

# The IRF family of transcription factors

## Inception, impact and implications in oncogenesis

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Members of the interferon-regulatory factor (IRF) proteins family were originally identified as transcriptional regulators of the Type I interferon system. Thanks to consistent advances made in our understanding of the immunobiology of innate receptors, it is now clear that several IRFs are critical for the elicitation of innate pattern recognition receptors, and—as a consequence—for adaptive immunity. In addition, IRFs have attracted great attentions as they modulate cellular responses that are involved in tumorigenesis. The regulation of oncogenesis by IRFs has important implications for understanding the host susceptibility to several Types of cancers, their progression, as well as the potential for therapeutic interventions.

### Introduction

The discovery of interferon-regulatory factors (IRFs) dates back to 1988, when a cDNA clone encoding a mouse protein that binds to a virus-inducible enhancer element of the interferon (IFN) $\beta$ -coding (*IFNB*) gene was identified.<sup>1</sup> In that period, no significant homology between this gene and other known proteins was recognized and hence the gene was named IFN-regulatory factor 1 (IRF1). The subsequent identification of a cDNA clone that cross-hybridizes to *IRF1* cDNA, named *IRF2*, marked the official recognition of the IRF family.<sup>2</sup> Since then, the IRF family has been shown to include nine members, IRF1–9 (Fig. 1). Although it has become customary to refer to these proteins as to IRFs, some of them were originally identified with different acronyms, such as PIP/LSIRF/ICSAT for IRF4, ICSBP for IRF8, and IFN-stimulated gene factor 3 $\gamma$  (ISGF3 $\gamma$ ) for IRF9 (refs. 3–8). Virus-encoded homologs of IRFs, named viral IRFs (vIRFs), have also been characterized.<sup>9,10</sup>

All IRF family members possess an N-terminal DNA-binding domain (DBD) that is characterized by a series of five relatively well-conserved tryptophan-rich repeats<sup>11,12</sup> (Fig. 1). The DBD forms a helix-turn-helix structure and recognizes a DNA sequence known as IFN-stimulated response element (ISRE)<sup>13</sup> which is characterized by the consensus sequence, 5'-AAN NGA

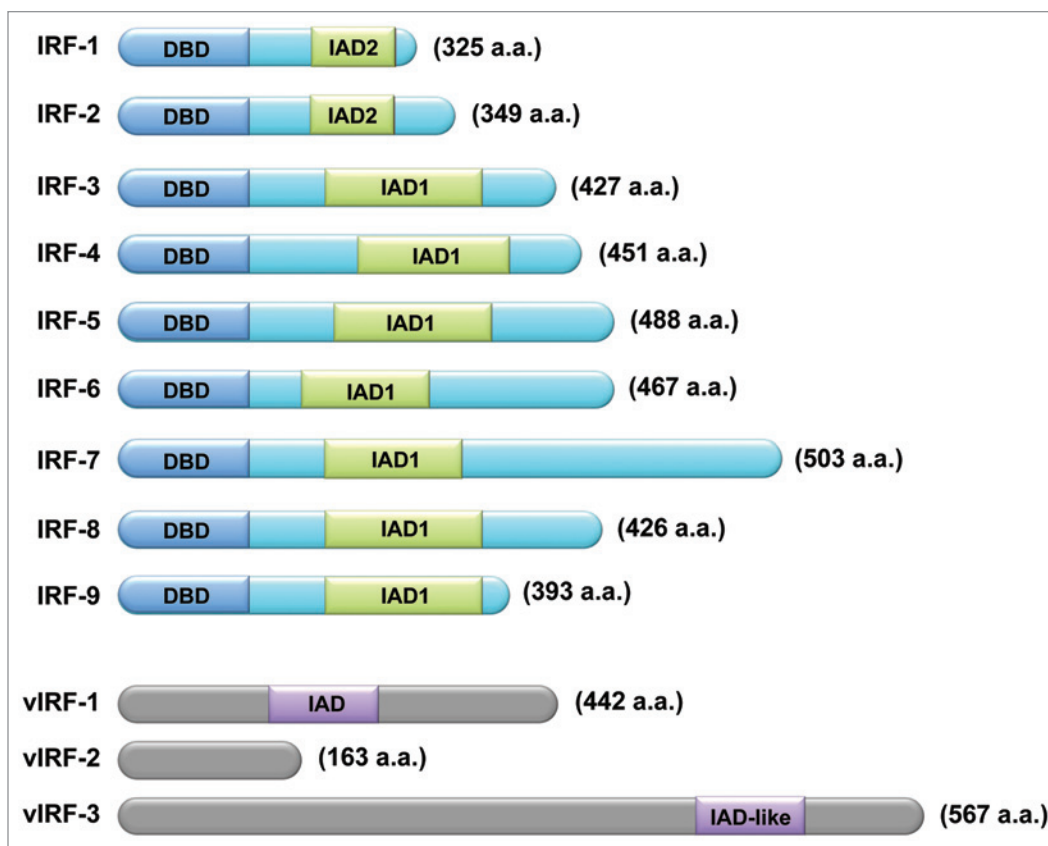
AA-3'.<sup>14</sup> The C-terminal region of IRFs is less well conserved and supposedly mediates the interactions of a specific IRF with other family members, other transcriptional factors, or cofactors, so as to confer specific activities upon each IRF. Even so, two Types of association modules have been identified within the C-terminal region of some IRFs:<sup>15</sup> IRF-associated domain 1 (IAD1),<sup>16</sup> which is conserved in all IRFs except IRF1 and IRF2 and is structurally similar to the Mad-homology 2 (MH2) domain of SMAD transcription factors; and IAD2,<sup>12</sup> which is shared by IRF1 and IRF2 only (Fig. 1). The nature of the protein-to-protein interactions dictated by these domains likely determines whether the resulting complex functions as a transcriptional activator or repressor, and define the nucleotide sequences adjacent to the core IRF-binding motif to which the transcriptional complex binds.<sup>12,16</sup>

There has been much progress in our understanding of the close connection between innate and adaptive immunity. Several IRFs play an essential role in this setting, by regulating the development and functions of various Types of immune cells (reviewed in refs. 12, 16–21). In addition, accumulating evidence indicates that IRFs play a critical function in the regulation of cellular responses linked to oncogenesis, thereby connecting the mechanisms governing immunity and cancer. In this review, we discuss current knowledge on how each IRF participates in the regulation of oncogenesis (see Table 1 for general overview). Although not extensively discussed in this review, all IRFs may play a broader and less direct role in the regulation of oncogenesis as they critically control the development and/or function of cells involved in antitumor immune responses.<sup>11,12,22,23</sup> Such and other aspects of the IRF biology have been extensively discussed in several excellent and comprehensive reviews.<sup>11,12,16–21</sup>

### IRF1

As IRF1 and IRF2 were the first IRF family members identified, studies on the regulation of oncogenesis by IRFs were initiated on these factors. The notion that IRFs participate in the regulation of oncogenesis originally came from studies demonstrating that the phenotype of NIH3T3 cells that underwent transformation upon IRF2 overexpression was reverted by the overexpression of IRF1 (ref. 24). Subsequent studies using *Irf1*<sup>-/-</sup> mouse embryonic fibroblasts (MEFs) revealed that these cells do not undergo a normal DNA damage-induced cell cycle arrest.<sup>25</sup> Together with the oncosuppressor protein p53, IRF1 transcriptionally activates the gene encoding the cyclin-dependent kinase (CDK) inhibitor

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**Figure 1.** Schematic illustration of human and viral IRF family members. Nine human IRF family members (IRF1 to IRF9) (upper) and three vIRFs (vIRF1, vIRF2, and vIRF3) (lower), all encoded by Kaposi sarcoma-associated herpesvirus (KSHV) are shown. Length (in amino acid) is reported. IRF family members possess an amino N-terminal DNA-binding domain (DBD) that is characterized by a series of five relatively well conserved tryptophan-rich repeats. All IRF family members, except for IRF1 and IRF2, contain an IRF association domain (IAD1). IRF1 and IRF2 share another IRF association domain (IAD2), which is structurally distinct from IAD1. IRF3 and IRF7 have multiple sites that—upon viral infection—are substrates for phosphorylation by the serine/threonine kinases TANK-binding kinase 1 (TBK1) and I $\kappa$ B kinase  $\epsilon$  (IKK $\epsilon$ ). Phosphorylation at these sites is required for the nuclear translocation of IRF3 and IRF7. KSHV encodes a cluster of three viral vIRFs, all of which show homology in their N-terminal regions to the DBD of IRFs but lack several tryptophan residues. For this reason, vIRFs are believed to be unable to directly bind DNA. vIRF1 contains an IAD domain which enables vIRF1 to associate with other IRFs, such as IRF1. vIRF3 has an IAD-like domain which shows 32% identity with the IAD of IRF4, although the exact function of this domain remains elusive.

p21<sup>WAF1/CIP1</sup> (official name CDKN1A) (ref. 25). Upon DNA damage, IRF1 protein levels normally increase as a result of increased mRNA expression and protein stability, so as to act on the *CDKN1A* promoter region containing the IRF1- and p53-binding sites.<sup>25,26</sup> In the context of DNA repair, IRF1 positively regulates the expression of the DNA repair protein BRIP1, also known as Fanconi anemia gene J (FANCF), and cells lacking IRF1 expression are hypersensitive to the DNA crosslinking agent melphalan, a characteristic phenotype of FANCF-deficient cells.<sup>27</sup>

Apoptosis is a mechanism by which pre-cancerous cells are actively eliminated from the host. In the context of an activated oncogene, such as *c-Ha-RAS*, wild-type (WT) MEFs undergo apoptosis rather than cell cycle arrest in response to anticancer drugs or ionizing radiation. This sign of tumor suppression was found to depend on both IRF1 and p53 (ref. 28). While DNA damage-induced apoptosis relies on IRF1 but not on p53 in activated mature T lymphocytes,<sup>29</sup> it depends on p53 but not IRF1 in thymocytes. Thus, depending on the cell type and differentiation stage, IRF1 and p53 regulate DNA damage-induced

apoptosis cooperatively or independently. Interestingly, a transcriptional activator of both IRF1 and p53, GAAP-1, has been shown to mediate pro-apoptotic effects.<sup>30</sup> In addition, IRF1 is important for apoptosis as activated (or enhanced) by other stimuli, such as IFN $\gamma$ .<sup>31–33</sup> The IRF1 target gene(s) that are responsible for apoptotic responses have not yet been firmly identified, but may include genes coding for caspases and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).<sup>11,23</sup> The lysyl oxidase-encoding (*LOX*) gene is also a transcriptional target of IRF1, and is involved in its tumor suppressive activity.<sup>34</sup> *LOX* plays a critical role in the biogenesis of connective tissue and de facto corresponds to the independently discovered Ras rescison gene (*Rrg*).<sup>35</sup> *Rrg* has been implicated in the reversion of Ras-transformed NIH 3T3 cells, owing to its ability of preventing the activation of NF $\kappa$ B.<sup>35</sup>

Consistent with these observations, an oncogenic transformation assay in which the introduction of a single oncogene, activated *c-Ha-Ras*, into *Irf1*<sup>-/-</sup> MEFs was sufficient to transform these cells.<sup>28</sup> This does not apply to WT cells, whose transformation

**Table 1.** A summary of IRF family members and their functions in oncogenesis

IRF	Molecular Size (a.a) (Human)	Molecular Size (a.a) (Mouse)	Chromosome (Human)	Functions associated with oncogenesis	Aberrant expression	References
IRF1	325	329	5q31.1	Suppresses oncogene-induced transformation Required for DNA damage-induced cell cycle arrest Required for apoptosis induced by DNA damage and other stimuli Required for DNA repair protein expression	CML <sub>↓</sub> Leukemia <sub>↓</sub> Melanoma <sub>↓</sub> Gastoric cancer <sub>↓</sub> Breast cancer <sub>↓</sub> Endometrial adenocarcinoma <sub>↓</sub> Esophageal squamous cell carcinoma <sub>↓</sub>	26–41, 46–52
IRF2	349	349	4q34.1-q35.1	Promotes oncogenesis by antagonizing Impairs p53 function	Pancreatic cancer <sub>↑</sub>	26, 53, 55–61
IRF3	427	419	19q13.3-q13.4	Promotes virus-induced apoptosis Stimulates apoptosis in MΦ upon bacterial infection May promote DNA damage-induced apoptosis	Non-small cell lung cancer (NSCLC) <sub>↑</sub>	63–70,72,73
IRF4	451	450	6p25-p23	Promotes oncogenesis in multiple myeloma Inhibits c-Myc function and proliferation of leukemia cells	Juman T-cell leukemia <sub>↑</sub> Multiple myeloma <sub>↑</sub> B cell leukemia <sub>↓</sub>	9,74–78, 80–83
IRF5	488	497	7q32	Suppresses oncogene-induced transformation Required for DNA damage-induced apoptosis Required for Fas-induced apoptosis Promotes virus-induced apoptosis	Leukemia <sub>↓</sub> Ductal carcinoma <sub>↓</sub> IRF-5P68 in ATL or CTL <sub>↑</sub>	68, 84–89
IRF6	467	467	1q32.3-q41	Suppresses p63 expression Required for cell cycle arrest during keratinocyte differentiation Promotes cell cycle arrest	Breast cancer <sub>↓</sub>	90–96
IRF7	503	457	11p15.5	Promotes bone metastasis	Breast cancer <sub>↓</sub> Lung cancer <sub>↓</sub>	98, 99
IRF8	426	424	16q24.1	Inhibits myeloid cell growth Promotes apoptosis induced by several Types of stimuli in myeloid cells and Fas-induced apoptosis in some cancer cells Its absence leads to a chronic myelogenous leukemia-like disease	CML <sub>↓</sub> AML <sub>↓</sub> Colon carcinoma <sub>↓</sub>	100–104, 109–115
IRF9	393	399	14q11.2	Mediates Types I IFN induction of p53 May promote DNA damage-induced responses		117, 118

require the activation of at least two oncogenes, indicating a tumor suppressor-like activity for IRF1. Moreover, conditions in which activated *Ras* paradoxically inhibits the growth of myeloid cells were found to involve IRF1 and the induction of p21<sup>WAF1/CIP1</sup> (ref. 36). The ectopic expression of IRF1 suppresses the malignant

properties of cancer cell lines and oncogene-transformed cell lines in vitro and in vivo.<sup>37</sup> Although the loss of IRF1 alone rarely promotes tumor development in mice, IRF1 deficiency dramatically exacerbates the incidence of tumors caused by the expression of a *c-Ha-Ras* transgene or by *Tp53* deletion.<sup>38</sup> Thus, IRF1 operates as

a tumor suppressor whose loss, in combination with other genetic alterations, significantly increases the tumor incidence in vivo.

Mechanisms other than mutations can lead to the loss of IRF1 function in cancer. For instance, an elevated level of SUMOylated IRF1 in tumor cells interferes with IRF1-mediated apoptosis.<sup>39</sup> Splicing aberrations of *IRF1* mRNA cause the loss of functional IRF1 in myelodysplastic syndrome (MDS) and leukemia.<sup>40,41</sup> Also, a putative ribosome assembly factor that is often overexpressed in leukemic cells, nucleophosmin, binds to IRF1 and inhibits its function.<sup>42</sup> Other IRF1 repressors, Y-box protein (YB-1) and tripartite motif-containing 28 (TRIM-28), both of which are overexpressed in various cancer Types, have been identified.<sup>43</sup>

A number of clinical studies have shown a correlation between the loss of IRF1 expression or function and human malignancies. IRF1 maps to chromosome 5q31.1, a genomic region frequently affected by cytogenetic abnormalities in MDS and leukemia, and IRF1 is consistently deleted at one or both alleles in patients with aberrations of 5q31 (ref. 44). The heterozygous loss of *IRF1* has also been reported in esophageal and gastric cancer patients,<sup>45,46</sup> and in one out of four cases of gastric cancers examined the deletion of one allele of *IRF1* is accompanied by an inactivating point mutation in the other allele.<sup>47</sup> It has been reported that approximately 11% of sporadic breast cancer patients exhibit the loss of chromosome 5q12–31 (ref. 48) and approximately 30% of neoplastic breast tissues lack *IRF1* (ref. 49). In woman with breast cancer, the relatively frequent allelic loss of *IRF1* is associated with an increased risk of recurrence and death, underscoring the relevance of the tumor suppressive role of IRF1 in this clinical setting.<sup>50</sup> The mechanisms by which IRF1 contributes to tumor suppression has not yet been fully clarified.

## IRF2

IRF2 is well known for its ability to exert pro-oncogenic activities. As mentioned above, the overexpression of IRF2 in NIH3T3 cells causes oncogenic transformation.<sup>24</sup> Consistently, elevated IRF2 expression levels have been observed in pancreatic cancer patients and are associated with an increased proliferative potential of pancreatic cancer cells.<sup>51</sup> A genetic screen of a retroviral library identified IRF2 as an inhibitor of activated *N-RAS*-induced growth suppression in leukemic cells.<sup>52</sup> The pro-oncogenic functions of IRF2 appear to be mediated—at least in part—by its ability to transcriptionally interfere with IRF1 and/or other IRF family members that bind to the same ISRE elements.<sup>53</sup> In addition, IRF2 can also regulate transcription under specific conditions,<sup>54</sup> for example by stimulating the expression of genes involved in oncogenesis such as histone H4 (refs. 55, 56). It has also been reported that IRF2 is post-translationally regulated in a cell growth-dependent manner. In particular, it appears that acetylated IRF2 preferentially binds to the H4 promoter in proliferating cells only.<sup>57</sup>

Interestingly, IRF2 has been shown to interact with murine double minute 2 (MDM2), the enzyme that catalyzes the ubiquitination of p53, targeting it to proteasomal degradation.<sup>58</sup> In this context, an oncosuppressive role of IRF2 has recently been reported. Indeed, *IRF2* has been found to be inactivated

specifically in hepatitis B virus (HBV)-related hepatocellular carcinoma patients. The lack of IRF2 may impair p53 function, since IRF2 silencing decreased p53 protein levels and p53 target gene expression.<sup>59</sup> Thus, IRF2 may be bifunctional in the regulation of oncogenesis and its function may be highly cell Type- and context-dependent.

## IRF3

IRF3 is best known for its critical role as a transcription factor promoting Type I IFN expression,<sup>18,60</sup> and its contribution to oncogenesis has not yet been extensively studied. IRF3 expression has been found to be significantly higher in the neoplastic lesions of non-small cell lung carcinoma patients surviving Stage I disease than in the tumors of patients who succumbed from cancer.<sup>61</sup> In human primary lung cancer, two novel protein variants of IRF3 have been identified.<sup>62</sup> One of these variants carries the A208(GCC) → D208(GAC) substitution, which was also found in squamous cell carcinoma cases, and exhibits reduced nuclear translocation in response to activation by IκB kinase εμ (IKKεμ). It remains to be determined whether this mutant contributes to the etiology of primary lung cancer.<sup>62</sup>

Apoptosis in response to viral infection may be mediated by IRF3 activation, as the expression of a constitutively active mutant of IRF3 triggers apoptosis, while dominant negative mutants of IRF3 strongly inhibit Sendai virus- and Newcastle disease virus (NDV)-induced apoptosis.<sup>63,64</sup> Interestingly, IRF3-mediated apoptosis appears to be independent of p53 as well as Type I IFN,<sup>64</sup> but to involve the gene encoding TRAIL, which is transcriptionally activated by the ectopic expression of IRF3 (ref. 65). However, the fact that vesicular stomatitis virus (VSV) infected *Irf3*<sup>-/-</sup> MEFs undergo apoptosis as efficiently as WT cells indicates that IRF3 does not mediate apoptosis as induced by all viruses.<sup>66</sup>

IRF3 also participates in a putative apoptotic instance that is promoted by bacterial infection and mediated by Toll-like receptor (TLR) activation. Some bacteria induce indeed the apoptotic demise of macrophages by producing virulence factors that inhibit cell survival pathways such as those mediated by p38 and NFκB, and this apoptotic response appears to require IRF3 along with protein kinase, RNA-activated (PKR) and TLR4 (ref. 67). Finally, IRF3 is suspected to play a role in DNA damage-induced apoptosis as it is phosphorylated and translocates from the cytoplasm to the nucleus in response to DNA damaging agents.<sup>64,68</sup> Of interest, DNA-dependent protein kinase (DNA-PK) is capable of phosphorylating human IRF3 at Thr135, a residue that is distinct from the site phosphorylated by the serine/threonine kinase TANK-binding kinase 1 (TBK1).<sup>69</sup> Moreover, IRF3 has a potential to inhibit the growth of cancer cell lines in vitro and in vivo.<sup>70,71</sup> Taken together, these studies suggest that IRF3 may also function as a tumor suppressor protein.

## IRF4

IRF4 is a key regulator of several steps of lymphoid, myeloid and dendritic cell (DC) differentiation. Particular attention has

recently been dedicated to the role of IRF4 in B-cell differentiation and function.<sup>72</sup> The functions of IRF4 in oncogenesis and tumor progression, in particular in relationship to hematopoietic malignancies, has been extensively studied. The expression of *IRF4* mRNA is induced upon human T cell leukemia virus-1 (HTLV-1) infection.<sup>8</sup> Moreover, in Jurkat T cells, the overexpression of the HTLV-1 oncoprotein Tax induces the upregulation of IRF4, while constitutive expression levels limit the 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-1-infected T cells,<sup>73,74</sup> suggesting a possible involvement of IRF4 in HTLV-1-induced leukemogenesis. Translocations involving *IRF4* have been detected in 12 out of 169 cases of peripheral T-cell lymphoma.<sup>75</sup> In some patients with multiple myeloma as well as in cell lines derived from this tumor, the chromosomal translocation t(p25;q32) juxtaposes the immunoglobulin heavy-chain locus to *IRF4/MUM1* (multiple myeloma 1), resulting in the overexpression of *IRF4* (ref. 76). Furthermore, *IRF4* mRNA expression levels are a prognostic marker for poor survival in patients with multiple myeloma.<sup>77</sup> Recently, IRF4 has emerged as a master regulator of an aberrant and malignancy-specific gene expression program in this disease.<sup>78</sup> 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 feedforward loop. Although *IRF4* is not genetically altered in most myelomas, this positive feedback loop is likely to be triggered by the initial oncogenic activation of *MYC*, which is often amplified and inserted at ectopic genomic locations in this disease. The overexpression of IRF4 alone in lymphocytes, however, is not sufficient for the development of T-cell leukemia and multiple myeloma in transgenic mice,<sup>79</sup> suggesting that additional factors are required for the development of these neoplasms. Since interfering with IRF4 expression is lethal for multiple myeloma cells, it has been argued that IRF4 may constitute an “Achilles’ heel” of multiple myeloma that may be exploited therapeutically.<sup>72</sup>

In the activated B cell-like (ABC) subType of diffuse large B cell lymphoma (DLBCL), oncogenic mutations activate the B-cell receptor (BCR) and myeloid differentiation primary response gene 88 (MYD88) pathways, engaging NFκB and IFNβ signaling. Lenalidomide, a drug showing clinical activity against DLBCL, antagonizes a central regulatory hub in ABC DLBCL governed by IRF4 and SPIB, which together suppress IFNβ while augmenting NFκB activity. In this setting, the oncogenic signaling of BCR to NFκB induces IRF4 expression. Inhibition of the BCR-IRF4 signaling axis by the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib coupled to lenalidomide kills ABC DLBCL cells, suggesting that this pathway may constitute an attractive therapeutic target.<sup>80</sup>

Interestingly, a tumor suppressive role of IRF4 has also been reported. In particular, *c-Myc*-induced leukemia appears to be greatly accelerated in *IRF4* heterozygous mice. Evidence has also been provided that IRF4 functions as a classical tumor suppressor gene to inhibit *c-Myc*-induced leukemogenesis. Thus, IRF4 deficiency appears to accelerate the loss of p27<sup>KIP1</sup> and reconstitution of IRF4 expression in leukemic cells restores p27<sup>KIP1</sup> expression and inhibits their proliferation in vivo.<sup>81</sup>

## IRF5

IRF5 has emerged as another IRF family member that possesses tumor suppressor activity. It has been reported that IRF5 expression is reduced in human leukemia and human ductal carcinoma and that this correlates with disease stage.<sup>82,83</sup> In addition, a single point missense mutation (G202C), leading to the IRF5 variant called IRF-5P68, was identified in peripheral blood mononuclear cells from patients with adult T-cell leukemia/lymphoma (ATL) and chronic lymphocytic leukemia (CLL).<sup>84</sup> IRF-5P68 acts as a dominant negative protein and hence interferes with IRF5 activity. Taken together, these reports suggest that IRF5 inactivation relates to the development of human cancer. In nude mice, activated *c-Ha-Ras*-expressing *Irf5*<sup>-/-</sup> MEFs fail to efficiently die of apoptosis in response to DNA damage but undergo neoplastic transformation.<sup>66</sup> *Irf5*<sup>-/-</sup> MEFs are resistant to VSV-induced apoptosis, resulting in enhanced viral propagation, although they produce normal levels of Type I IFNs and interleukin-6 (IL-6) in response to infection.<sup>66</sup> The *IRF5* mRNA is induced upon viral infection through Type I IFN signaling and upon DNA damage by p53 (refs. 66, 85). Because several p53 targets, such as the genes coding for PUMA and NOXA, are induced even in *Irf5*<sup>-/-</sup> MEFs, it seems that IRF5 may operate in an apoptotic pathway that is distinct from that controlled by p53 (ref. 66). Indeed, overexpression of IRF5 inhibits in vitro and in vivo B-cell lymphoma growth in the absence of WT p53 (ref. 82). Furthermore, the ectopic expression of IRF5 sensitizes p53-proficient and p53-deficient colon cancer cells to DNA damage-induced apoptosis.<sup>86</sup> IRF5 has been involved in FAS/CD95-induced apoptosis, which typically occurs in a p53-independent manner.<sup>87</sup> *Irf5*<sup>-/-</sup> mice are resistant to liver apoptosis as well as to death induced by the administration of a FAS-activating monoclonal antibody. IRF5 is also required for FAS-induced apoptosis in DCs activated by hypomethylated CpG oligonucleotides, but not in thymocytes and MEFs. Thus, IRF5 is required for the death receptor-induced apoptosis in a cell Type-dependent manner. Interestingly, *IRF5* expression is suppressed in human leukemia cells, pointing to a possible involvement of IRF5 gene inactivation in human leukemogenesis.<sup>82</sup> Further studies are required to clarify the transcriptional pathway(s) by which IRF5 stimulates apoptosis.

## IRF6

Unlike all other IRFs, IRF6 is not involved in innate immunity, but is rather essential for the normal development and differentiation of the epidermis. Mutations of *IRF6* have been found in patients affected by the Van der Woude and popliteal pterygium syndromes, which are characterized by cleft palate and lip pits, skin folds, syndactyly and oral adhesions.<sup>88</sup> In mice, loss of *IRF6* results in severe defects in limb and skin development with compromised differentiation of keratinocytes in the interfollicular epidermis.<sup>89,90</sup> It has been shown that p63 (a member of the p53 tumor suppressor family) binds to an *IRF6* enhancer to stimulate gene expression, while IRF6 negatively regulates p63 levels, hence limiting growth of keratinocytes.<sup>91</sup> Furthermore, IRF6 has been shown to constitute a primary target of Notch signaling in

keratinocytes and to exert pro-differentiation and tumor suppression functions in this setting.<sup>92</sup>

IRF6 may also act as a tumor suppressor via its interaction with the mammary serine proteinase inhibitor (maspin), a known tumor suppressor gene.<sup>93</sup> Similar to maspin, IRF6 expression inversely correlates with breast cancer invasiveness. IRF6 is unphosphorylated in quiescent mammary epithelial cells, but during cell division IRF6 becomes phosphorylated and undergoes proteasome-dependent degradation.<sup>94</sup> Ectopic expression of IRF6 results in cell cycle arrest, a process that is exacerbated by maspin.<sup>94</sup>

### IRF7

IRF7 is best known as a master regulator of Type I IFN-dependent innate immune responses.<sup>95</sup> Most studies on the role of IRF7 in the regulation of oncogenesis have been performed in the context of Type I IFN responses. In a mouse model of spontaneous bone metastasis, a substantial number of genes suppressed in metastatic lesions are regulated by IRF7, and restoration of IRF7 in tumor cells has been shown to limit metastatic dissemination. Furthermore, in > 800 breast cancer patients, elevated expression of IRF7-regulated genes in the primary lesion has been associated with prolonged metastasis-free survival, suggesting that Type I IFN-mediated immunity is critical for preventing metastasis.<sup>96</sup> Lenalidomide has been shown to kill ABC DLBCL cells by augmenting Type I IFN production. This drug apparently downregulates IRF4 and SPIB, transcription factors that together prevent Type I IFN production by repressing IRF7 and amplify pro-survival NF $\kappa$ B signaling.<sup>80</sup> Furthermore, disruption of the IFN pathway in lung cancer cell lines and primary tumor tissues appears to be often caused by the epigenetic silencing of the critical IFN-responsive transcription factors IRF7 and/or IRF5.<sup>97</sup>

### IRF8

IRF8 is a key transcription factor for myeloid cell differentiation, and its expression is frequently lost in hematopoietic cells obtained from myeloid leukemia patients. Accumulating evidence indicates an antagonizing relationship between IRF8 and myeloid leukemia, in particular chronic myelogenous leukemia (CML). It has been shown that *Irf8*<sup>-/-</sup> mice develop a CML-like syndrome.<sup>98</sup> In CML and acute myelogenous leukemia patients, *IRF8* transcripts are absent and a number of the expression of IRF8 target genes, such as *BCL2* and *PML*, is limited.<sup>99,100</sup> Conversely, the ectopic expression of IRF8 is able to override the mitogenic activity of BCR-ABL (the etiological determinant of a vast majority of human CML cases), in vitro, by activating several proteins that interfere with the *c-Myc* pathway (a downstream target of BCR-ABL)<sup>101</sup> and to ameliorate BCR-ABL-mediated murine myeloid leukemia in vivo.<sup>102</sup> In addition, the administration of IFN $\alpha$  to CML patients induces IRF8 expression in vivo,<sup>103</sup> and—in this setting—IRF8 expression levels positively correlated with pre-treatment risk factors as well as with cytogenetic responses to IFN $\alpha$ .<sup>104</sup> Thus, IRF8 expression may be a major factor against the development of human CML. Interestingly, *IRF4* transcript

levels are also significantly reduced in CML patients,<sup>105,106</sup> suggesting that IRF4 may have an activity similar to that of IRF8 in myeloid cell development and CML pathogenesis, as it is the case for DC and B-cell development.

It is likely that IRF8 exerts its anti-leukemic activity not only by direct controlling cell growth, differentiation and apoptosis but also by modulating anti-tumor immunity. Since human CML cells are susceptible to T cell-mediated immune responses, the ability of IRF8 to support the differentiation and function of professional antigen-presenting cells (APCs) such as macrophages (M $\Phi$ s), DCs and B cells may be important for the elimination of CML cells by the immune system. In mice, the expression of IRF8 in BCR-ABL-transformed pro-B cells causes a CD8<sup>+</sup> cytotoxic T-cell response that prevents the establishment of leukemia in vivo.<sup>107</sup> Given the efficacy of IFN $\alpha$ -based therapy for human CML, it is also interesting to note that IRF8 is required for the development of plasmacytoid DCs (pDCs), which produce high levels of Type I IFNs, and that IRF8 is a transcriptional activator of Type I IFN genes.<sup>108</sup> In addition, acid ceramidase (A-CDase) has been identified as a general transcription target of IRF8. IRF8 expression is regulated by promoter DNA methylation in myeloid leukemia cells and restoration of IRF8 expression has been shown to repress A-CDase expression, resulting in C16-ceramide accumulation and increased sensitivity of CML cells to FASL-induced apoptosis.<sup>109</sup>

IRF8 has been reported to exert anti-tumor activity even in non-hematopoietic tumors. IFN $\gamma$ -induced IRF8 sensitizes human colon carcinoma cells to FAS-mediated apoptosis,<sup>110</sup> and IRF8 represses *PTPN13*, a gene that encodes a ubiquitously expressed protein-tyrosine phosphatase, FAS-associated phosphatase 1 (ref. 111). IRF8 expression is repressed by DNA methylation in human metastatic colon carcinoma cell lines and lung metastasis of murine mammary carcinoma, in vivo.<sup>112</sup> *IRF8* localizes to 16q24, a chromosomal region that is frequently deleted in several Type of solid tumor. In 78% of primary nasopharyngeal carcinoma and in 36–71% of other carcinoma samples, *IRF8* is associated with transcriptional silencing and promoter methylation.<sup>113</sup>

### IRF9

IRF9 is best known for its integral role in Type I IFN-mediated cellular responses, to which it contributed by forming a trimeric complex, termed ISGF3, with STAT1 and STAT2 (refs. 5, 12, 114). 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 *TP53* via ISGF3 binding to ISREs that are located in *TP53* promoter and first intron.<sup>115</sup> As a component of ISGF3, IRF9 stimulates the p53 pathway when cells are exposed to endogenously induced or exogenously administered Type I IFNs. Accordingly, *Irf9*<sup>-/-</sup> MEFs fail to upregulate p53 upon IFN $\beta$  stimulation,<sup>115</sup> a setting in which IFN $\beta$  normally suppresses oncogene-induced malignant cell transformation and enhance DNA damage-induced apoptosis. The link between Type I IFNs and p53 also exemplifies the relationship between tumor suppression and

antiviral immunity. On another note, it has been reported that *IRF9* is directly activated by *c-Myc*, and a cell line lacking *IRF9* expression is more susceptible to cytotoxic chemotherapeutic drugs,<sup>116</sup> suggesting an hitherto elusive role of *IRF9* in cell cycle regulation. Additional research is required to get further insights into these functions of *IRF9*.

### Viruses and IRFs in the Regulation of Oncogenesis

Many viruses have evolved mechanisms to counteract the activity of the host immune system. Given the important role of IRFs in the regulation of immune responses as well as their prominent tumor suppressive functions, it is not surprising that these transcription factors and their activation pathways are targeted by many viral factors.

The vaccinia virus-encoded proteins N1L and K7 antagonize TLR signaling at the level of I $\kappa$ B kinases (IKKs) plus TBK1 and DEAD box protein 3 (Ddx3), respectively.<sup>117,118</sup> Hepatitis C virus (HCV) encodes the nonstructural proteins 3 and 4A (NS3/4A), which function as protease and cleave IFN $\beta$  promoter stimulator-1 (IPS-1) and TIR domain-containing adaptor-inducing IFN $\beta$  (TRIF), thereby inhibiting the activation of *IRF3* and/or *IRF7* during HCV infection.<sup>119,120</sup> The rotavirus nonstructural protein 1 (NSP1) mediates the degradation of *IRF3*, *IRF5* and *IRF7* (refs. 121, 122). 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.<sup>123</sup> Furthermore, KSHV encodes a cluster of three viral IRFs (vIRFs), vIRF1, vIRF2, and vIRF3/latency-associated nuclear antigen 2 (LANA2) (Fig. 1).<sup>21,124</sup> The N-terminal region of all vIRFs is homologous of the DBD of mammalian IRFs but lacks several of the tryptophan residues that are essential for DNA binding. Thus, vIRFs are believed to be unable to directly bind DNA. Although the underlying mechanism has not yet been precisely elucidated, vIRF1 has been shown to function as a repressor of virus-mediated induction of Type I IFN genes in a transient transfection assay.<sup>125,126</sup> Additionally, vIRF2 and vIRF3/LANA2 reportedly inhibit the transactivation of Type I IFN genes, perhaps by interfering with host IRFs. Finally, vIRF3/LANA2 has been demonstrated to bind to and therefore inhibit the DNA binding activity of *IRF7* and *IRF5* (refs. 127–129).

These viral proteins not only contribute to the persistence of viral infection, but also they may constitute risk factors for virus-induced carcinogenesis. Epstein-Barr virus (EBV) latency has been associated with various human cancers.<sup>130</sup> The EBV-encoded latent membrane protein 1 (LMP-1) transforms B lymphocytes into a proliferating lymphoblastoid cell line. LMP-1 has been demonstrated to induce the expression of *IRF7* and to activate *IRF7* through receptor-interacting protein kinase 1 (RIPK1) and TNF receptor-associated factor 6 (TRAF6).<sup>131–133</sup> 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, the LMP-1-mediated activation of *IRF7* is thought to potentiate the transformation process driven by EBV.<sup>133</sup>

Human papillomavirus (HPV) is a causative agent of cervical dysplasia and cervical cancer.<sup>134</sup> 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 binds to p53 and promotes its proteolysis, whereas E7 binds to the hypophosphorylated form of RB and interferes with its binding to E2F.<sup>134</sup> Furthermore, these HPV oncoproteins target IRF family members and inhibit their activities. Thus, both E6 and E7 interfere with *IRF3*-mediated Type I IFN gene induction and *IRF1*-mediated tumor suppressor activity, respectively, hence promoting the development of cervical tumors.<sup>135,136</sup>

### Implications and Future Prospects

Since the discovery of *IRF1*, a number of critical roles for the IRF family have been revealed. Although this review focused on the regulation of oncogenesis, IRF members impact a number of aspects of the host defense system, ranging from the activation or attenuation of immune responses (essentially all IRFs) to the regulation of immune cell differentiation (*IRF1*, *IRF2*, *IRF4* and *IRF8*) as well as to the regulation of cell growth or death (again, essentially all IRFs).<sup>11,12,16,18,20,21</sup> While each member of the IRF family may be assigned a specific function, considerable overlapping exists between the functional profile of distinct IRFs. For instance, many IRFs are activated by pattern recognition receptors (PRRs) during innate immune responses. This occurs because many IRFs (i.e., *IRF1*, *IRF4*, *IRF5*, *IRF7* and *IRF8*) 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 the nucleic acid-sensing cytosolic receptors and TLRs.<sup>11,18,20,21</sup> Active 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 relay signals originating from PRR stimulation. In another example of overlapping and distinct activities, *IRF8* and *IRF4* contribute to the development of multiple DC subsets, thereby contributing to the functional heterogeneity of DCs.<sup>11,20</sup>

Of note, an IRF-related gene has been identified in *Schistosoma mansoni*, a digenetic platyhelminth trematode.<sup>137</sup> Hence, IRFs may have an ancient evolutionary origin and may have been lost in Ecdysozoa, such as *Drosophila melanogaster* and *Caenorhabditis elegans*, while they persisted in Lophotrochozoa and probably even in Ctenophora and Cnidaria.<sup>137,138</sup> Given that the Type I IFN genes have been found so far in vertebrates only, IRFs may have arisen much earlier than this cytokine system. Thus, one may speculate that the Type I IFN system was acquired by vertebrates together with the adaptive immune system, and since then it shaped the complex and efficient defense system of the host against viruses and cancer.

Further molecular insights into the versatile functions of each IRF are needed. Indeed, in spite of the extensive body of knowledge that scientific research has generated on the function of IRFs, critical questions remain. For example, the mechanisms accounting for the oncosuppressive activity of IRFs remain to be fully clarified. Also, as our understanding of the roles of IRFs

in the regulation of innate immunity improves, the broader view becomes increasingly complicated by the interrelationships between IRFs and other regulatory systems. The cooperation and antagonism between IRFs and NF $\kappa$ B are particularly intriguing. Both are activated by a remarkably common set of stimuli, such as pathogen associated molecular patterns (PAMPs) and DNA damage, and cooperatively regulate the expression of many cytokines. Still, IRFs and NF $\kappa$ B appear to exert opposite effects on cell growth and survival. In contrast to the tumor suppressive effects of several IRFs, NF $\kappa$ B acts as a potent pro-survival transcription factor and contributes to oncogenesis and tumor progression, in particular of inflammation-associated cancers.<sup>139</sup> Therefore, precisely how and to what extent these two transcription factor families cooperate or antagonize each other is an important issue to be addressed. Ultimately, a comprehensive understanding of interacting partners and target genes whereby IRFs and NF $\kappa$ B

cross-talk in various Types of cells and in response to multiple stimuli must be achieved.

Since IRFs are critical for two aspects of host defense, i.e., immunity against pathogens and tumor suppression, the IRF family may constitute an attractive therapeutic target for the treatment of malignancies, infectious diseases as well as other disorders with an immune component.

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