CD8α$^+$ DCs and pDCs	
	Stimulates MΦ differentiation and maturation	Blimp-1, METS and lysosomal/endosomal enzyme-related genes; represses Disabled-2
	Supports B cell development	EBF and Ig light chains
	Stimulates the germinal center program	BCL6 and AID
	Promotes Th1 differentiation	IL-12p40 and p35 in MΦs/DCs

IRFs in the development of dendritic cells

Dendritic cells (DCs) are crucial in the initiation of innate and adaptive immune responses. Upon sensing invading pathogens through PRRs, they typically secrete a variety of cytokines and up-regulate the expression of major histocompatibility complex (MHC) II and costimulatory molecules on their cell surfaces. As professional antigen presenting cells (APCs), DCs also process captured antigens and present antigenic peptides on MHC molecules to T cells, thereby eliciting Th responses or inducing tolerance. It is important to note that DCs are a heterogeneous population comprised of multiple cellular subtypes that express different sets of genes and manifest extensive and distinct functions. Mouse splenic DCs are classified into at least four subsets: CD4$^+$ DCs, CD8α$^+$ DCs, CD4$^-$CD8α$^-$ (double negative, DN) DCs, and plasmacytoid DCs (pDCs).

Within various DC cell types the expression of IRF8 and IRF4 is varied [87–89]. IRF8 is highly expressed in CD8α$^+$ DCs, a subpopulation of DN DCs, and pDCs, while IRF4 is expressed in CD4$^+$, DN DCs and pDCs. Analysis of *Irf8*$^{-/-}$, *Irf4*$^{-/-}$ and *Irf8*$^{-/-}$*Irf4*$^{-/-}$ (DKO) mice reveal that the above pattern of IRF8/IRF4 expression correlates with their requirement for DC subset development [62, 87–90]. Thus, IRF8 is essential for the generation of CD8α$^+$ DCs, while IRF4 is required for that of CD4$^+$ DCs. Both IRFs support the development of DN DCs. IRF8 and, to a lesser degree, IRF4 contribute to pDC development. It was also shown that fms-like tyrosine kinase 3 ligand (Flt3L)-mediated DC differentiation in vitro depends mainly on IRF8, whereas granulocyte macrophage colony-stimulating factor (GM-CSF)-mediated differentiation depends on IRF4 [87, 88]. Relevant to this, GM-CSF has recently been shown to inhibit pDC development by employing STAT5 to suppress IRF8 [91]. Gene transfer experiments into DKO bone marrow progenitor cells demonstrate that both IRFs have an overlapping activity to drive common processes of DC development, such as the induction of *Ciita* (encoding CIITA), while they also possess distinct activities to stimulate subset-specific gene expression, leading to the generation of functionally divergent DCs [88]. Recent findings indicate there is a mechanistic separation that underlies the development of DC subsets by IRF8; the R294C mutation in IRF8, which abrogates binding to PU.1, SpiB and IRF2, abolishes the development of CD8α$^+$ DCs without impairing pDC development in vivo [92]. Upstream of IRF8, the basic helix-loop-helix transcription factor E2-2/Tcf4, which is preferentially expressed in murine and human pDCs and is essential for the development of pDCs, directly activates the *Irf8* and *Irf7* genes, critical for pDC development and

function, respectively [93]. Indeed, the development of E2-2-deficient pDCs is blocked at an immature stage, and E2-2 haploinsufficiency in mice and in human Pitt-Hopkins syndrome patients is associated with impaired phenotypes and IFN responses of pDCs. Finally, epidermal Langerhans cells and dermal DCs have been reported to require IRF8 for their full differentiation and function [94].

DC subset development is also regulated by IRF1 and IRF2. *Irf1*$^{-/-}$ mice show a modest but constant increase in pDC and decrease in CD8α^{+} DC counts [95]. Moreover, a DC-intrinsic role for IRF1 in the inhibition of T cell tolerogenesis has also been shown [95]. *Irf2*$^{-/-}$ mice, on the other hand, demonstrate a selective loss of splenic and epidermal CD4^{+}CD8α^{-} DCs as a result of an abnormally augmented type I IFN signaling [96, 97].

In conclusion, multiple IRFs are critically involved in the regulation of DC development and function. Future studies for identifying IRF target genes and elucidating their interactions with co-factor proteins and relationships with other transcription factors will further clarify the molecular program for the development and function of DCs.

IRFs in the development of myeloid cells

Common myeloid progenitor cells (CMPs) give rise to granulocytes and MΦs. There is a cell-intrinsic role for IRF8 in the differentiation, growth, and apoptosis of myeloid cells. In a condition that resembles human chronic myelogenous leukemia (CML), *Irf8*$^{-/-}$ mice exhibit a systemic expansion of neutrophils followed by a fatal blast crisis [98]. Also, cell transfer studies show an intrinsic leukemogenic potential and long-term reconstitution capability of *Irf8*$^{-/-}$ CMPs. Not only is there an increase in the frequency of CMPs but these progenitor cells are hyper-responsive to both GM-CSF and granulocyte colony-stimulating factor (G-CSF) [99]. Their response to macrophage colony-stimulating factor (M-CSF), on the other hand, is strongly reduced and, surprisingly, even in the presence of M-CSF most *Irf8*$^{-/-}$ CMPs differentiate into granulocytes. Indeed, there are significantly fewer cells of the MΦ lineage in *Irf8*$^{-/-}$ bone marrow than in wild type [99].

Studies with *Irf8*$^{-/-}$ myeloid progenitor cell lines and freshly isolated bone marrow progenitor cells from *Irf8*$^{-/-}$ mice confirm IRF8 drives CMP differentiation toward MΦs and inhibits granulocytic (neutrophilic) differentiation [100, 101]. Consistent with these findings, IRF8 expression is detected in mouse and human hematopoietic progenitor cell populations and persists in MΦs, but declines in granulocytes [101, 102]. Importantly, IRF8 strongly inhibits cell growth and positively regulates apoptosis in myeloid cells [100, 101, 103]. Furthermore, IRF8 transcript levels are severely reduced in cells from human CML patients [104–106]. In demonstrating IRF8's role in the development of myeloid cells, these data reveal why the loss of IRF8 leads to a CML-like syndrome.

IRF8 controls several key genes that regulate cell growth and apoptosis in myeloid cells and induce expression of genes important for MΦ function. For example, IRF8 directly induces *Prdm1* and *Etv3,* genes that encode for transcriptional repressors of *Myc*, Blimp-1 and METS, respectively [107]. In addition, IRF8 inhibits the cell cycle by inducing *Cdkn2b*, which encodes an inhibitor for cyclin-dependent kinase p15$^{\mathrm{Ink4b}}$, while promoting apoptosis by repressing anti-apoptotic genes *Bcl2l1* (encoding Bcl-X_L) and *BCL2* [103, 108, 109]. Interestingly, the *Nf1* gene which encodes the Ras-GAP neurofibromatosis 1 (NF1) protein that inactivates Ras in hematopoietic cells, has been reported to be a direct target gene for IRF8; *Nf1*$^{-/-}$ hematopoietic cells cause myeloproliferative symptoms because of a hypersensitivity to GM-CSF [110, 111]. Another recent finding describes IRF8 as indispensable for the expression of the *Pml* gene and the formation of nuclear bodies in myeloid cells [112]. IRF8 also directly induces several endosomal/lysosomal enzyme-related genes such as those encoding Cathepsin C, Lysozyme, Cystatin C, and Prosaposin [113], and represses the *Dab2* gene encoding Disabled-2 that stimulates MΦ adhesion and spreading [114], enabling MΦ to establish their proper functionality.

IRF8 interacts with PU.1, the master regulator of MΦ and B cell differentiation. This interaction, which is thought to be essential for the development of these cell types but not pDCs as mentioned above, enables IRF8 to bind to several composite DNA elements such as the Ets-IRF composite element (EICE, GGAANNGAAA), the Ets/IRF response element (EIRE, GGAAANNGAAA, a subset of the ISREs), or the IRF-Ets composite sequence (IECS, GAAANN(N)GGAA) [113, 115, 116]. The regulation of IRF8 binding to chromatin by PU.1 is also observed in live cells by fluorescence recovery after photobleaching [117]. It appears that the EICE is especially critical in the B cell lineage, while during MΦ differentiation the IECS is responsible for the regulation of multiple IRF8 target genes such as those encoding Blimp-1, Cathepsin C, and Cystatin C [113]. Other DNA elements that do not fall into the above consensus sequences, for instance those found in *Cdkn2b* and *Nf1* genes, are also targeted by IRF8 during MΦ differentiation [109, 111].

Recently, IRF8 has been shown to be required for the development of eosinophils [120]. IRF2 is required for limiting the generation of basophils; naïve *Irf2*$^{-/-}$ mice display an expansion of basophils, resulting in an increase in IL-4 production and the excess Th2 polarization [118]. IRF1 has also been reported to stimulate myeloid cell differentiation [119].

IRFs in natural killer (NK) cells

Irf1$^{-/-}$ mice are deficient in NK, NKT, and intestinal intraepitherial T cells because IRF1 is required for the transcriptional induction of the gene encoding IL-15, a cytokine essential for the development of these cells, in bone marrow stromal cells [121–123]. *Irf2*$^{-/-}$ mice are also defective in NK cell development [124]. However, IRF2 affects NK cell development in an NK cell-intrinsic manner; probably due to an acceleration of apoptosis, *Irf2*$^{-/-}$ mice selectively lack mature CD11b^{high}Dx5^{high} NK cells [125].

IRFs in B and plasma cells

IRF8 has recently been reported to direct lineage specification of common lymphoid progenitors (CLP) toward the B cell lineage [126]. Furthermore, IRF8 has been shown to directly activate the expression of the gene encoding EBF through direct binding to an IECS (an IRF8-binding consensus DNA elements described above) within the EBF gene promoter [126]. EBF is a transcription factor responsible for the activation of several genes involved in B cell lineage commitment, such as *Pax5*, *Cd79a*, *Vpreb1*, and *Igll1*.

As in the myeloid lineage, IRF4 and IRF8 also cooperate during B cell differentiation. Both are expressed in immature states of B cells including pre-B cells in the bone marrow [127]. In centroblasts within the dark zone of the germinal center (GC), IRF8 expression increases while IRF4 expression is suppressed [127, 128]. Finally, as centrocytes in the light zone differentiate into high-affinity antibody-producing plasma cells, the expression of IRF8 declines while the expression of IRF4 gradually increases [127, 129].

There is a redundant role for IRF4 and IRF8 in promoting the transition from pre-B to IgM^{+} B cell. B cells from *Irf4*$^{-/-}$*Irf8*$^{-/-}$, but not *Irf4*$^{-/-}$ or *Irf8*$^{-/-}$ mice, arrest at the cycling pre-B stage [130], and either IRF4 or IRF8 is able to rescue the maturation arrest of *Irf4*$^{-/-}$*Irf8*$^{-/-}$ B cells in vitro [131]. IRF4 and IRF8 induce conventional immunoglobulin (Ig) light chain (i.e., κ and λ) gene transcription and rearrangement and inhibit expression of surrogate light chain *VpreB* and *λ5* genes to down-regulate the pre-antigen receptor complex [130, 131]. Molecularly, IRF4 and IRF8 physically associate with the Ets transcription factors PU.1 or SpiB to bind to the Ets-IRF composite elements (EICEs) found in the Igκ 3′ and λ enhancers where they activate transcription [115, 132, 133]. Similarly, a recent study demonstrates that IRF4 and IRF8 down-regulate pre-B-cell receptor and stimulate the transition from large pre-B to small pre-B cells by inducing the expression of *Ikaros* and *Aiolos*, although it is unknown whether the induction is direct or indirect [57]. Moreover, IRF4 attenuates IL-7 signaling. IL-7 is essential for pre-B cell proliferation and survival, but must be down-regulated for efficient light chain rearrangement. IRF4 upregulates the chemokine receptor *Cxcr4* and, in doing so, is thought to promote migration of pre-B cells away from IL-7 expressing stromal cells in response CXCL12, the ligand of CXCR4; CXCL12-secreting stromal cells are located separate from IL-7-producing stromal cells [133].

IRF8 is also involved in the GC program. GCs in *Irf8*$^{-/-}$ mice show less organized morphology and *Irf8*$^{-/-}$ B cells express reduced expression levels of *Aicda* and *Bcl6* genes [134]. IRF8 has been found to directly regulate the induction of these two critical genes during the GC reaction, both in human and mouse [134]. The *Aicda* gene encodes activation-induced cytidine deaminase (AID), which is required for both class switch recombination (CSR) and somatic hypermutation, and the *Bcl6* gene encodes B cell lymphomas 6 (Bcl6) protein, a Krüppel-type zinc finger transcriptional repressor that functions as a master regulator in the GC program.

Irf4$^{-/-}$ mice display a profound reduction in serum immunoglobulin, fail to produce antigen-specific antibodies, and do not generate GCs [135]. *IRF4*, induced by CD40 engagement in the light zone of the GC through the NF-κB canonical pathway, directly downregulates BCL6 expression to allow terminal differentiation to post-GC lymphocytes [136]. In addition to GC formation, IRF4 is also required for CSR, somatic hypermutation, and plasma cell differentiation [129, 137]. IRF4 is indispensable for the induction of *Aicda* gene induction, illustrating the molecular basis for the failure of CSR and somatic hypermutation in *Irf4*$^{-/-}$ B cells. One of these reports also indicates that the *Prdm1* gene is a direct target of IRF4 [129], reminiscent of the regulation of this gene by IRF8 in myeloid progenitor cells. The *Prdm1* gene encodes the zinc-finger transcriptional repressor Blimp-1, which is a master regulator of plasma cell differentiation.

Finally, *Irf4*$^{-/-}$ mice between 10 and 15-weeks-old, in addition to the above developmental defects, also display a generalized lymphadenopathy because of an expansion of B and T cells in lymph nodes and spleen (but not thymus). This suggests that IRF4 is also important for the homeostasis of mature lymphocytes [135].

IRFs in T cell differentiation

CD8^{+} T cells

There is a lineage-specific defect in thymocyte development of *Irf1*$^{-/-}$ mice; these mice display a pronounced decrease in mature CD4^{-}CD8^{+} T cells in the thymus and peripheral lymphoid organs [138]. Although *Irf1*$^{-/-}$ thymic stromal cells show decreased levels of low molecular

weight protein-2 (LMP2), antigen processing-1 (TAP1), and MHC I expression [138, 139], the defect in $CD8^+$ T cell development does not reside in the thymic environment but is instead due to a thymocyte-intrinsic defect in the differentiation from immature T cells ($TCR\alpha\beta^-CD4^+CD8^+$) to mature $CD8^+$ T cells [140]. IRF1 expression is induced following TCR stimulation in immature thymocytes, while *Irf1*$^{-/-}$ thymocytes are defective in TCR-mediated signal transduction. Thus, in developing thymocytes, IRF1 may regulate gene expression required for lineage commitment and positive and negative selection of $CD8^+$ thymocytes [140]. Consistent with the impairment of $CD8^+$ T cell in *Irf1*$^{-/-}$ mice, the cytotoxic T lymphocyte (CTL) response to lymphocytic choriomeningitis virus (LCMV)-infected target cells is significantly reduced in these mice. There is also data to suggest that IRF4 and IRF8 contribute to the regulation of CTL activity during viral infection [98, 135].

Naïve *Irf2*$^{-/-}$ mice display a spontaneous inflammatory skin disease resembling psoriasis [138, 141]. *Irf2*$^{-/-}$ $CD8^+$ T cells exhibit a hyperresponsiveness to antigen stimulation in vitro accompanied by abnormally up-regulated type I IFN-inducible gene expression. Importantly, the disease development and $CD8^+$ T cell abnormality are suppressed when genes that positively regulate the type I IFN signaling pathway are disrupted [141]. Thus, IRF2 is a unique negative regulator of type I IFN-induced gene transcription necessary for balancing the beneficial and harmful effects of type I IFN signaling in the immune system.

$CD4^+$ T cells

Although naïve $CD4^+$ T cells do develop in *Irf1*$^{-/-}$ mice, IRF1 is indispensable for the differentiation of T helper type 1 (Th1) cells, and the absence of IRF1 leads to the induction of Th2-type immune response [142, 143]. A severe defect in the production of and response to IL-12, which is essential for Th1 differentiation, is present in the absence of IRF1 in multiple cell types. IRF1 regulates the expression of genes encoding IL-12p40 and IL-12p35 in MΦs and DCs. *Irf1* itself is a target gene of IL-12 signaling [144, 145], and *Irf1*$^{-/-}$ $CD4^+$ T cells are hyporesponsive to IL-12 [143]. IRF1 directly controls and is indispensable for the expression of the gene encoding IL-12 receptor β1 subunit in $CD4^+$ T cells [146]. In addition, the lack of NK cells in *Irf1*$^{-/-}$ mice may also contribute to the defective IL-12 production because NK cells produce IFN-γ that stimulates MΦs to secrete IL-12. Aside from its positive regulation of Th1 differentiation, IRF1 has recently been reported to be a key negative regulator of $CD4^+CD25^+$ regulatory T (Treg) cells through the direct repression of *Foxp3* gene expression, the gene that encodes the master transcription factor for Treg cell development [147].

Unexpectedly, *Irf2*$^{-/-}$ mice show a defect in Th1 differentiation due to the impaired production of IL-12 in MΦs [124, 148]. It appears that IRF2 contributes to IL-12p40 gene expression in cooperation with IRF1 and other factors, rather than functioning as a transcriptional repressor as described above. It is also possible that the defective NK cell differentiation in *Irf2*$^{-/-}$ mice contributes to the impaired Th1 responses. On the other hand, there is an excessive Th2 polarization in naïve *Irf2*$^{-/-}$ mice due to the expansion of basophils as described above and their production of IL-4 [118]. Interestingly, IFN-γ promotes Th1 and attenuates IL-4-driven Th2 responses via the induction of IRF1 and IRF2, respectively [149].

IRF8 and IRF4 promote Th1 and Th2 differentiation, respectively. *Irf8*$^{-/-}$ mice fail to mount Th1 responses [150, 151], while *Irf4*$^{-/-}$ mice are defective in Th2 responses [152–154]. The defective Th1 response in *Irf8*$^{-/-}$ mice is attributed to the defects in MΦs and DCs rather than T cells [155]. In particular, IRF8 is required for the production of IL-12, a major Th1-promoting cytokine, and for the development of $CD8\alpha^+$ DCs, which also produce IL-12 [61, 156]. IRF4 is constitutively expressed in mature T cells and is further induced by concanavalin A or CD3 cross-linking in mature T cells [157]. IRF4 induces the expression of the Th2-promoting cytokine IL-4 via IRF4's physical interaction with NFATc2 and/or NFATc1 transcription factors [153, 158]. Moreover, *Irf4*$^{-/-}$ $CD4^+$ T cells fail to express GATA3, a transcription factor critical for Th2 development, following in vitro IL-4 treatment [152, 154]. Together, these data clearly demonstrate that IRF4 has a T cell-intrinsic role in Th2 differentiation. In addition, IRF4's role in the development of $CD4^+$ DC subset may also contribute to Th2 differentiation, because this subset is thought to stimulate Th2 responses. A recent study, based in mouse on the Th2-biased BALB/c genetic background, shows that while IRF4 indeed promotes Th2 development and Th2 cytokine production in effector/memory $CD4^+$ cells, it instead inhibits Th2 cytokine production in the early activation phase of naïve $CD4^+$ T cells [159]. These data suggest a dual role for IRF4 in Th2 cytokine production by $CD4^+$ T cells.

IRF4 is also critical for the generation of IL-17-producing T helper (Th17) cells [160]. *Irf4*$^{-/-}$ mice not to develop experimental autoimmune encephalomyelitis due to the inability of *Irf4*$^{-/-}$ naïve T helper cells to differentiate into Th17 cells. The molecular basis of this defect is the result of *Irf4*$^{-/-}$ T helper cells express less RORγt and more Foxp3, transcription factors important for the differentiation of Th17 and regulatory T cells, respectively [160]. Furthermore, IRF4 directly induces the genes encoding IL-17 and IL-21 [161]. Interestingly, mice deficient in IRF4-binding protein (IBP) rapidly develop rheumatoid arthritis-like disease and large-vessel vasculitis because IBP inhibits

Table 4 A summary of the role for IRFs in cell growth and apoptosis

IRF	Roles in cell growth and apoptosis	Proteins encoded by target genes
IRF1	Suppresses oncogene-induced transformation	Lysyl oxidase
	Required for DNA damage-induced growth arrest	p21/WAF1/CIP1
	Required for apoptosis induced by DNA damage and other stimuli	Caspase-1, Caspase-7, Caspase-8, GAAP-1, and TRAIL
IRF2	Promotes oncogenesis by antagonizing IRF1 or its own transactivation activity	Histone H4
	Promotes survival of erythroid cells	Bcl-XL
IRF3	Stimulates apoptosis in MΦs upon bacterial infection	TRAIL
	Promotes virus-induced apoptosis	
	May promote DNA damage-induced apoptosis	
IRF4	Promotes oncogenesis in multiple myeloma	Myc
IRF5	Suppresses oncogene-induced transformation	
	Required for DNA damage-induced apoptosis	
	Required for Fas-induced apoptosis in a cell type-specific manner	
	Promotes virus-induced apoptosis	
IRF6	Required for cell cycle arrest during keratinocyte differentiation	
IRF8	Inhibits myeloid cell growth	Blimp-1, METS, and p15/INK4B
	Promotes apoptosis induced by several types of stimuli in myeloid cells and Fas-induced apoptosis in some cancer cells	NF1 and PML; represses BCL-XL, BCL-2, and Fap-1
	Its absence leads to a chronic myelogenous leukemia-like disease	
IRF9	Mediates type I IFN induction of p53	p53

IRF4-mediated induction of IL-17 and IL-21 by sequestering IRF4 from the promoters of these cytokine genes [161].

IRF2 in erythroid cells

Irf2$^{-/-}$ mice suffer from normocytic anemia, and their bone marrows contain a decreased number of late erythroblasts accompanied by an increased number of early erythroid progenitors [162]. *Irf2*$^{-/-}$ erythroblasts show decreased Bcl-X_L expression levels and enhanced apoptosis due to excessive type I IFN signaling, suggesting a cross-talk between type I IFN and erythropoietin signaling pathways during erythropoiesis. Furthermore, IRF2 has been shown to preserve the self-renewal and multi-lineage differentiation capacity of hematopoietic stem cells by inhibiting type I IFN-induced cell cycle in these cells [163, 164].

Regulation of non-immune cell differentiation by IRFs

Mutations in the *IRF6* gene in humans cause two related orofacial clefting disorders: Van der Woude syndrome and popliteal pterygium syndrome [165]. The *Irf6* deficiency in mice also leads to abnormal skin, limb, and craniofacial development. These abnormalities are the result of IRF6 being required for cell cycle arrest and terminal differentiation of keratinocytes [166, 167].

Recently, an unexpected and novel role for IRFs in adipogenesis is reported [168]. All IRFs are expressed in adipocytes, and their expression is regulated during adipogenesis. Moreover, several IRFs bind to specific genomic DNA regions surrounding key adipocyte genes that display differentiation-dependent changes in DNase hypersensitivity. Multiple IRFs, especially IRF3 and IRF4, can repress adipogenesis in vitro. These data suggest an interesting possibility that the IRF family is critical in the link between immunity and metabolic diseases.

Regulation of cell growth and apoptosis by IRFs

Another critical function of IRFs is the regulation of cell growth, apoptosis, and oncogenesis (Table 4). Thus, IRFs connect the mechanisms governing immunity and tumor suppression.

Antioncogenic IRFs

IRF1

The notion that IRFs participate in the regulation of oncogenesis first came out of studies performed on IRF1. *Irf1*$^{-/-}$ MEFs are deficient in their ability to undergo DNA damage-induced cell cycle arrest. Similar to the tumor suppressor p53, IRF1 transcriptionally activates the gene encoding the cyclin-dependent kinase (CDK) inhibitor p21$^{WAF1/CIP1}$ [169]. Upon DNA damage, IRF1 protein level increases via the regulation of mRNA expression and protein half-life, so as to act on the p21 promoter region containing the IRF1- and p53-binding sites [169, 170].

Apoptosis is one mechanism by which pre-cancerous cells are eliminated from the host. An activated oncogene, such as c-Ha-Ras, will induce wild-type MEFs to undergo apoptosis rather than cell cycle arrest when treated with an anticancer drug or ionizing radiation. This hallmark of tumor suppression was found to be dependent on both IRF1 and p53 [171]. While DNA damage-induced apoptosis is dependent on IRF1 and independent of p53 in mitogenically activated mature T lymphocytes [172], in thymocytes it is dependent on p53 but not IRF1. Thus, depending on the type and differentiation stage of the cell, IRF1 and p53 regulate DNA damage-induced apoptosis cooperatively and independently. Interestingly, a transcriptional activator of both IRF1 and p53, GAAP-1, has been shown to have pro-apoptotic activity [173].

In addition, IRF1 is important for apoptosis that is activated or enhanced by other stimuli, such as IFN-γ [174–176]. The target gene(s) of IRF1 responsible for apoptotic responses have not been firmly identified, but may include genes encoding Caspase 1, Caspase 7, Caspase 8, and TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) [9, 10].

Consistent with these observations, an oncogenic transformation assay in which a single oncogene, activated c-Ha-Ras, was introduced in *Irf1*$^{-/-}$ MEFs which was sufficient to transform these cells, indicating that there is a tumor suppressor-like activity for IRF1 [171]. This is in contrast to WT cells, which required at least two oncogenes. Moreover, conditions under which activated Ras paradoxically inhibited cell growth of myeloid cells are found to involve IRF1 and the induction of p21$^{WAF1/CIP1}$ [177]. Ectopic expression of IRF1 suppresses the malignant properties of cancer cell lines and oncogene-transformed cell lines in vitro and in vivo [10]. Although the loss of IRF1 alone rarely induces tumor development in mice, IRF1 deficiency dramatically exacerbates tumor predispositions caused by the expression of a c-Ha-Ras transgene or by nullizygosity of the p53-encoding gene, *Trp53* [178]. This accelerated tumor development may not be due to the above-mentioned immunological disorders caused by the absence of IRF1 [178]. Thus, *Irf1* is a tumor susceptibility gene whose loss in combination with other genetic alterations significantly increases the incidence of tumors. The lysyl oxidase (*Lox*) gene is an IRF1 target gene involved in mediating IRF1's tumor suppressive activity [179]. Lox plays a critical role in the biogenesis of connective tissue matrices and is identical to the independently discovered ras recision gene (*rrg*) implicated in the reversion of Ras-transformed NIH 3T3 cells by preventing the activation of NF-κB [180].

A number of clinical studies have correlated the loss of IRF1 expression or function to human cancers. *IRF1* maps to the chromosomal region 5q31.1, a region where frequent cytogenetic abnormalities occur in leukemia and preleukemic myelodysplastic syndrome (MDS). Among the number of genes located in this region, only *IRF1* is consistently deleted at one or both alleles in patients with aberrations of 5q31 [181]. In esophageal and gastric cancers, the loss of one IRF1 allele is also reported [182, 183], and in one out of four cases of gastric cancers examined the deletion is accompanied by an inactivating point mutation in the other allele [184]. Furthermore, several other mechanisms can lead to the loss-of-function of IRF1 in cancers. For instance, an elevated level of SUMOylated IRF1 in tumor cells interferes with IRF1-mediated apoptosis [185]. Splicing aberrations in the *IRF1* gene cause the loss of functional IRF1 in MDS and leukemias [186, 187]. Also, a putative ribosome assembly factor often over-expressed in leukemic cells, Nucleophosmin, binds to IRF1 and inhibits its function [188]. Finally, a decreased expression of *IRF1* mRNA in several types of cancers, such as chronic myelogenous leukemia, breast cancer, endometrial cancer, and hepatocellular carinoma, is reported [9, 10].

IRF8

IRF8 is expressed predominantly in hematopoietic cells, and accumulating evidence indicates an antagonizing relationship between IRF8 and myeloid leukemia, especially chronic myelogenous leukemia (CML). As already discussed above, *Irf8*$^{-/-}$ mice develop a CML-like syndrome [98]. In CML and acute myelogenous leukemia patients *IRF8* transcripts are absent and a number of IRF8 target genes, such as *Bcl2* and *Pml*, are decreased [108, 112]. On the other hand, ectopic expression of IRF8 is able to override the mitogenic activity of Bcr/Abl (a causal fusion oncoprotein in human CML) in vitro by activating several genes that interfere with the c-Myc pathway, a downstream target of Bcr/Abl [107] and, in fact, ameliorates Bcr/Abl-mediated murine myeloid leukemia in vivo [189]. In addition, IFN-α treatment for human CML induces *IRF8* expression in vivo [104], and *IRF8* expression correlates

positively with pre-treatment risk features and cytogenetic response to IFN-α in CML [105]. Thus, IRF8 expression may be a major factor in inhibiting the development of human CML, while the restoration of its expression can antagonize the oncogenic activity of Bcr/Abl. IRF8's target genes in cell growth and apoptosis in myeloid cells are described in the previous section. Interestingly, *Irf4* transcript levels are also significantly low in CML patients [190, 191] implying that IRF4 has an activity similar to IRF8 in myeloid cell development and CML pathogenesis, as in the case of DC and B cell development.

It is likely that IRF8 can exert its anti-leukemic activity not only by the direct control of cell growth, differentiation and apoptosis but also by modulating anti-tumor immunity. Since human CML cells are susceptible to T cell-mediated immunity, IRF8's ability to support the differentiation and function of professional APCs such as MΦs, DCs and B cells may be important in the elimination of CML by the immune system. In mice, co-expression of IRF8 in Bcr/Abl-transformed pro-B cell line causes a $CD8^+$ cytotoxic T-cell response that prevents the establishment of leukemia in vivo [192]. Given the effectiveness of IFN-α therapy in human CML, it is also interesting to note that IRF8 is required for the development of pDCs, cells which produce high levels of type I IFNs, and that IRF8 is a transcriptional activator of type I IFN genes [25].

IRF8 has been reported to manifest anti-tumor activity even in non-hematopoietic tumors. IFN-γ-induced IRF8 sensitizes human colon carcinoma cells to Fas-mediated apoptosis [193], and IRF8 represses the *PTPN13* gene that encodes a ubiquitously expressed protein-tyrosine phosphatase, Fas-associated phosphatase 1 [194]. *IRF8* expression is repressed by DNA methylation in human metastatic colon carcinoma cell lines and murine mammary carcinoma with lung metastasis in vivo [195]. The *IRF8* gene localizes to 16q24, a region frequently deleted in multiple solid tumors. In 78% of primary nasopharyngeal carcinoma and between 36 and 71% of other carcinoma samples, the *IRF8* gene is associated with transcriptional silencing and promoter methylation [196].

IRF5

IRF5 has emerged as another IRF family member that possesses tumor suppressor activity. Activated c-Ha-Ras-expressing $Irf5^{-/-}$ MEFs fail to efficiently apoptose in response to DNA damage, and undergo transformation to form tumors in nude mice [21]. $Irf5^{-/-}$ MEFs are resistant to VSV-induced apoptosis as well, resulting in enhanced viral propagation in spite of being capable of producing normal levels of type I IFNs and IL-6 [21]. *Irf5* mRNA is induced upon viral infection through type I IFN signaling and upon DNA damage by p53 [21, 197]. Because several p53 targets, such as the genes encoding Puma and Noxa, are induced even in $Irf5^{-/-}$ MEFs, it is suggested that IRF5 may act on an apoptotic pathway that is distinct from that for p53 [21]. Indeed, overexpression of IRF5 inhibits in vitro and in vivo B cell lymphoma tumor growth in the absence of wild type p53 [198]. Furthermore, ectopic expression of IRF5 sensitizes p53-proficient and p53-deficient colon cancer cells to DNA damage-induced apoptosis [199]. Recently, IRF5 has been shown to be involved in Fas/CD95-induced apoptosis, which typically occurs in a p53-independent manner [200]. $Irf5^{-/-}$ mice are resistant to hepatic apoptosis and lethality in response to the in vivo administration of a Fas-activating monoclonal antibody. IRF5 is also required for Fas-induced apoptosis in DCs activated by hypomethylated CpG but not in thymocytes and MEFs. Thus, IRF5 is required for the death receptor-induced cell death in a cell type-selective manner. Interestingly, *IRF5* mRNA expression is suppressed in human leukemia cells, implying the possible involvement of IRF5 inactivation in human cancers [198]. Further studies are required to clarify the transcriptional pathway by which IRF5 stimulates apoptosis.

IRF6

IRF6 may also act as a tumor suppressor via its interaction with Maspin, a known tumor suppressor gene [64]. Similar to Maspin, IRF6 expression inversely correlates with breast cancer invasiveness. IRF6 is unphosphorylated in quiescent mammary epithelial cells, but during cell division becomes phosphorylated and undergoes proteasome-dependent degradation [201]. Ectopic expression of IRF6 results in cell cycle arrest, a process augmented by Maspin.

IRF3

Virus-induced apoptosis may be mediated by activated IRF3 as the expression of a constitutively active mutant of IRF3 triggers apoptosis, while dominant negative mutants of IRF3 strongly inhibit Sendai virus- and NDV-induced apoptosis [202, 203]. Interestingly, IRF3-mediated apoptosis is shown to be independent of p53 and IFN [203] and, instead, likely involves the gene encoding TRAIL because it is transcriptionally activated by ectopic expression of IRF3 [204]. However, that VSV infected $Irf3^{-/-}$ MEFs efficiently undergo apoptosis as well as infected WT cells indicates that IRF3 does not mediate virus-induced apoptosis against all viruses [21].

IRF3 also participates in a putative, bacterium-induced apoptosis mechanism that is triggered upon TLR activation. Certain bacteria induce MΦ apoptosis by producing virulence factors that inhibit cell survival pathways such as the p38 or NF-κB pathways. This pro-apoptotic pathway in

MΦs requires IRF3 along with PKR and TLR4 [205]. Finally, IRF3 is suspected to also play a role in DNA damage-induced apoptosis as IRF3 protein is phosphorylated and translocates from the cytoplasm to the nucleus in response to DNA damaging agents [203, 206]. DNA-dependent protein kinase (DNA-PK) is capable of phosphorylating human IRF3 at Thr135 [207], which is distinct from the phosphorylation sites targeted by TBK1. Consistent with a putative role in DNA damage-induced apoptosis, several overexpression studies have shown that IRF3 inhibits the growth of cancer cell lines in vitro and in vivo [208, 209]. Taken together, these studies suggest that IRF3 may also function as a tumor suppressor gene.

IRF9

A critical link between type I IFNs and the p53 pathway, which is required for virus-induced apoptosis, has been established by the finding that type I IFNs transcriptionally activate the tumor suppressor p53 gene through ISGF3 binding to ISREs within its promoter and first intron. As a component of ISGF3, IRF9 augments the p53 pathway when cells are exposed to endogenously induced or exogenously administered type I IFNs. As a result, *Irf9*$^{-/-}$ MEFs fail to upregulate p53 upon IFN-β stimulation [210] in which IFN-β can normally suppress oncogene-induced malignant cell transformation and enhance DNA damage-induced apoptosis of cancer cells. The link between type I IFNs and p53 also demonstrates a link between tumor suppression and antiviral immunity.

On the other hand, it has been reported that the *Irf9* gene is directly activated by c-Myc, and a cell line lacking *IRF9* expression is more susceptible to cytotoxic chemotherapeutic drugs [211], suggesting an undiscovered role for IRF9 in cell cycle regulation. Additional research is required to clarify this point.

Oncogenic potential of IRFs

IRF2

In addition to its role as an IFN attenuator, IRF2 manifests a pro-oncogenic activity. It was shown previously that overexpression of IRF2 in NIH3T3 cells causes oncogenic transformation [212]. A genetic screen of a retroviral library then identified IRF2 as an inhibitor of activated N-Ras-induced growth suppression in leukemic cells [213]. The pro-oncogenic function of IRF2 appears to be mediated by its transcriptional interference of IRF1 and/or other IRF family members that bind to the same ISRE elements [214]. Indeed, the concomitant expression of IRF1 in IRF2-overexpressing NIH3T3 reverts these cells to a non-transformed phenotype [212]. On the other hand, however, IRF2 itself can also activate gene transcription under certain conditions [215] and, in fact, stimulates the expression of genes involved in oncogenesis such as histone H4 [216, 217]. It was also reported that IRF2 is post-translationally regulated in a cell growth-dependent manner in which acetylated IRF2 preferentially binds to the H4 promoter in proliferating cells only [218].

IRF4

A connection between IRF4 and lymphoid malignancies has been indicated by several groups. For instance, the expression of *IRF4* mRNA is induced upon human T cell leukemia virus-1 (HTLV-1) infection [219]. Moreover, in Jurkat T cells overexpression of the HTLV-1 oncoprotein Tax induces *IRF4* mRNA transcription while the constitutive expression of IRF4 in these cells results in the reduced expression of the G2-M checkpoint gene Cyclin B1 and several DNA repair genes. These transcriptional changes are strikingly similar to those that occur in HTLV-infected T cells [220, 221], suggesting a possible involvement of IRF4 in HTLV-1-induced leukemogenesis. Translocations involving *IRF4* has been shown to have occurred in 12 out of 169 cases of peripheral T cell lymphomas [222]. In some patients with multiple myeloma and cell lines derived from this tumor, a chromosomal translocation t(p25;q32) juxtaposes the immunoglobulin heavy-chain locus to IRF4/MUM1 (multiple myeloma 1) [6, 14], resulting in the overexpression of IRF4 [223]. Furthermore, *IRF4* mRNA expression is a prognostic marker for poor survival in patients with multiple myeloma [224]. Recently, IRF4 has emerged as a master regulator of an aberrant and malignancy-specific gene expression program in multiple myeloma [225]. In fact, IRF4 is required for the survival of multiple myeloma cell lines. This is because IRF4 transactivates the *MYC* gene while Myc activates *IRF4*, thereby establishing a positive autoregulatory loop. Although IRF4 is not genetically altered in most myelomas, this positive feedback loop is likely to be triggered by the initial oncogeneic activation of *MYC*, the locus of which is often amplified and inserted at ectopic genomic locations in this disease. Overexpression of IRF4 alone in lymphocytes, however, is not sufficient for the development of T cell leukemia and multiple myeloma in transgenic mice [226], suggesting a requirement for additional factors in the etiology of the diseases.

Possible opportunities for intervention

Because of their role in promoting apoptosis or cell cycle arrest, several IRFs have therapeutic potential in the treatment of cancer. Indeed, as described above, the ectopic expression of IRF1, IRF3, IRF5, IRF6, and IRF8 has already been demonstrated to halt the growth of or sensitize

to apoptosis various cancers under experimental conditions. Furthermore, as a number of these genes also regulate immune cell development, they may offer additional promise in affecting host tumor immunity against certain cancers. This may be particularly true of IRF1, which regulates NK and NKT cell development, and IRF8, which drives macrophage, DCs and B cell differentiation. IRF3, IRF5, IRF7, IRF8, and IRF9 may also be particularly interesting areas of study given their role in the regulation of type I IFNs and the connection between type I IFN and antitumor immunity and immunotherapy. Finally, that the pro-oncogenic IRF2 appears to act by transcriptional interference of other (anti-oncogenic) IRFs makes it and its novel mechanism-of-action additional targets of investigation.

Conclusion

Since the discovery of IRF1 in 1988, remarkably vital and broad roles for the IRF family have been revealed. IRF members impact a number of aspects of the host defense system, from the activation or attenuation of immune responses by essentially all IRFs; to the regulation of immune cell differentiation by IRFs 1, 2, 4, and 8; to the regulation of cell growth or death by most IRFs. While each member may be assigned a specific function, we also find considerable overlapping features between family members. Multiple IRFs, for instance, are activated upon stimulation by various PRRs during innate immune responses. This occurs because many IRFs (IRF1, 4, 5, 6, 7, and 8) share the ability to interact with the common adaptor protein MyD88 and/or TRAF6 in the TLR-MyD88 pathways, and also because IRF3 and IRF7 can be activated by TBK1, a common kinase in the cytosolic nucleic acid sensor and the TLR-TRIF pathways. Once activated, the IRFs stimulate an overlapping but distinct set of target genes to shape the appropriate immune response. In this regard, IRFs appear to form a "hub" that integrates and outputs signals from PRR stimulation. In another example of overlapping and distinct activities, IRF8 and IRF4 dictate the development of multiple DC subsets and, thereby, form the basis of DC's diverse functions. In addition, several IRFs share an ability to regulate oncogenesis in part by their common ability to respond to genotoxic stresses. Thus, through both their common and specific features, IRF family members contribute to the establishment of an indispensable diversity in the host defense system. Given that the IRF-IFN system likely arose at the boundary of invertebrate–vertebrate evolution, the function of the IRF family may represent a vertebrate-specific mechanism to shape the complex and efficient host defense system.

In spite of the extensive body of knowledge that scientific research has generated, ample questions remain about the biology of the IRF family. For example, the detailed mechanism for how IRFs act as tumor suppressors remains poorly understood. Also, as our understanding of IRFs' immediate roles in the regulation of innate immunity improves, our broader view becomes increasingly complicated by the interrelationships between IRFs and the other regulatory systems involved. The cooperation and antagonism between IRFs and NF-κB is particularly intriguing. Both are activated by a remarkably common set of stimuli, such as PAMPs and DNA damage, and cooperatively regulate the expression of many cytokine genes; however, they appear to exert opposite effects on cell growth and survival. In contrast to the tumor suppressive effects of several IRFs, NF-κB acts as a potent pro-survival transcription factor and contributes to the development of tumors, including inflammation-linked cancers. Therefore, precisely how and to what extent these two transcription factor families cooperate and antagonize one other is an important future issue to address. Ultimately, the comprehensive understanding of their interacting proteins and target genes in various types of cells upon various stimuli must be achieved.

Because the IRF family is critical for the two aspects of host defense, i.e., immunity against pathogens and tumor suppression, further studies will make this family an attractive target not only for the therapy of infectious diseases and immune disorders but also in the multidisciplinary therapy of cancers.

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