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Genetic and Epigenetic Regulation of Interferon Regulatory Factor Expression: Implications in Human Malignancies

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Abstract

Originally identified as regulators of the type I Interferon system, the nine mammalian members of the Interferon Regulatory Factor (IRF) family are transcriptional regulators with multiple biologic functions, among which the best known are those involved in initiating and regulating many aspect of host immunity, downstream pattern recognition receptors in response to cell injuries. In addition, these versatile proteins also regulate cell differentiation, cell growth and apoptosis in several cell types, and when mutated or disregulated significantly contribute to susceptibility to and progression of several cancers. IRF-1 is the most versatile member of the family, not essential for IFN gene expression and implicated in a variety of cellular functions spanning from the development and function of various immune cells to tumor suppression activity. IRF-3, IRF-7 and IRF-9 are more specifically involved in IFN induction and antiviral responses while IRF-5 is the regulator of inflammatory cytokines expression downstream pattern recognition receptors and IRF-6 is implicated in epithelial differentiation. IRF-8 as IRF-1 is considered a tumor suppressor gene, while IRF-2 and IRF-4 have generally oncogenic activity.

The present review focuses principally on the current knowledge on IRF genetic characteristics, including mutations, polymorphisms and epigenetic regulation that are implicated in oncogenesis.

Keywords: Cancer; Interferon regulatory factor; Mutations; Oncogenesis; Transcriptional regulation; Cytokines

Abbreviations: IFN: Interferon; IRF: Interferon Regulatory Factor; ISGs: Interferon-inducible Genes; IAD IRF Association Domain; ABC DLBCL: Activated B-cell-like Subtype of Diffuse Large B cell Lymphoma; AML: Acute Myelogenous Leukemia; LOH: Loss of Heterozygosity; UTR: Untranslated Region; CML: Chronic Myelogenous Leukemia; CLL: Chronic Lymphocytic Leukemia; GWAS:Genome-Wide Association Study; NPC: Nasopharyngeal Carcinoma; SNP: Single Nucleotide Polymorphism; IFNGR IFN-γ Receptor; MDS: Myelodysplastic Syndrome; MM: Multiple Myeloma; HDAC: Histone Deacetylases; HCC: Hepatocarcinomas; HBV: Hepatitis B Virus; MUM1: Multiple Myeloma Oncogene-1; HTLV: Human T Cell Leukemia Virus; FISH: Fluorescence *in situ* Hybridization; EBV: Epstein Barr Virus; DLBCL: Diffuse Large B Cell Lymphoma; B-CLL: B-Lymphoblastic Leukemia; PML: Promyelocytic Leukemia Protein; NSCLC: Non-Small Cancer Cell Lung; Cancer; ISGF3: IFN-Stimulated Gene Factor 3; ESCC: Esophageal Squamous Cell Carcinomas; BCL: B-cell Lymphoma; MEF: Mouse Embryo Fibroblasts

Introduction

Members of the Interferon Regulatory Factor (IRF) family were originally identified as transcriptional regulators of type I Interferon (IFN) and Interferon-Inducible Genes (ISGs) [1]. Subsequent studies recognized the critical involvement of different family members in multiple aspects of cell physiology, also beyond their function in the IFN system, that include cell differentiation and function of hematopoietic cells, regulation of gene expression in inflammation and immunity in response to pathogen- and danger-derived signals and regulation of oncogenesis. As regulators of various immune cells these factors also bridge innate and adaptive immune responses [2-8].

The IRF family is currently composed of nine mammalian members coded by distinct, but related genes phylogenetically linked with the appearance of multicellularity in animals and in vertebrates. They are subdivided in four groups IRF-1-G (IRF-1, IRF-2), IRF-3-G (IRF-3, IRF-7), IRF-4-G (IRF-4, IRF-8, IRF-9), and IRF-5-G (IRF-5, IRF-6) [9].

In vertebrates, the well-characterized IRF family members share a relatively high degree of similarity in genomic structure and syntenic gene arrangement, implying that they might have been evolved in a similar pattern and with similar selective pressure in different classes of vertebrates.

Nucleotide sequence for the human IRF-1 gene, show that the IRF-1 gene spanned 5.528 kb of DNA and included 9 translated exons and 8 introns. Among different species, the most conserved exons were exons 2, 3, and 4, in which the putative DNA-Binding Domain (DBD) for the IRF-1 protein is located. Comparison of the exon-intron organization of IRF-1vsIRF-2 genes revealed very high conservation of the organization and structure of exons from exons 2 to 4 for both genes. Although IRF-1 and IRF-2 genes show structural similarity, they differ in chromosomal localization. The other IRF family members have weak but significant homologies with IRF-1 and IRF-2 only within the N-terminal DBD, but clearly the genes for these factors are more distantly related to the two IRF genes as the primary amino acid sequences of the C-terminal region show more diversity. Indeed, the IRF family can be viewed as consisting of two large supergroups distinct by two IRF association domain (IAD):eight IRF proteins comprising three of these groups (IRF3-G, IRF4-G, and IRF5-G) share a common C-terminal IAD1 domain, while IRF-1 and IRF-2 (IRF1-G) group have

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a different C-terminal associated domain (IAD2) that is not related to any other known domain [9].

Each protein contains a well conserved DNA-binding domain, with a wing-type helix-loop-helix structure and a motif containing five regularly spaced tryptophan residues (120 aa), responsible for binding to DNA consensus sequences characterized by conserved GAAA repeats, in the context of differently defined sequences named as IFN-regulatory factor element (IRF-E) interferon-stimulated response element (ISRE) a subset of designated ETS/IRF response element (EIRE, EICE, IECS) and the more recently identified, activating protein 1 (AP-1)-IRF composite elements (AICEs) [10-14]. Functionally, the less conserved C-terminus, contains the IAD (180 aa) that mediates interactions with other IRFs, other transcription factors or cofactors and determines IRF transcriptional activity that can result in activation, repression or dual activity on target genes. IAD1, initially identified inIRF-8, which is conserved in all IRFs except IRF-1 and IRF-2 and has a structure similar to the Mad-homology 2 domains of the Smad family of transcription factors and the IAD2 which is shared by IRF-1 and IRF-2 only.

Slightly different DNA binding specificity within the broad IRF consensus sequence indicated above, patterns of expression and/or association with other regulators, are thought to be responsible for the distinct and not overlapping functions of each family member [15,16].

IRF-1, originally identified together with IRF-2, as the regulator of virus-inducible enhancer-like elements of the human IFN-β gene, was then recognized as the most versatile member of the family, not essential for IFN gene expression, even if involved in IFN-induced antiviral and antibacterial immunity. It is implicated in a variety of cellular functions spanning from the development and function of various immune cells to tumor suppression activity; IRF-3, IRF-7 and IRF-9 are more specifically involved in IFN induction and antiviral responses while IRF-5 has a distinct role in inflammatory cytokines expression and IRF-6 in epithelial differentiation. IRF-8 as IRF-1 is considered a tumor suppressor gene but as IRF-4 and IRF-2 also profoundly affects the development and function of various immune cells, as extensively reviewed elsewhere [2,4,6,7].

A number of genes regulated by most IRFs extend beyond antiviral and antibacterial activities and affect cell growth survival and apoptosis thereby implicating IRFs in cancer susceptibility and progression also independently from the regulation of immune responses. Losses of expression or function as well as IRF overexpression are observed in several human cancers. Related to oncogenesis, IRFs may thus function as anti-oncogenic or oncogenic factors.

In this review we summarize the current knowledge of IRF genetic alterations found in tumors (Figure 1) and how deregulated IRF expression/function is implicated in regulation of oncogenesis (Figure 2) briefly touching mechanisms and target genes involved. For more detailed analyses of such and other aspects of IRF function the readers are referred to other extensive reviews [2,3,5,6,8,15-17].

The Classical Tumor Suppressor IRF: IRF-1 and IRF-8

IRF-1

IRF-1, the first member of the IRF family identified, is a transcription factor that has been historically associated with type I IFN activation and anti-oncogenic properties. Even if identified as a regulator of the virus-inducible enhancer-like elements of the human IFN-β gene promoter it is actually considered not essential for IFN gene expression except in specific cell types and settings [18-20]. Intensive functional studies have revealed that, among IRFs, IRF-1 is the most multifunctional being deeply implicated in the regulation of a broad spectrum of biological functions including hematopoietic differentiation, development and activation of immune cells, antiviral and antibacterial responses, cell growth control, susceptibility to transformation by oncogenes and induction of apoptosis in response to a variety of stimuli as reviewed in [2,6,7,15]. For these last abilitiesIRF-1 is the prototype of the family recognized as a tumor suppressor gene.

IRF-1 ability to regulate oncogenesis was initially revealed by studies in knock-out-mice where a single activated oncogene, as c-Ha-Ras, introduced in Mouse Embryo Fibroblasts (MEFs) induced transformation [21]. Moreover, MEFs from IRF-1 null mice were unable to undergo DNA damage-induced cell cycle arrest, while in MEFs from wild type mice IRF-1 in cooperation with p53 transcriptionally induced the cell-cycle inhibitor p21 (WAF1, CIP1) [22]. So, although the loss of IRF-1 alone, *per sé,* rarely induces tumor development in mice, IRF-1 deficiency dramatically exacerbates tumor predisposition caused by the expression of a c-Ha-Ras transgene or by nullizygosity of the p53-encoding gene [23]. IRF-1 induces cell growth arrest and apoptosis also upon different stimuli and in other cell types as hepatocytes and cancer cell lines [24-27].

Besides being a tumor susceptibility gene, IRF-1 also behaves as a tumor suppressor-like gene since ectopic expression of IRF-1 can suppress the malignant properties of cancer cell lines and oncogene-transformed cell lines *in vitro* and *in vivo* [28-31].

As for human cancers, genetic alterations in IRF-1 expression have so far been reported in several hematological as well as solid malignancies. In humans, the IRF-1 gene maps to the chromosomal region 5q31.1, is 7.72 kb long and comprises 10 exons. A number of defects in one or both alleles including deletions, exon-skipping, alternative splice variants have been observed in human cancers. Deletions or inactivating rearrangements have been observed in human Acute Myelogenous Leukemia (AML) and preleukemic myelodisplasia [32]. In particular, 20% of patients with myeloysplastic syndrome or leukemia developing from myelodysplastic syndrome carry an exon 2 and 3 skipping of IRF-1 [33].

Large deletions in the region of the chromosome representing IRF-1 have been reported also in solid tumors. Loss of IRF-1 Heterozygosity (LOH) has been reported in esopharingeal, gastric cancer and renal cell carcinomas [34-37]. In the gastric cancer a missense point mutation in the second exon of the *IRF-1* gene of the residual allele was also identified [38]. This mutated form of IRF-1 showed markedly reduced transcriptional activity and similarly the exon-skipped form of IRF-1 lacked DNA-binding and tumor-suppressive activity. In cervical cancer alternative splicing in exons 7, 8 and 9 is an important mechanism for negatively regulating IRF-1 [39]. IRF-1 alterations have been previously associated also with breast cancer [40,41]. More recently, loss of 5q12-31 has been reported in 11% of sporadic breast cancers and in 50% of breast cancers with a mutated BRCA1 gene. Moreover analysis of microarray data sets have indicated that in breast cancer patients low IRF-1 mRNA expression is strongly correlated with both risk of recurrence and death [42].

Genetic alterations of IRF-1 genotypes are only a part of IRF-1 loss of function in malignancy and several other mechanisms can lead to the loss-of-function of IRF-1 in cancers. Decreased expression or modifications that impair IRF-1 transcriptional activity as sumoylation or binding of nucleophosmin that inhibits its DNA-binding and transcriptional activity have been reported [43,44].

	Genomic structure	Genetic mutations	SNPs	Epigenetics	REF
IRF-1	Chr(Hu) 5q31.1 5028 bp	Inactivating rearrangements of one IRF-1 allele, deletion of the second allele, exon 2 and 3 skipping ; alternative splicing in exons 7, 8, and 9 , deletions; LOH; missense point mutation (exon 2, DBD)	5q31.1: rs17622656	mir23a	[32], [33], [34], [35], [65]
IRF-2	Chr(Hu) 4q34.1 – q35.1 40307 bp	Homozygous deletion or splice-site ; missense mutations (Phe34, Lys 137)	4q34.1–q35.1: rs965225, rs2797507, rs3733473, rs3756093, rs3756094, rs3775554, rs3775556, rs3775574, rs3822118, rs6812958, rs6827018, rs6856910, rs7655800, rs9684244		[65], [84], [91],
IRF-3	Chr(Hu) 19q13.3 – q13.4 5151 bp		19q13.3–q13.4: rs2304204		[65]
IRF-4	Chr(Hu) 6p25 – p23 14446 bp	Chromosomal translocations	6p25–p23: rs872071, rs1050975, rs11242865, rs3778607, rs3800262, rs7768807, rs12211228 3'UTR:Rs1050979, rs9391997 rs1050976 and rs872071 6p25.3 : rs872071	Promoter hyper-methylation	[65], [99], [105], [106], [110], [111], [112], [117], [118]
IRF-5	Chr(Hu) 7q32 6277 bp	Chromosomal aberrations and deletions; missense point mutation (Pro68)	7q32:rs752637, rs1874328, rs10954213 miR-22	Promoter hyper-methylation	[65], [141], [142], [146]
IRF-6	Chr(Hu) 1q32.3 – q41 12994 bp		1q32.3–q41:rs861020 rs2013162, rs2013196, rs17015218		[65]
IRF-7	Chr(Hu) 11p15.5 2720 bp		11p15.5: rs1131665	Promoter hyper-methylation	[65], [151], [152], [174], [175], [176]
IRF-8	Chr(Hu) 16q24.1 18267 bp	Deletions, intronic variants	16q24.1: rs305084, rs1044873, rs305071, rs1333894; rs1044873	Promoter hyper-methylation and deacethylation miR-22	[58], [59], [60], [65], [72], [73], [74]
IRF-9	Chr(Hu) 14q11.2 4052 bp				

Figure 1: The IRF family members: genomic structure and mutations in tumors. Genomic structure of each member of the IRF family. Exons are expressed as boxes, and introns as lines. The size of exons is indicated above the boxes in bp. Principal genetic mutations and SNPs associated with malignancies are also indicated.

	STRUCTURE	FUNCTIONS IN ONCOGENESIS	ALTERATED EXPRESSION
IRF-1	WWWWW IAD2 325aa	• Suppresses oncogene-induced transformation [21,23,29-31] • Required for DNA damage-induced cell cycle arrest and apoptosis [22,28,29] • Mediated growth-inhibition by IFN-γ [24-27,80]	• AML, PML, MDS-derived leukemia [32,33] • Breast cancer [40-42] • Esopharingeal, Gastric, Renal caricinoma [34-38] • Cervical cancer [39]
IRF-2	WWWWW IAD2 349aa	• Promotes oncogenesis by antagonizing IRF-1 [41,50,85] • Impairs N-Ras function [86] • Regulates apoptosis effectors [89]	• Pancreatic cancer [89] • ESCC [88] • Breast cancer [41] • HCC [50] • Pancreatic cancer (mutation) [84] • HBV-induced HCC (mutation) [91]
IRF-3	WWWWW IAD1 427aa	• Promotes virus-induced and virus/p53/IFN-independent apoptosis [119,121] • TRAIL-dependent apoptosis [122] • Promotes damage-induced apoptosis [120] • Tumor suppressor activity [124,125]	• Lung cancer [127,128]
IRF-4	WWWWW IAD1 450aa	• Promotes oncogenesis in MM [93,103,104] • Promotes c-Myc function and proliferation of leukemia cells [104] • Tumor suppressor functions [54,107-109,118]	• MM [93,103,104] • HTLV-1-induced leukemia [96-98] • Peripheral T cell lymphoma [99] • B-malignacies [101,102] • BCL [105] • CLL (SNPs) [110,112] • CML [54,109], B-ALL [107] , • B-CLL [108], Gastric cancer [118]
IRF-5	WWWWW IAD1 504aa	• Required for DNA damage- [136,137] and for Fas/TRAIL-induced apoptosis [139,140] • Suppresses oncogene-induced transformation [134] • Cell cycle arrest [138] • Increases proliferation rate and clonogenic potential of malignant cells [155,156]	• CLL, AML [137,138], BCL [141], SML [144,145] • Ductal carcinoma [143], Gastric cancer cell lines [118], Lung cancer [152] • IRF-5 mutation (G202C) in ATL and CLL [146] • IRF5 SNP mediates melanoma immunotherapy responsiveness [150] • Oncogenic in Thymic lymphoma [156] • Tumor promoter in thyroid cancer cells [155]
IRF-6	WWWWW IAD1 467aa	• Regulates p63 expression [161] • Required for cell cycle arrest during keratinocyte differentiation [157,158]	• Breast cancer [160] • Keratinocytes-derived SCC [162,163] • Colon and Rectal cancer (mutation) [65] • Head and neck SCC (mutation) [164]
IRF-7	WWWWW IAD1 503aa	• Antitumor effect related to IFN-mediated growth suppression [129,130,171] • Inhibits bone metastasis [169]	• DLBCL [102] • Breast cancer [166,169,170] • Fibrosarcoma, Astrocytoma [172,173] • Gastric cancer cells [175] • HCC [151,176] • Lung cancer cells [152,174]
IRF-8	WWWWW IAD1 424aa	• Mediated growth-inhibition by IFN-γ [79,80] • Inhibits myeloid cell growth [52-55] • Promotes apoptosis in tumor cells [57,66,67]	• AML, MDS, CML, MM [56-58,69,72] • Solid tumors [62-68] • CLL (mutation, SNP) [59,60]
IRF-9	WWWWW IAD1 393aa	• Essential mediator of type I IFN signaling [15,179] • Mediates Types I IFN induction of TRAIL and p53 [181,182]	

Figure 2: The IRF family members: function and alteration in tumors. Summary of main functional characteristics of each member of the IRF family. Functional domains, in particular the conserved tryptophan repeats (WWWWW) in the DNA-binding domain and the IRF association domain (IAD) are indicated. A summary of IRF functions in oncogenesis and altered expression in human malignancies is also provided. Colors distinguish differential expression of the proteins in pathological conditions (green: decreased; red: increased; black: not altered/undefined).

Very recently, IRF-1 has been identified as one of the effectors of miR-23a-mediated suppression of paclitaxel-induced apoptosis and promotion of the cell proliferation and colony formation ability of gastric adenocarcinoma cells. MiR-23a is frequently up-regulated in gastric adenocarcinoma tissues and acts as an oncogene in gastric cancer, whereas IRF-1 is down-regulated. miR-23a directly binds the IRF1 mRNA 3' Untranslated Region (UTR) and specifically down-regulates IRF-1 expression to regulate pro-proliferative and anti-apoptotic activity in gastric cancer cells [45].

By mechanistic studies, several stimulated or inhibited IRF-1-target genes have been implicated in IRF-1-mediated effects, including genes encoding Caspase 1, 3, 7, 8, TRAIL, lysyl oxidase, proapoptotic genes as BAK and BAX or prosurvival genes as BCL-2 as extensively reviewed elsewhere [2,15,16,46]. Recently, the proliferation-related gene Ki-67 and SMAD7, a negative regulator for the transforming growth factor-beta signaling pathway, have also been identified as IRF-1-target genes [47,48].

Consistent with its role in tumor suppression, IRF-1 over expression in tumor lesions has been recently associated with better prognosis and response to immunotherapy [49,50]. In this respect, IRF-1 is also an effector of the Interferon -γ ability to restore breast cancer sensitivity to the anti-estrogen drug Fulvestrant used in the treatment of hormone receptor-positive metastatic breast cancer [51].

IRF-8

IRF-8 is the other family member considered a bona fide tumor suppressor gene and it is now widely accepted that both genetic and epigenetic alterations contribute to IRF-8-mediated tumor initiation and progression.

IRF-8 was originally discovered as a leukemia suppressor gene that regulates apoptotic cell death [52-55]. At variance with IRF-1 that is found ubiquitously expressed, IRF-8, is normally expressed in hematopoietic cells, including monocytes, macrophages and subsets of lymphocytes. Genetically deficient mice for IRF-8 display a severe immunodeficiency due to profound impairment in monocyte/ macrophage and Dendritic cell subset differentiation and develop a Chronic Myelogenous Leukemia (CML)-like syndrome [55]. Interestingly, CML and acute meylogenous patients lack expression of IRF-8 while therapeutic treatment of human CML with IFN-α induces IRF-8 expression *in vivo* [56-58]. IRF-8 expression levels also positively correlate with pretreatment risk features and cytogenetic response to IFN-α treatment [58]. The importance of reduced levels of IRF-8 in the pathogenesis of CML is further underscored by the observation that forced expression of IRF-8 counteracts the BCR/ ABL-induced leukemic phenotype *in vivo* and *in vitro* [57].

Due to its important role in B-cell development, the IRF-8 gene is a strong candidate also for Chronic Lymphocytic Leukemia (CLL), a B-cell malignancy and one of the most common non-Hodgkin lymphomas. A Genome-Wide Association Study (GWAS) of CLL indeed identified 4 highly correlated intronic variants within *the IRF-8 gene* associated with CLL. These results were further supported by a recent meta-analysis of this and two others GWAS that confirmed a strong role of IRF-8 for CLL risk [59]. The same Authors, very recently, identified a strongest association specifically with CLL risk with a common Single-Nucleotide Polymorphism (SNP) located within the 3' UTR of IRF-8 [60].

In the recent past, many reports have identified IRF-8 also as a crucial determinant in solid tumors [61]. IRF-8 localizes to 16q24, a chromosomal region that is frequently deleted in multiple solid tumors including cancer of nasopharynx, esophagus, breast, prostate and liver [62,63]. In Nasopharyngeal Carcinoma (NPC) cell lines a 16q24 hemizygous deletion, where the only down-regulated gene is IRF-8, is one of the critical tumor suppressor loci [64].

Associated with colorectal cancer eight SNPs in IRF8 as well as in other IRFs and in IFN-γ receptor (IFNGR)1 and IFNGR2, have recently been described [65].

Interestingly, the suppression of IRF-8 function has been correlated to enhanced metastatic potential of sarcoma cells and of human metastatic melanoma cells with respect to cells from primary tumors. Moreover, IRF-8 expression has been demonstrated fundamental for both apoptotic responsiveness and host antitumor immune surveillance mechanisms [66-68]. A control by IRF-8 of melanoma progression by regulating the cross talk between cancer and immune cells within the tumor microenvironment has also been reported in mice [68].

Epigenetic silencing of the IRF-8 promoter, for the greater part by methylation, has been found in several human cancers and multiple primary tumor cells. In some settings, as human carcinoma cells, hypermethylation of the IRF-8 promoter represents the molecular determinant for the apoptosis resistance and for the metastatic phenotype of tumor cells, with hypermethylation observed in metastatictumorcells but not in primary tumorcells [66,69]. In 78% of primary nasopharyngeal carcinoma and in 36-71% of other carcinoma samples, IRF8 was found associated with transcriptional silencing and promoter methylation [64]. IRF8 protein level also inversely correlated with the methylation status of the IRF8 promoter and the metastatic phenotype in human colorectal carcinoma specimens in vivoand in lung metastasesin mice [66,70].

In myeloid malignancies IRF-8 promoter methylation seems to be the main mechanism of gene inactivation [69,71]. By analysis of IRF-8 promoter related to clinical, diagnostic and cytogenetic characteristics of patients with Myelodysplastic Syndrome (MDS) or AML, the IRF-8 promoter was found methylated in a substantial proportion of patients and may be functionally important for accumulation of chromosome aberrations during leukemic progression [69]. DNA methylation of the IRF8 gene is a frequent event also in MultipleMyeloma(MM) cell lines and primary CD138^{+} MM cells [72]. Interestingly, endogenous IRF-8 expression could be restored by the DNA Methyltransferases Inhibitor (DNMTi) 5-aza-2'-Deoxycytidine (5AzadC) and a synergistic effect has been observed in cells treated with 5AzadC in combination with the pan-inhibitor of histone deacetylases (HDAC), Trichostatin A [72]. Consistently, it has been recently reported that IRF-8 expression is important for the response to HDACi-based antitumoractivity. Trichostatin A, alone and more so in combination with IFN-γ, enhanced both IRF-8 expression and Fas-mediated death of tumor cells in vitro. IRF-8 was required for this death response *in vivo* in mice [73].

Overall, these findings indicate that IRF-8 silencing through epigenetic regulation may represent a crucial mechanism occurring in several hematological and not hematological tumors and a major determinant of apoptosis resistance and metastatic potential phenotype.

Finally, as for IRF-1, a miRNA-mediated regulation of IRF-8 has been recently reported. In particular, overexpression and knockdown of miR-22 has shown significant effects on the mRNAabundance of IRF-8 in Dendritic cells [74]. Since miR-22 has recently been implicated in tumorigenesis by controlling tumor cell proliferation, migration/ invasion and apoptosis IRF-8 could bean effector of these functions [75-77]. Recently, the microRNA gene expression of 27 patients with

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AML with normal cytogenetics, revealed six candidate microRNAs that target several key myeloid factors, including IRF-8, and that were significantly down-regulated, suggesting that these microRNAs may potentially be involved in the maturation block of leukemic blasts [78].

As IRF-1, IRF-8 regulates several apoptosis-related genes, such as the antiapoptotic Bcl-2, Bcl-xL and FAP-1 (Fas-AssociatedPhosphatase-1), or pro-apoptotic genes, such caspase-3 and mediates growth-inhibition and apoptosis induced by IFN-γ in tumor cells [79,80]. Moreover, it is likely that both IRF-1 and IRF-8 exert their antitumor activities not only by directly controlling cell growth/differentiation and apoptosis but also by modulating antitumor immunity through their ability to support the differentiation and function of professional antigen-presenting cells such as macrophages, DCs, B and T cells.

The Oncogenic IRF: IRF-2 and IRF-4

IRF-2

IRF-2 was initially identified as a transcriptional repressor of the IFN-β gene and some ISGs by competing for binding of IRF-9 and IRF-1 to conserved ISRE/IRF-E sequences [10,81]. Further studies have shown that IRF-2 can function also as an activator of some genes including the cell-cycle-regulated Histone H4 genes and, in cooperation with IRF-1, the IFN-γ-gamma-inducible MHC class II Trans Activator (CIITA) type IV promoter [82-84].

In contrast to the anti-oncogenic activity of IRF-1, IRF-2 is considered a potential oncogene since its overexpression causes anchorage-independent growth in NIH 3T3 cells and tumor formation in mice, effects that are reversed by the concomitant expression of IRF-1 [85]. By a genetic screen of a retroviral cDNA library, IRF-2 was also identified as an inhibitor of N-Ras-induced growth inhibition in leukemic cells [86]. This pro-oncogenic function seems at least in part mediated by transcriptional interference with IRF-1 or other IRFs, binding to the same sequences, that exert proapoptotic and growth regulatory functions and/or by the stimulation of genes directly involved in oncogenesis as H4. Interestingly, by modulating its sub cellular localization IRF-2 regulates the activity of NF-κB, whose constitutive activation has been observed in a broad variety of solid tumors and hematological malignancies and is persistently active during cancer progression [87].

An increased IRF-2 expression compared with normal adjacent tissues has been reported in several cancers including Esophageal Squamous Cell Carcinomas (ESCC) where the tumorigenicity of ESCC cells was dramatically attenuated after forced expression of IRF-1 in breast cancer and in pancreatic cancer patients where IRF-2 expression was associated with tumor size, differentiation, tumor-node-metastasis stage and survival of the patients [41,88,89]. In this case, IRF-2 modulated the growth of pancreatic cancer cells by regulating proliferation and apoptosis effectors, such as cyclin D1 and BAX [89]. An association between increased IRF-2 expression and increased recurrence probability was also reported in a cohort of 332 human Hepato Carcinomas (HCC) patients. The IRF-2/IRF-1 ratio was associated with tumor invasion, probably through modulation of MMP9 expression in human HCC cell lines [50].

IRF-2 seems however bi-functional in regulating tumorigenesis as being able to act also as a tumor suppressor. Related to its ability to induce expression of the CIITA type IV promoter in response to IFN-γ, an inactivating point mutation in the DNA binding domain of IRF-2 has been identified in a human pancreatic tumor cell line that does not express CIITA or MHC class II [84]. The lack of MHC class II inducibility by IFN-γ in tumors may lead to a reduction in tumor immunogenicity, reducing the immune surveillance potential of IFN-γ. A subsequent screening of fresh pancreatic tumor explants identified two IRF-2 point mutations in 1 of 31 tumor specimens. Mutations occurred in the DNA binding domain and impaired the binding to the CIITA promoter [90]. In Hepatitis B Virus (HBV)-associated HCC, IRF-2 acts as a tumor suppressor by regulating the p53 pathway. By whole exome-sequences of 125 HCC, IRF-2 inactivation caused by homozygous deletion or splice-site or missense mutations has been found in 6 of 125 HBV-related hepatocellular carcinoma patients where IRF-2 inactivation led to impaired function of the tumor suppressor gene TP53 [91]. Interestingly, splicing and missense mutations affected the Lys137 residue which is known to be sumoylated, a posttranslational modification that increases IRF-2 ability to inhibit IRF-1 transcription while decreases its ability to activate the ISRE and H4 promoters [92].

IRF-4

The other IRF traditionally considered an oncogene is IRF-4, also known as multiple myeloma oncogene-1 (MUM1) [93]. IRF-4 expression is restricted to immune cells such as lymphocyte, macrophage and dendritic cells where it is a key factor in the regulation of differentiation and is required during an immune response for lymphocyte activation and the generation of immunoglobulin-secreting plasma cells [94,95]. Consistently, IRF4 expression deregulation is associated with many lymphoid malignancies.

A link between IRF-4 and Human T Cell Leukemia Virus (HTLV)-1-induced leukemogenesis has been initially suggested. IRF-4 mRNA expression is induced by HTLV-1 and accordingly, upregulation of IRF-4 is induced by the HTLV-1 oncoprotein Tax, in Jurkat T cells. Moreover, constitutive IRF-4 expression in T cells results in reduced expression of cyclin B1 and several DNA repair genes as in HTLV-1-infected cells [69-98].

More recently, recurrent translocations involving the IRF-4 locus have been reported in a percentage of patients with peripheral T-cell lymphoma where the majority of translocated cases were cutaneous anaplastic large cell lymphomas. Interestingly, a recent large multicenter study has demonstrated the clinical utility of Fluorescence in situ hybridization (FISH) for IRF4 in the differential diagnosis of T-cell lymphoproliferative disorders in skin biopsies, a particularly challenging issue for the pathologists [99,100].

In B cell malignancies, high levels of IRF-4 have been associated with Epstein Barr Virus (EBV) type III latency and EBV transformation of human primary B cells *in vitro*. The EBV protein LMP1, by activating the NF-κB pathway, upregulates IRF4 [101]. Moreover, IRF-4 is expressed in a significant number of specimens of primary central nervous system lymphomas, an EBV-associated malignancy, where the expression of IRF4 correlates with expression of LMP1 [101]. Similarly, IRF4 is characteristically expressed at high levels in the Activated B-Cell-like (ABC) subtype of Diffuse Large B Cell Lymphoma (DLBCL). In this setting the oncogenic signaling arising from the mutated B-cell receptor induces NF-κB and IRF-4 expression, instead of NF-κB and IFN-β signaling. Interestingly, the drug Lenalidomide shows clinical activity against ABC DLBCL cells by augmenting IFN-β expression through downregulation of IRF-4 and SPIB that together prevent IFN-β production by repressing IRF-7 [102].

The role of IRF4 in promoting malignancy has been most clearly shown in Multiple Myeloma (MM). In cells derived from multiple myeloma as well as in some patients with multiple myeloma a translocation t(6;14(p25;q32) that juxtaposes the Ig heavy-chain locus

to IRF-4, results in overexpression of IRF-4 [93]. In patients with MM, IRF-4 levels are also a negative prognostic marker for survival [103]. At the mechanistic level, gene expression profiling and genome-wide chromatin immune precipitation analysis have uncovered an aberrant and malignancy-specific network ofgenes controlled by IRF-4, including the *MYC* gene which has a prominent role in the pathogenesis of myeloma. Interestingly, IRF-4 itself is a direct target of MYC thus generating a positive regulatory loop in myeloma cells in which IRF4 and MYC mutually reinforce the expression of each other and sustain myeloma cell survival. In keeping with this model, myeloma patient samples express both MYC and IRF4 mRNA more highly than normal plasma cells [104]. These data and the observation that interfering with IRF-4 expression is lethal for the maintenance of multiple myeloma, highlighted the crucial role of IRF-4 in this disease making IRF-4 an attractive therapeutic target for this malignancy [94].

Chromosomal translocations juxtaposing the *IRF4* oncogene next to one of the Immunoglobulin (IG) loci has been reported also as a recurrent aberration in a subtype of mature B-cell lymphoma affecting predominantly children and young adults [105] and recently, also in 3 low-grade B-cell lymphoma cases [106].

As for IRF-2, a tumor suppressive role of IRF-4 in some settings has been suggested. In particular, IRF-4 may functions as a tumor suppressor in the myeloid lineage and in early stages of B cell development. In contrast to its oncogenic function in late stages of B lymphopoiesis, indeed, expression of IRF-4 is down-regulated in certain myeloid and early B-lymphoid malignancies. This is in accord with IRF-4/IRF-8 cooperation in the development of both myeloid and lymphoid lineages [94,95]. Mice deficient in both IRF-4 and IRF-8 develop, from a very early age, a more aggressive CML-like disease than mice deficient in IRF-8 alone and eventually develop and die of a B-lymphoblastic leukemia/lymphoma [54]. IRF-4 deficiency also enhances BCR/ABL transformation of B-lymphoid progenitors in vitro and accelerates disease progression of BCR/ABL-induced acute B-lymphoblastic leukemia (B-ALL) in mice while forced expression of IRF-4 reverts these effects *in vitro* and *in vivo* [107].

In patients, low levels of IRF4 were found to correlate with poor prognosis in B-CLL and the down regulation of IRF-4 has been reported in T cells of CML patients [108,109]. In a genome-wide association study a single SNP in the 3' UTR region of IRF-4 that exhibited strong statistical association with CLLsusceptibility, has been observed in several independent patient cohorts [110]. Interestingly, this phenotype was associated more strongly with the subtype of CLL that has mutated immunoglobulin genes, in accord with the crucial role of IRF-4 in the differentiation of plasma cells [95]. This allele isalso associated with an increased risk of developing Hodgkin lymphoma [111]. Subsequent, fine-scale mapping analysis identified four SNPs mapped to a 3-kb region in the 3'-UTR of the *IRF-4* gene [112]. Further analysis suggested that the presence of the SNPs was associated with a downregulation of IRF-4 [112].

A causal relationship between low levels of IRF-4 and the development of CLL has been recently demonstrated in immunoglobulin heavy chain Vh11 knock-in mice bred into IRF-4 deficient mice. IRF4$^{-/-}$Vh11 mice develop spontaneous early onset CLL with 100% penetrance and CLL cells from these mice are resistant to apoptosis while reconstitution of IRF4 expression inhibits their survival [113]. Similarly, in IRF-4 heterozygous mutant mice in the New Zealand Black mice (NZB) background (NZB IRF-4$^{+/-}$) CLL development is dramatically accelerated [114]. Other polymorphisms in IRF-4 have also been associated with B cell malignancies [115,116].

Alterations in the expression and/or function of IRF-4 due to promoter silencing by DNA methylation have been also reported in leukemia and expression of IRF-4, together with that of IRF-5, and IRF-8 was frequently suppressed due to methylation of the three genes in gastric cancer cell lines [117]. Among a cohort of 455 gastric cancer and noncancerous gastric tissue samples, methylation of IRF-4 was frequently observed in both gastric cancer specimens and noncancerous specimens of gastric mucosa from patients with multiple gastric cancers, suggesting that IRF-4 methylation could be a useful molecular marker for diagnosing recurrence of gastric cancers [118].

Thus, depending on the context and stage of hematopoietic cell differentiation in which its expression is deregulated, IRF-4 may act as an oncogene or a tumor-suppressor like factor.

The Cell Growth or Death Regulator IRF : IRF-3, IRF-5 and IRF-6

IRF-3

IRF-3, as its highly homologous IRF-7, has been mostly studied as the inducer of type I IFN expression after activation upon engagement of Pattern Recognition Receptors in response to invading pathogens and as a mediator of virus-induced apoptosis [5]. However, IRF-3 stimulates apoptosis also in the absence of viral infection and in response to DNA damaging agents [119,120]. IRF-3-mediated apoptosis seems to be independent of IFN or p53 but dependent on TRAIL which is transcriptionally activated by IRF-3 [121,122]. Direct transcriptional activation of Promyelocytic Leukemia protein (PML) by IRF-3 that results in the p53-dependent growth inhibition of cancer cells *in vitro* and *in vivo* has also been reported [123]. Consistently, a dominant negative mutant IRF-3 lacking the DNA-binding domain has demonstrated oncogenic potential [124]. In accord with its role in DNA damage-induced apoptosis, IRF-3 overexpression can inhibit the growth of cancer cell lines *in vitro* and *in vivo* blocking DNA synthesis, inducing apoptosis and causing infiltration of inflammatory cells in transplanted tumors [124,125]. Recently, it has been reported that *in vitro* adenovirus-mediated IRF-3 gene transfer in glioma cells modulates IL-1/IFNγ-induced cytokine and chemokine genes, resulting in upregulation of IFN-β and IP-10 and downregulation of proinflammatory and angiogenic genes resulting in inhibition of glioma cells proliferation, migration and invasion [126].

While much information on IRF-3 has been derived from tissue culture studies, expression and role of IRF-3 in oncogenesis, in humans, is poorly understood. Since so far no loss-of-function mutations of IRF3 have been reported in any human cancers this has fueled a debate about whether IRF3 can be actually considered a tumor suppressor gene. One study reported normal IRF-3 expression in lung epithelial cells but altered expression in lung cancer where two protein variants of IRF-3 have been identified even if their significance in the etiology of primary lung cancer has not been established [127]. Moreover, using genome wide cDNA microarray screening, higher IRF3 expression in patients with a better prognosis after curative resection of non-small cell lung cancer, as compared to those with a poor prognosis, has been detected [128].

IRF-3 could induce tumor suppression also by transcriptional reprogramming of macrophages [129,130].

Further studies are, however, necessary to elucidate molecular mechanisms involved and the exact role, if any, of IRF-3 in human tumors.

IRF-5

IRF-5 has been shown to be a critical mediator of host immunity and cellular responses to DNA damage [131-134]. IRF-5 expression is constitutive in B cells and DCs but it is also inducible by type I IFN and Toll like Receptor signaling upon viral infection and by p53 upon DNA damage [131-136].

Beside the IRF-5 extensively investigated and well-recognized function in pathogen-induced immunity where its distinct signature is the induction of early inflammatory cytokines and chemokinesIRF-5 is also a target of p53 suggesting a role in DNA damage response and tumor suppression [2,6,7,133,134,136,137]. Cells lacking *Irf5* are resistant to DNA damage-induced apoptosis and overexpression of IRF-5 restores their sensitivity to apoptosis [136-138]. MEFs from *Irf5*-deficient mice expressing activated c-Ha-Ras fail to die of apoptosis in response to DNA damage and undergo neoplastic transformation [134]. In response to DNA damage, IRF-5 translocates into the nucleus where it may regulate apoptosis-related genes [134,137].

Interestingly, although IRF-5 is a downstream target of p53, its functional activity on apoptosis and cell cycle arrest is distinct from that of p53, since several p53 targets are normally induced in *Irf5*-null MEFs [134,138].

A role of IRF-5 in tumor suppression independent of p53 has also been suggested [134,137,138]. IRF-5 overexpression inhibits B cell lymphoma tumor growth *in vitro* and *in vivo* in the absence of p53 and sensitizes p53-deficient colon cancer cells to DNA-damage-induced apoptosis [137,138]. IRF-5 is also involved in Fas-induced apoptosis, which is known to be a p53-independent pathway, in a cell-type-specific manner [139]. Independently of p53, IRF-5 promotes apoptosis also upon signaling through TRAIL binding to its Death Receptor (DR). TRAIL indeed, induces a signaling cascade that leads to the phosphorylation and nuclear localization of IRF-5, resulting in transactivation of key DR signaling components [140].

Following initial observations that, while IRF-5 is constitutively expressed in lymphoid tissues and DC, it is not detected in B- and T-cell leukemia cell lines nor in clinical samples from patients with CLL and AML several evidences supporting an involvement of IRF-5 in human cancer have been reported [132,137,138].

IRF-5 was mapped to chromosome 7q32 that contains a cluster of imprinted genes and/or known chromosomal aberrations and deletions in lymphoid and solid cancers [141,142]. In human leukemia and in human ductal carcinoma, IRF-5 expression levels have been found reduced and related to disease stage and metastatic potential, supporting the concept that IRF-5 inactivation is closely related to human cancer [138,143]. Recently, high-throughput sequencing and expression analysis identified a deletion in 7q32.1–q32.2 in patients with splenic marginal zone lymphoma and comparative expression analysis found a significant reduction in IRF-5 expression in splenic marginal zone lymphoma with the 7q32 deletion versus non-deleted tumors [144,145].

In peripheral blood from CLL and Adult T-Cell Leukemia/Lymphoma (ATL) patients a single missense point mutation (G202C) in DNA binding domain of IRF-5 (IRF-5P68) has been described. The IRF-5 (P68) mutant functions as a dominant negative molecule leading to the inhibition of IRF-5 DNA binding and transactivation activity [146].

Starting from the observation that the development of autoimmunity in patients with malignant melanoma is linked to tumor regression following several types of immunotherapy and that several evidences have associated genetic variants of IRF-5 with the risk to develop autoimmunity an involvement of IRF-5 also in responsiveness to cancer immunotherapy has been recently highlighted [147-150]. The lack of the A allele in the single nucleotide polymorphismsrs10954213 (G>A) in IRF-5, that is protective against the development of SLE is, indeed, associated to complete non-responsiveness to treatment among 140 patients with metastatic melanoma who received adoptive therapy with tumor infiltrating lymphocytes. Interestingly, significant differences in global transcription, enriched in genes related to immune regulation, were observed between melanoma cell lines carrying or not the A allele. The *IRF-5* polymorphism appears to be a predictor of immune responsiveness of melanoma metastases to immunotherapy, linking, at least in part, immune responsiveness to the genetic background of the host [150].

Even if there are no convincing evidence, so far, of an epigenetic control of IRF-5 expression directly associated with cancer, it has been showed that IRF-5, together with IRF-4 and IRF-8 was frequently suppressed in gastric cancer cell lines and methylation of the three genes correlated with their silencing. Treating the cells with the Demethylating Agent 5-aza-2'-deoxycytidine (DAC) restored their expression and the suppressive effects of IFN on cell growth. This suggests a role for epigenetic IRF inactivation in tumorigenesis of gastric cancer, however this relationship has not yet been defined in cancer and noncancerous gastric tissue samples [118]. Promoter hypermethylation of *IRF-5* with inactivation of gene expression has been reported also in hepatocellular carcinoma even if clinicopathological implications have not been defined [151]. Epigenetic silencing by methylation of *IRF-5* gene promoter has been observed also in lung cancer cells and together with silencing of *IRF-7* is believed to be the major mechanism of disruption of the IFN pathway in these cells and in primary tumor tissues [152].

Recently IRF-5 has been reported as one of the miR22-target gene. miR-22, activated by the oncogene Myc, promotes proliferation in primary human cells downregulating the anti-proliferative p53 and IFN pathways by directly targeting several cell-cycle arrest genes that mediate the effects of p53, the high mobility group box-1 and IRF-5 [153].

IRF-5 is also targeted by IRF-4 to regulate EBV transformation. IRF-4 negatively regulates IRF-5 promoter reporter activities and binds to IRF-5 promoters *in vivo* and *in vitro*. Knockdown of IRF-5 rescues IRF-4 knockdown-mediated growth inhibition and IRF-5 overexpression alone is sufficient to induce cell growth inhibition of EBV-transformed cells [154].

Even if most of these evidences suggest a role of IRF-5 in tumor suppression, IRF-5 expression relating to the development of human cancer has recently also been reported. IRF5 was found highly expressed in thyroid cancer cells and in both primary and immortalized thyroid carcinomas but not in normal thyrocytes. Furthermore, ectopic IRF-5 increased both the proliferation rate and the clonogenic potential of malignant thyroidcells, protecting them from the cytotoxic effects of DNA-damaging agents. However, thyroid cancer cells localize IRF-5 to the cell cytoplasm implying that the protein is transcriptionally inactive [155]. Similarly in low-dose gamma-Irradiation (IR)-induced thymiclymphomagenesis mice model, *IRF-5* deletion significantly suppressed thymic lymphoma development [156]. Suppression seemed primarily due to reduced thymocyte and hematopoietic stem cell apoptosis, even if loss of both DNA damage-induced apoptosis and inflammation cannot be excluded.

These observation would suggest that the effects of IRF-5 in tumorigenesis may be cell-type-specific, related to those tissues were it is constitutively expressed in non-pathological conditions, or that a cell-type-specific regulation of IRF-5 target genes may occur. Further studies are, however, required to elucidate a clear picture of the role of IRF-5 in tumorigenesis.

IRF-6

Despite structurally related to IRF-5, IRF-6 has completely different functions andhas not been linked to functions or regulatory pathways described for other members of the family. IRF-6 is, indeed, required for the normal development of epidermis regulating the switch from proliferation to differentiation of keratinocytes [157,158]. In humans,mutations of the *IRF-6*gene are associated with two related syndromes, the Van der Woude syndrome and the popliteal pterygium syndrome both characterized by cleft lip and palate [159].

A role of IRF-6 in tumor suppression is based on its interaction with the mammary serine proteinase inhibitor (maspin) a known tumor suppressor gene that promotes apoptosis and inhibit cell invasion and whose expression is decreased in breast carcinomas. Similarly to maspin, IRF-6 expression inversely correlates with breast cancer invasiveness, IRF-6 acts, indeed, in a coordinated manner with maspin, in promoting mammary epithelial cell differentiation by inducing cell-cycle arrest [160].

In keratinocytes, a feedback regulatory loop does exist where DeltaNp63 isoform of p63 (a member of the p53 tumor suppressor family) activates transcription of IRF6 that in turn induces proteasome-mediated DeltaNp63 degradation. This loop allows keratinocytes to exit the cell cycle, thereby limiting their ability to proliferate [161]. Furthermore, in keratinocytes and keratinocyte-derived squamous cell carcinoma (SCC cells) IRF-6 is a primary target of Notch contributing to the role of this pathway in differentiation and tumor suppression [162]. Consistently, a function for IRF-6 in suppression of tumorigenesis in stratified epithelia has been reported. Genome-wide analysis in primary human keratinocytes, indeed, identified a subset of direct IRF-6-target genes. Most of these genes are involved in cell cycle, cell adhesion and motility and control of epidermal precursor proliferation/differentiation switch [163]. Recently, whole-exome sequencing data from 92 head and neck squamous cell carcinoma patients, identified in at least 30% of cases mutations in genes that regulate squamous differentiation including *NOTCH1*,*IRF-6* and *TP63* known as DeltaNp63 [164]. SNPs *IRF-6* inversely associated with colon and rectal cancer have been also reported [65].

The Mediators of type I IFN Antitumor Activities: IRF-7 and IRF9

IRF-7

IRF-7 is recognized as the master regulator of type I IFN gene expression upon infections, that is also part of a positive feedback regulatory loop essential for sustained IFN responses and in this context has been extensively studied [165].

The antitumor effects of IRF-7 seem mostly related to its ability to induce type IIFN where the growth suppressive IFN pathway may be a necessary early event in the development of cancer, particularly associated with immortalization.

As mentioned before, in ABC DLBCL, the drug Lenalidomide has been shown to kill ABC DLBCL cells by augmenting type I IFN production through downregulation of IRF-4 and SPIB that prevent type I IFN production by repressing IRF-7 [102]. IRF-7 has also been shown to be a transcriptional target of the tumor-suppressor gene BRCA1 mutation of which is involved in hereditary predisposition to breast and ovarian cancer. BRCA1 is also essential in cellular processes as DNA repair, cell-cycle regulation and chromatin remodeling [166-168]. Silencing of IRF-7 in breast cancer cells promotes bone metastasis. These findings have been confirmed in the clinical setting in over 800 patients in which high expression of IRF7-regulated genes in primary tumors was associated with prolonged bone metastasis-free survival [169]. A synergistic stimulation of IRF-7 by IFN-γ and BRCA1, coincident with the synergistic induction of apoptosis, also occurs [170]. Whether IRF-7 exerts some tumor suppressor functions or may affect the tumor suppressor function of BRCA1 and/or whether in this settingits antitumor effects are mostly related toits ability to induce type I IFN requires, however, further studies.

In macrophages, IRF-7 overexpression induces production of type I IFN and increased expression of genes encoding TRAIL, Interleukin (IL)-12, IL-15, and CD80 and negatively regulates the transcription of pro-tumorigenic genes as vascular endothelial growth factor and matrix metalloproteinase-2. Furthermore, IRF-7-transduced macrophages exert a cytostatic activity on different cancer cell lines [129,130].

IRF-7 is also involved in the effects of IFN-γ in tumor immune surveillance by affecting either immune cells or tumor cells. The responsiveness of IRF-1, -3, -4, and -7 in the Noxa promoter region in response to IFN-γ might, indeed, be crucial in LPS-induced tumor elimination [171].

The *IRF-7* gene is locatedon human chromosome 11p15.5 in a region rich in CpG. Hypermethylation of the CpG island in the *IRF-7* promoter has been shown to be responsiblefor silencing the *IRF-7* gene in the 2fTGH fibrosarcoma cell line and human astrocytoma tissues [172,173]. Epigenetic silencing by methylation of *IRF-7* and *IRF-5* gene promoters has been observed in different cancer cell lines and is believed to be the major mechanism of disruption of the IFN pathway in lung cancer cells and primary tumor tissues [152,174]. Promoter hypermethylation of *IRF-7* promoter was also observed in gastric cancer cell lines [175] and hepatocellular carcinoma [151,176]. Recently, the analysis of hundreds of primary Non-Small Cancer Cell Lung Cancer (NSCLC) samples from The Cancer genome Atlas project (TCGA), revealed a low basal expression signature associated with low IRF-7 expression and promoter methylation in squamous tumors and the positive therapeutic effect of epigenetic modulation supported an antitumor activity mainly related to type I IFN responses (Wrangle et al. Epigenetic therapy and sensitization of lung cancer to immunotherapy. Abstract n. 4619 AACR annual meeting April 2013 Washington, DC).

A role of IRF-7 in cell transformation has been reported in a cell-type specific manner and in the context of viral infection as reviewed in [177,178]. This is the case of EBV infection where EBVhijacks IRF-7 to regulate its replication and to induce transformation. The EBV-encoded latent membrane protein 1 (LMP1) that transforms B lymphocytes into proliferating lymphoblastoid cells, indeed, induces and activates IRF-7 that potentiates the transformation induced by EBV probably stimulating anchorage-independent growth of infected cells. IRF-7 also induces the expression of LMP1 in a regulatory loop that potentiates oncogenic properties of both factors.

IRF-9

IRF-9 as part of a ternary complex termed the IFN-stimulated gene factor 3 (ISGF3), is an essential mediator of type I IFN signaling

[15,179]. IRF-9 role in tumor suppression is specifically exerted in the context of type I IFN antitumor activities where TRAIL is one of the principal mediator of the IFN-α effect [180,181]. Most of the ISGs with antitumor activities also require IRF-9 to be transcriptionally activated, including some IRFs as IRF-5 and IRF-7. Some of these ISGs can mediate tumor-suppressor activities directly in tumor cells or indirectly through the activation of tumor immunity. Moreover, IFN-induced p53 upregulation is mediated by ISGF3 and contributes to boost the activation of the p53-mediated proapototic pathway following treatment with DNA-damaging agents. Thus a cross-talk between the type I IFN-mediated signaling and p53 pathway is implicated in both tumor suppression and antiviral immunity [182].

Conclusions and Perspectives

During the last decade mechanistic studies and genome-wide analysis have revealed the genomic landscapes of common forms of human cancerand a new field of research named "cancer genomics" started to develop [183,184]. In the present review we describe the specific impact of IRF functions in oncogenesis, focusing on genetic and epigenetic alterations that deregulate their expression as summurized in Figures 1 and 2.

IRFs represent a sparkling and versatile family of transcriptional regulators that exert critical roles in the maintenance of homeostasis of mammalian systems. Since their discovery, more than 20 years ago, members of the family have grown in number and diversity of their functions. Most well-known are their roles in regulating/initiating host immunity downstream danger sensors, but IRFs also crucially impact several other aspects of host defense systems as regulation of hematopoietic differentiation and control of cell-cycle and apoptosis and thus oncogenesis and antitumor immunity in several cancers, with overlapping as well as unique functions.

IRF implication in tumorigenesis has been recognized for a long time, yet little is still known of their expression in primary human tumors or of their roles in disease development/progression.

According to the old concept that two main types of cancer-causing genes exist, oncogenes and tumor suppressor genes, some IRFs have been classified as oncogenes, IRF-2 and IRF-4, or as tumor suppressor genes, IRF-1 and IRF-8. However, as described above, many IRFs including IRF-2, -4, -5, -7 can serve as both tumor promoting or tumor-suppressor genes depending on the cellular context in which they are expressed or on the stage of cell differentiation in which their expression is deregulated. Although only briefly mentioned in the present review, some IRFs also play a role in antitumor immunity. Many of them are indeed stimulators of type I IFN expression and some of them are effectors of both type I as well as type II IFN, whose roles in growth inhibition and immune surveillance, respectively, are well established [185]. In addition, most IRFs regulate the development of hematopoietic cells including differentiation and function of professional antigen-presenting cells as Dendritic cells that are sensors of not only pathogens but also cancer cells.

Although our knowledge of IRF biology has enormously expanded in the last decade, the picture arising from the recognized role of IRFs in oncogenic transformation is still fragmentary and incomplete and several further insights are needed.

IRFs, exert their varying functions by stimulating a partially overlapping but distinct set of target genes that impacta number of cellular functions, often in association with other transcriptional regulators, even of the same family, and co-regulators. In this respect, beside elucidation of signaling pathways downstream specific stimuli, a comprehensive understanding of genes that are transcriptional targets of IRFs, often in a cell-type and expression level-specific fashion and of IRF- interacting partners awaits to be fully elucidated. Of particular interest, are interactions with NF-κB with which IRFs share common features including activation by a common set of stimuli as pathogens and DNA damage and cooperatively regulate many target genes, while appear to exert opposite effects on cell growth and survival.

Moreover, while post-translational modifications that regulate the activity of some IRFs have been clearly defined in the setting of pathogen-stimulated immunity, modifications of IRFs that impact on IRF tumorigenic or antioncogenic functions are much less investigated.

Our comprehension of the epigenetic regulation of gene expression and of its complexity has enormously increased in the last few years thank to the development of the new global proteomic and genomic technologies. Even though cancer is a disease initiated and driven by genetic anomalies indeed, it is now clear that misregulation in DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting are central to many facet of transformed cells including self-renewal, differentiation blockade, evasion of cell death, and tissue invasiveness. In the last few years, studies on epigenetic regulation as well as on targeting of IRFs by microRNA in cancer started to appear, highlighting a new layer of complexity in IRF regulation that may account for differential activities of IRF in a cell-type and stimuli-specific context and for deregulation of their expression in oncogenesis. However, these studies are still in their infancy and the picture arising still too fragmentary to indicate a causal relationship with cancer. Studies of IRF epigenetic regulation, significance of IRF polymorphisms as well as functional deregulation of IRF activation in cancer must thus be actively pursued.

Finally, interrelationships between the role of IRFs in immunity/oncogenesis andother regulatory pathways as metabolism is still an unexplored area of research. An association between cancer and altered cellular metabolism has been known for decades and the discovery of cancer-associated mutations in several metabolic enzymes has recently fueled the interest on the role that altered metabolism plays in tumor development and maintenance. Some existing chemotherapies already target metabolic enzymes while developing new cancer drugs that interfere with metabolism is an expanding area of research [186,187]. To date little is known on the role of IRFs in metabolic homeostasis even if an involvement in the regulation/interference with some metabolic pathways, linked to IRF-mediated immune responses, is emerging, as recently discussed [178].

Thus, future studies aimed at the elucidation of the full range of target genes triggered by IRFs as well as of IRF cross-talk with other transcriptional regulators, functional deregulation of their activation, epigenetic regulation and significance of IRF polymorphisms in the context of tumorigenesis, by using system biology strategies, will aid in defining an holistic understanding of IRF activities with important therapeutic implications.

Translation of these basic knowledges on the multifarious activities of IRFs into novel therapeutic strategies for the treatment not only of infectious and inflammatory diseases but also of cancer represents a future challenging goal.

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