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INTERFERONS AND THEIR STIMULATED GENES IN THE TUMOR MICROENVIRONMENT

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Abstract

Constitutive expression of interferons (IFNs) and activation of their signaling pathways have pivotal roles in host responses to malignant cells in the tumor microenvironment. IFNs are induced from the innate immune system and in tumors through stimulation of Toll-like receptors (TLRs) and through other signaling pathways in response to specific cytokines. Although in the oncologic context IFNs have been thought of more as exogenous pharmaceuticals, the autocrine and paracrine actions of endogenous IFNs probably have even more critical effects on neoplastic disease outcomes. Through high-affinity cell surface receptors, IFNs modulate transcriptional signaling, leading to regulation of over 2000 genes with varying patterns of temporal expression. Induction of the gene products by both unphosphorylated and phosphorylated STAT1 after ligand binding, results in alterations in tumor cell survival, inhibition of angiogenesis, and augmentation of actions of T, natural killer (NK), and dendritic cells. The interferon-stimulated gene (ISG) signature can be a favorable biomarker of immune response but, in a seemingly paradoxical finding, a specific subset of the full ISG signature indicates an unfavorable response to DNA damaging interventions such as radiation. IFNs in the tumor microenvironment thus can alter the emergence, progression, and regression of malignancies.

Although in an oncologic context IFNs have been often thought of more as exogenous pharmaceuticals, the autocrine and paracrine actions of endogenous IFNs probably have even more critical effects in contributing to tumor outcomes in patients. Constitutive expression of interferons (IFNs) and activation of their signaling pathways have pivotal roles in host responses to malignant cells in the tumor microenvironment. Induction of IFNs in immune effector cells, together with sustained effects of STAT1, can result in direct alterations in tumor cell survival, inhibition of angiogenesis, and augmentation of actions of T, NK cells and dendritic cells. These effects derive from immune cell recognition of tumors, endothelial cell proliferation, and response of tumors to exogenous DNA damage. With receptors present on almost every cell type, IFNs through their cellular actions can

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alter the emergence, progression, and regression of malignancies (Table 1). The interferon-stimulated gene (ISG) signature can be a favorable biomarker of immune response but, in a seemingly paradoxical finding, a specific subset of the ISG signature indicates an unfavorable response to DNA damaging interventions such as radiation.

IFNs, a family of secreted α-helical cytokines, are induced by the innate immune system through stimulation of Toll-like receptors (TLRs) and other signaling pathways in response to specific extracellular biomolecules (pathogen- or damage-associated molecular patterns, PAMPs or DAMPs). Through high-affinity cell surface receptors, IFNs activate kinase-driven signaling, leading to the induction of over 2000 transcriptionally regulated ISGs with varying patterns of temporal expression after ligand binding. Although most genes (>1500) are stimulated, some are suppressed (~300).[1–7] These ISGs, stimulated by exogenous IFNs at the RNA level up to 100 fold include structural proteins, transcription factors, adaptors, enzymes, and secreted proteins.[5]

Expression arrays and cytogenetic analyses have identified somatic, homozygous deletions of the chromosomal locus for IFNs-α and IFN-β and germline mutations of ISGs in colon, lung, prostate, breast, head and neck, and pancreatic carcinomas, melanoma, and hematologic malignancies.[8–17] Epigenetic and genetic silencing of signaling pathways stimulated by IFNs is also likely to influence tumor development.[18–21] Although we will draw on insights from studies of actions of exogenously added IFNs, our focus is to illustrate how endogenous host IFNs can potently influence early regression or later either stability or progression of the neoplastic process. Since tenets regarding their protein structure, receptors, and intracytoplasmic signaling have been the basis for new insights concerning endogenous IFNs and their activation, we will begin with a short overview of canonical findings and understandings.

GENES, RECEPTORS, PROTEINS, AND CANONICAL SIGNALING

Classification of the several types and families of IFNs comes from commonality in both primary structures and their influence on three dimeric target receptors. Based on similarities and differences, there are three major classes of IFNs.[22–25] Type I IFNs include the IFN-α family with its many isoforms, IFN-β, and other IFNs of less studied significance in humans, IFN-ω, IFN-τ, IFN-κ, and IFN-ε.[23, 26] The sole type II IFN is IFN-γ.[27] A more recently discovered family, type III IFNs or IFNs-λ (IL-28/29) and its isoforms are produced by mucosal epithelial cells.[24] Type III IFNs share structural homology and induction pathways with type I IFNs but with cell lineage distribution of its unique receptor restricted to mucosal epithelial cells and plasmacytoid dendritic cells (pDC).[24, 28]

The genes for the human type I IFNs including those encoding 14 subspecies of IFN-α, are clustered at 9p21.[22, 26] As proteins, the human IFN-α subspecies have about 50% sequence identity; IFN-β is about 20% identical to IFN-α2. IFNs-α and IFN-β have 186–190 amino acids and have a cleavable signal peptide resulting in secreted proteins of 165 or 166 amino acids. Structure–function analyses have shown that the NH_2 terminus of type I IFNs is important for biological activity.[26] The gene encoding IFN-γ, located on human chromosome 12, has three introns, encodes a protein of 146 amino acids, functions as a

dimer, and has minimal homology with type I IFNs.[27] NK and T cells are major sources of IFN-γ. Type I IFNs are produced predominantly by dendritic cells but can be induced in all cell types including T cells, monocytes, fibroblasts, and epithelial cells.

Virus or microbial gene products, such as dsRNA, ssRNA, dsDNA, ssDNA, or cell wall constituents (PAMPs) bind to specific membrane proteins (TLRs) to trigger type I IFN synthesis.[29–34] dsRNA can be recognized by TLR3 and also by two cytosolic RNA-helicases, RIG-I and MDA5, both of which are ISGs.[33–35] Viral single-stranded RNAs are recognized by TLR7 and TLR8 and viral and cellular DNAs (DAMPs) by TLR9 and STING, all present in endosomal membranes.[29, 30, 32, 33] Adaptor proteins connect TLRs to specific protein kinases such as TBK1 and IKK to activate transcription factors NFκB, IRF3, IRF7, and AP-1.[32, 33]

For IFN-β induction, NFκB, the AP-1 complex composed of ATF2/c-jun and IRF1, and IRF3 or IRF7 are required.[35, 36] IFN-β induces further IRF7 synthesis, which, in turn, induces transcription of IFN-α1 and other IFN-α genes.[31] Inhibition of IFN signaling blocks robust production of IFNs-α. Synthesis of various IFNs is, therefore, intimately linked and further influenced by interferon regulatory factors (IRFs), a family of nine transcription factors that have common DNA binding domains in their N-terminus. IRFs were first identified through the role of IRF1 in inducing IFN-β.[37–39] IRF1 is expressed constitutively and also in response to IFN-γ as is IRF8.[40] Although IRF3 and IRF7 are important in inducing Type I IFNs, IRF1 and possibly IRF5 may determine which species of IFNs are induced by TLR activation. IRF7 amplifies the phosphorylated activation of constitutive IRF3 leading to additional synthesis of IFNs and probably also induction of specific ISGs such as CXCL10.[37–39]

IFNs themselves, once secreted, bind to glycosylated, species-specific, heterodimeric cell surface transmembrane proteins that trigger signaling through their cytoplasmic domains.[22, 25, 27, 41–43] To elicit responses, IFNs-α and IFN-β bind to two receptor subunits, IFNAR-1 and IFNAR-2. IFN-β interacts with the receptor heterodimer differently than does IFN-α2; specific anchor points for IFN-β induce a different conformational change in IFNAR1 with greater induction of a subset of ISGs.[43, 44] IFNAR1 is at least in part degraded by an E3 ubiquitin ligase, which when decreased in activity increases IFNAR1 and suppresses tumorigenicity of a human melanoma xenograft.[45] IFN-γ binds to a different heterodimeric receptor consisting of two subunits, IFNGR-1 and IFNGR-2.[27] The critical event in signaling by IFNs is this ligand-initiated dimerization of the subunits of the receptors that results in cascades of downstream phosphorylation. The activated cytoplasmic domains of receptors for IFNs signal by binding to JAKs (Janus-activated kinases) and STATs (signal transducers and activators of transcription), which in turn phosphorylate STAT1 and STAT2.[25, 46–48]

After phosphorylation by JAKs, STATs form active homomeric or heteromeric dimers that bind to *cis*-acting sequences in the promoters of ISGs. For full activation of STATs, further phosphorylation at specific serine residues may be required. ISGF3, the canonical transcription factor activated by type I IFNs, is composed of STAT1, STAT2 and IRF9. It binds to ISREs (IFN-Stimulated Response Elements) in ISG promoters.[49] In the IFN-γ

signaling pathway, the two receptor subunits, JAK1, and JAK2, activate Gamma-Activated Factor (GAF), a homodimer of tyrosine-phosphorylated STAT1, which binds to the Gamma-Activated Sites (GAS) in ISG promoters.[28] In addition to the canonical STAT pathways, IFNs can additionally activate transcription through other pathways.[23, 47, 50] For example, type I IFNs can also trigger GAF formation and gene induction by through GAS elements. Furthermore, STAT1 can form heterodimers with other STATs.[50] Other kinases, such as PI3K and p38 MAPK, can be activated by type I IFNs and can influence specific patterns of induction of ISGs.[47, 50, 51] Protein tyrosine phosphatases (PTP) have a regulatory role in suppressing signaling by IFNs. Inhibition of PTPs can prolong signaling and potentiate antitumor activities of IFNs.[52–54] Inhibition of the PTP SHP-1 can be accomplished by inhibitors with potentiation of effects of IFNs.[55–57] NK cells in which SHP-2 has been silenced have elevated cytolytic activity with increased IFN-γ consistent with immune activation.[56] Also vitally important in negatively regulating activity of IFNs in immune and other cell types are the ISG SOCS proteins, especially SOCS1.[58–60]

CONSTITUTIVE ENDOGENOUS IFNs

Constitutive production of type I and II IFNs was suggested to have potentially important roles in the absence of viral infection over 30 years ago.[61–63] In contrast to “emergency” production of IFNs induced by virus infection, “physiological” low levels of IFNs may be produced continuously and remain localized with no systemic release or effects.[61, 63–65] Transcriptional regulation of the constitutive expression of IFNs has not been studied as extensively as that of virus-induced IFN expression but in part may result from different induction mechanisms.[66] Constitutive expression of IFN-β may be maintained in part by IRF7 but also of importance may be non-canonical binding by c-Jun and RelA of the IFN-β gene promoter.[66–68] The expression of IFNs-α and IFN-β may additionally be regulated by repressors, IRF2 and a homodimer of the p50 NF-κB subunit.[69–72] Constitutive low levels of IFNs achieve various physiological functions not only through downstream events but also by maintaining signaling of other cytokines. A small amount of IFNs-α and IFN-β has proven to be important for efficient response to cytokines including IFN-γ and IL-6 through signaling crosstalk.[73–76] In addition to signaling crosstalk, adequate expression of signaling components, such as IRF7 and STAT1 and STAT2, can be constitutively maintained by low levels of type I and II IFNs.[66, 77, 78] Constitutive expression of endogenous IFNs may thus maintain physiological functions, such as homeostasis of immune cell activities, hematopoietic stem cell niches, and bone remodeling.[63, 66, 68, 79–81]

ANTICANCER EFFECTS OF ENDOGENOUS IFNS

Endogenous IFN-γ is the basis of a tumor surveillance system for both chemically induced and spontaneously arising tumors in mice. IFN-γ receptor (*ifngr1*)-deficient mice or *stat1*-deficient mice developed tumors more rapidly compared to wild-type mice.[82] Endogenous type I IFNs were also required to inhibit the growth of primary carcinogen-induced and transplantable tumors.[83] The responsiveness to endogenous IFNs was critical in preventing tumorigenesis through tumor surveillance; loss of sensitivity to endogenous IFNs can contributed to escape of tumor cells from host immune surveillance.

Among aberrant IFN responses in cancer have been decreased responses in some human lymphoblastoid cells.[84] Furthermore, about 30% of melanoma and lung carcinoma cell lines have inactivated IFN-γ pathway components, including inactive JAK2 and the lack of JAK1 or IFN-γR.[82] Lack of STAT1, STAT2, and IRF9 was observed in melanoma cell lines and primary melanocytes; expression of STAT1 was also missing in some chronic myeloid leukemia (CML) cells obtained from patient tissues.[85–87] Thus, loss of responsiveness to IFNs may be a critical component of the host response to tumors.

Additionally suggesting a critical role of induction and signaling by IFNs in cancer pathogenesis has been the identification of genotypic variants that affect tumor initiation and progression. Gene expression arrays and cytogenetic analyses have identified somatic homozygous deletions in the 9p21 chromosomal locus for IFNs; furthermore mutations of ISGs have been found in melanoma, colon, lung, and hematologic malignancies.[8, 11–14, 17] IFN-β-deficient or IFNAR1^{-} deficient mouse embryo fibroblasts underwent spontaneous transformation *in vitro*.[88] Oncogenes such as RAS or the human papillomavirus protein E6E7 have downregulated TLR signaling.[88, 89] Other viral oncoproteins can block signaling by interfering with functions of ISGs or ISGF3.[90–92] Alterations in TLR signaling have been suggested to be important in oncogenesis because of gain of function mutations in the major adaptor proteins, MYD88, in a subset of aggressive diffuse B cell lymphomas.[93] In chronic lymphocytic leukemia, heterozygous mutations in the DNA binding domain of IRF4, both constitutively expressed and induced through TLR ligation, have been identified.[94] Other genetic alterations of IRF4 have been identified in a subset of B cell lymphomas (a translocation) and cutaneous carcinomas (a germ line SNP).[95, 96] Overexpression of IRF5 in breast carcinoma cells inhibited *in vitro* and *in vivo* cell growth and furthermore IRF5 was downregulated in human breast carcinomas.[97]

A controlled study of over 4000 individuals has correlated SNPs in IRFs, IFN-γ, and IFN-γR2 with colorectal carcinoma risk and progression.[17] Further confirming the potential importance of IFN signaling pathways in the development of colorectal carcinoma has been correlation of SNPs in JAKs and STAT1 with increased risk.[98] Overexpression of IRF8 in transformed cells with the CML Bcr-Abl translocation inhibited leukemogenesis overcame resistance to the tyrosine kinase inhibitor, imatinib, and was correlated with reduced BCL-2 expression.[99] IRF4 inhibited granulocytic differentiation; its loss enhanced progression of a CML-like disease in IRF8$^{-/-}$ mice.[100] An additional role for the IFN system in CML was suggested by identification of a genomic SNP in the promoter for IFN-γ that resulted in a better response to imatinib.[101] Germ line mutations in the ISG, *RNASEL*, have been correlated with increased risk for prostate, breast, head and neck, and pancreatic carcinomas.[9, 16] Indeed GWAS analyses have identified at STAT1 and IRF1 as among the transcription factors overall most commonly containing SNPs in cancer.[102] Thus, aberrant and augmented IFN signaling can result in significant modulation of early events of tumor pathogenesis.

INCREASED ENDOGENOUS IFNS IN PATHOLOGICAL CONDITIONS

Although endogenous IFNs may be important for cellular homeostasis and resistance to cancer growth, production of endogenous IFNs can also contribute to pathology. Aberrantly

regulated constitutive production of IFNs can also influence development of autoimmune diseases. In patients with autoimmune diseases, including type I diabetes mellitus (DM), systemic lupus erythematosus (SLE), or Sjögren's syndrome, type I IFN expression or an ISG signature has been identified.[66] The IFN-α pathway wss activated in a subgroup of SLE patients with increased disease severity and more double stranded DNA (dsDNA).[103] Accelerated IFNs-α and IFN-β responses has led to a psoriasis-like skin inflammation.[70, 104] SLE symptoms were ameliorated in IFNAR-deficient mice.[105] A monoclonal neutralizing antibody against IFN-α has thus been in clinical trials to treat SLE.[106]

Increased expression of ISGs has been identified in cancer cells compared to corresponding normal primary cells or normal tissues with correlations to the degree of tumor invasion.[107–110] Expression of some IFN-induced genes was higher in metastatic cancer cells than non-metastatic cells.[111, 112] Depletion of IRF2, a repressor of IFN-α/β expression, significantly increased tumor growth in a xenograft model with increased proliferation and decreased apoptotic cell death[113]. Recurrent alteration in IRF2 and its inactivation has been identified in HBV-related hepatocellular carcinoma[113].

CAUSES OF INCREASED ENDOGENOUS IFN PRODUCTION

Oncoviruses

About 18% of human cancers can be caused by infection with about 12% being caused by one of seven different pathogens including *Helicobacter pylori* (approximately 5% of all cancers), human papilloma viruses (HPV, 5%), hepatitis B and C viruses (HBV and HCV, 5%), Epstein-Barr virus (EBV, 1%), human immunodeficiency virus (HIV, 1%), and human herpes virus 8 (HHV, 1%).[114] Tumor development in carriers with latent or persistent infections often occurs decades after initial exposure to the virus.[115] Although RNA viruses are potent inducers of IFN production, DNA viruses are known to be relatively poor.[116] Therefore, consistent exposure to a low level of IFNs-α and IFN-β, induced by persistent infection with DNA- or retro-viruses, might contribute to the increase of resistance to DNA damage through the expression of IFN-related DNA damage resistant gene products over a long period[117] (Figure 1).

Cytosolic dsDNA from DNA viruses can also induce IFNs-α and/or IFN-β in a TLR-independent fashion.[30, 118] Host cytosolic DNA as well as virus DNA has also induced expression of type I IFNs, which may be linked to autoimmune diseases in humans. Failure to clear self-DNA leads to an inappropriate activation of type I IFN production through TLR-independent signaling.[119, 120] Both self and non-self cytosolic DNAs may trigger production of type I IFNs through STING (stimulator of interferon genes)-dependent cytosolic DNA sensing pathways.[30] Cytoplasmic DNA triggers this signaling pathway by binding to a the DNA-sensing protein, cyclic GMP-AMP synthase (cGAS).[121] The DNA-bound activated cGAS synthesizes cyclic guanosine monophosphate-adenosine monophosphate (cGMP-AMP or cGAMP), a second messenger that activates an adaptor protein and traffics rapidly to peri-nuclear endosomes with tank binding kinase 1 (TBK1), through the autophagosome in response to cytoplasmic DNA.[122] TBK1 activates IRF3 and IRF7, which translocate into the nucleus to stimulate the expression of type I IFNs. In addition to cGAS, many other proteins, including meiotic recombination 11 homolog A

(MRE11), DEAD-box helicase family 41 (DDX41), and IFI16, also recognize cytoplasmic DNA and facilitate STING activity[30].

DNA damaging agents

In addition to virus infection, DNA damaging agents including ultraviolet (UV) light and constituents of cigarette smoke can be causative factors in cancer. UV irradiation initiated melanoma genesis with a persistent ISG response signature.[123] Damaged DNA leaking into the cytoplasm may also trigger STING-dependent signaling with induction of type I IFNs. MRE11-RAD50, a DNA damage-sensing complex, physically interacted with damaged DNA in the cytoplasm, activated STING and IRF3, and induced the production of type I IFNs.[124] Aberrant self DNA was normally eliminated by cellular DNAses such as DNAse II and DNAse III (3′ repair exonuclease I, TREX1). Defects in these DNAses caused inefficient removal of cytosolic DNA, leading to increased type I IFNs.[125] When dsDNA was oxidized by reactive oxygen species (ROS) or superoxide induced by UV irradiation or activated neutrophils, it became more resistant to DNAse III (TREX1), increasing the expression of type I IFNs.[126] Thus, through the STING and/or other nucleotide recognition proteins, damaged self-DNA fragments may be causative in constitutive production of IFNs.

Loss of p53 function

The tumor suppressor p53, frequently mutated in tumors, functions as transcription factor to promote or repress transcription of many protein-encoding genes and noncoding RNAs.[127] Wild-type p53 is inactivated in tumors by various means including overexpression of the p53 inhibitor MDM2.[128] Loss of p53 function has an important role in cancer progression and resistance to therapy. DNA demethylation in p53-null cells resulted in a lethal induction of IFN-β and ISGs through the IFNAR type I receptor.[20] These strong responses were triggered by dsRNAs expressed from multiple noncoding genes, including major classes of short, interspersed nuclear elements (SINEs) B1/B2. The transcription of noncoding RNA, normally repressed by the combination of p53 and DNA methylation, was increased >100 fold in the absence of both p53 and DNA methylation. Resulting high levels of IFN-β and ISGs led to caspase activation and apoptosis in p53 null mouse embryo fibroblasts. Cells that escaped the suicidal IFN responses survived to develop into tumors. [20]

Loss of responsiveness to IFNs or the inability of cells to produce IFNs in cells with aberrant p53 function may be an important major mechanism of tumor progression. Loss of p53 function has been correlated with resistance to DNA damaging agents independent of other risk factors.[129] However, while p53 deficiency increased apoptosis in the presence of DNA demethylating agent, decitabine, it decreased apoptosis induced by a DNA damaging agent, doxorubicin.[20] Whether loss of p53 increases in resistance to DNA damage through induction of an IFN-response induced by low levels of IFNs has not been examined. However, higher levels of STAT1 proteins have been identified in cells expressing mutant p53 or no p53.[117, 130] Increased levels of STAT1 protein had pro-tumor and metastatic effects,[112, 131] and also are able to induce high levels of the IRDS gene products,[132, 133] suggesting that p53 deficiency induces DNA damage resistance, at least partially, through the induction of the IRDS genes.

PROCANCER EFFECTS OF INCREASED ENDOGENOUS IFNS

Although the production of endogenous IFNs is increased under pathological conditions, the amount is still much lower compared to therapeutically applied IFNs. The pattern of ISG expression correlated to the concentration of IFNs present in the cancer microenvironment. Constitutive low levels of IFNs were able to induce steady-state upregulation of ISGs in cancer cells, including *IFI27, ISG15*, and *BST2*, with no increase of pro-apoptotic and anti-proliferative ISGs, which were induced by the higher doses of IFNs used therapeutically.[133, 134]

Some studies have identified expression of ISGs in tumors from patients with various different types of cancers resistant to chemotherapy and radiation therapy.[135–137] Interestingly, only a minor subset of ISGs (about 30 out of >100 total ISGs) were consistently overexpressed in therapy-resistant cancer cells. This subgroup of ISGs included *IFI27 (ISG12), ISG15 (G1P2), BST2, OAS1, OAS3, OASL*, and others. These genes, comprising an IFN-related DNA damage-resistant signature (IRDS), were also upregulated in cancers compared to normal tissues.[107–110, 137] High expression of IRDS genes promoted tumor growth and metastasis as well as resistance to chemotherapy and radiation.[112, 138–140]

Selective induction of IRDS genes can be mediated by unphosphorylated STAT1 (U-STAT1).[132, 133] STAT1 overexpression in mice conferred protection from radiation and mediated amplification of metastatic potential.[112, 131] U-STAT1, together with U-STAT2 and IRF9, formed un-phosphorylated IFN-stimulated gene factor 3 (U-ISGF3).[117] High levels of the component proteins, STAT1, STAT2, and IRF9 phosphorylated and unphosphorylated, were induced in response to IFNs (Figure 1). Chronic exposure to low levels of IFN-β and increased U-ISGF3 levels thus may lead to enhanced expression of IRDS genes with no increase of other ISGs that are anti-proliferative and/or pro-apoptotic with resulting resistance to DNA damage.[117]

The unresolved puzzles in understanding actions of IFNs in tumor cell survival and apoptosis can be, however, exemplified by two ISGs, ISG12 (IFI27) and ISG 6–16 (G1P3), commonly induced in IFN-responsive cells.[141–143] ISG 6–16 gene encodes a low-molecular-weight mitochondrial protein that stabilized mitochondrial function and opposed apoptosis. ISG 6–16 antagonized TRAIL-mediated apoptosis and cytotoxicity in both cell lines and fresh myeloma cells through antagonism of TRAIL-mediated mitochondrial potential loss and cytochrome c release. In contrast, ISG12 expression has sensitized cells to apoptotic stimuli through mitochondrial membrane destabilization.

THERAPEUTIC APPLICATION OF IFNS

While it has been known for more than 40 years that IFNs could influence outcomes of both transplantable and viral-induced experimental murine tumors,[23] a precursor to studies considering a mechanistic role of IFNs and STATs in the microenvironment have studies evaluating whether IFNs could influence an induced, non-viral (carcinogen) malignancy. The first such study used an unpurified mouse IFN preparation and identified inhibition of development of subcutaneous fibrosarcomas after 3-methylcholanthrene.[144] A subsequent study with purified IFN-β after the bladder-specific carcinogen N-[4-(5-nitro-2-furyl)-2-

thiazolyl]formamide (FANFT) introduced into the diet identified complete inhibition of transitional carcinoma development by IFN-β.[145] Similar effectiveness occurred with an oral TLR inducer of IFNs. [145]

Subsequent studies have further confirmed the role of IFNs-α, IFN-β, and IFN-γ in inhibiting carcinogen-induced malignancy. IFN-γ inhibited hepatic carcinogenesis in mice in response to diethylnitrosamine with an increase in infiltration of CD8 T cells and NK cells but additionally an accumulation of p53 in hepatocytes sensitizing them to apoptosis.[146] In rats treated with IFN-α for carcinogenesis induced by diethylnitrosamine both preneoplastic foci and tumors in the liver were reduced, an effect that was increased with more sustained administration of IFN-α.[147] Furthermore, IFN-α seemed to reduce frequency of hepatocellular carcinomas in hepatitis B virus-infected patients with cirrhosis after surgical resection.[148]

Activation of anti-tumor immunity

Induced IFNs and ISG proteins have potent influences on lytic activity and ISG products from immune effector cells, on induction of angiogenesis, and on tumor cell invasiveness. Unraveling mechanisms of anti-tumor effects of IFNs and aberrations in their signaling pathways has been a complex and a still evolving, uncompleted research challenge. Further complexities but also increased clarity has begun to emerge in elucidating cellular effects of IFNs and the protein products of ISGs on host cellular mechanisms, particularly new understandings of influences on immune effector cells (Figure 2), of resistance to malignant development and progression.

Amplification of innate and specific immune responses has resulted from both Type I and Type II IFNs with influences on antigen recognition and processing and cytolytic activity.[149–154] Plasmacytoid dendritic cells have been found to secrete high levels of IFNs-α and IFN-β in response have been identified in the T cell zone of lymphatic tissue in tumors of various types.[150, 155–157] Activated NK and T cells have a critical role in production and action of IFNs for protection from oncogenesis and in controlling growth of syngeneic and transplanted tumors. Maturation of dendritic cells, themselves a primary source in the innate immune system for production of IFNs-α and IFN-β, was also influenced by IFNs.[155–157]

IFNs have stimulated activity of cytotoxic and helper T cells, natural killer (NK) cells, macrophages, and dendritic cells. One of the first immune effectors identified as augmented in activity by IFNs were NK cells whose cytotoxic activity in both mouse and man could be augmented. Activation of NK cells and monocytes was identified both *in vitro* and *in vivo*.[158–164] Effects of IFNs on NK cells can be further amplified by production of the ISG IL-15 by dendritic cells resulting in their initial priming for cytotoxicity.[165]

Molecular and cellular effects of IFNs and ISG proteins provide a basis for understanding effects on innate and acquired host immune responses in the tumor microenvironment. Equivalent antitumor effectiveness of IFNs *in vivo* for syngeneic tumor cells occurred regardless of whether tumor cells were sensitive or resistant to antiproliferative effects of IFNs *in vitro*.[166, 167] Subsequent studies, using genetically mutant mice, have more rigorously suggested the critical importance of immune cell regulation in antitumor effects

of IFNs. *STAT1* knockout mice implanted with IFN-sensitive tumors and treated with exogenous IFN-α did not survive longer than control mice.[168] Conversely, wild-type (*STAT1*$^{+/+}$) mice implanted with *STAT1*-null tumor cells were able to mount an effective antitumor response following IFNs, suggesting the importance of host cells.[169] Extension of these studies to either IFN-γR or STAT1 deficient mice identified development of both spontaneous tumors of diverse histologies and methylcholanthrene-induced fibrosarcomas at significantly greater frequency than in wild-type littermates, emphasizing further the critical role of endogenous IFN in host response to primary tumor.[82, 170] In addition to IFN-γ, endogenous type I IFNs were required to prevent carcinogen-induced and transplantable tumors.[83] In contrast to IFN-γ for which tumor cells were important targets, host hematopoietic cells (NK cells, dendritic cells) were critical targets for the protective antitumor responses leading to tumor elimination by IFNs-α and IFN-β.[83, 171]

This solid initial groundwork in understanding on immune effectors cells has been now followed by additional by excellent insights into T cell and dendritic cell interactions as modified by IFNs.[2, 3, 150–153] These findings in the last few years emphasize importance of the CD8a+ DC subset as critical for CD8+ T cell priming and tumor rejection.; [2, 3, 172] Histologic identification of a tumor-infiltrating lymphocyte that has been correlated with a favorable clinical outcome in diverse malignancies including melanoma has identified activated CD8+ T cells that had with a ISG expression signature.[153] Effects of IFNs on innate immune responses can then be subsequently translated into longer lived memory of not only response of T but also of B cells.[173, 174]

Following binding of IFNs to immune effector cells, upregulated ISGs include major histocompatibility (MHC) components leading to eventual activation of CD8^{+} cytotoxic T cells.[93, 175, 176] IFNs increased transcription of MHC class I genes and induced expression of additional proteins required for surface expression of the mature MHC class I complex. MHC Class I proteins associate with β2-microglobulin, also an ISG, in the endoplasmic reticulum for transport to the cell surface; augmentation of β2-microglobulin has been identified in patients after IFN-α2 or IFN-β.[177, 178] Processing of potential antigenic peptides for loading onto class I molecules occurs in the proteasome whose three subunits (LMP-2, LMP-7, and LMP-10) together with Transporter for Processing (TAP) are all ISGs that can also be induced by IRF7.[179–182] Findings of increases in MHC Class II and other ISGs *in vitro* led to assessment of changes in monocyte cell-surface markers using treatment of patients with IFN-β with significantly increased monocytes positive for HLA-DQ.[183, 184] Additionally, levels of OASs were significantly increased in patient peripheral blood mononuclear cells.[184] These translational results of increases in ISGs in cells from treated patients were founded and initiated based upon the findings a few years prior of increases in these stimulated RNAs in IFN-treated cells.[183] Additional translational studies subsequently confirmed increases in patients of the *in vitro* demonstrations of MHC Class I and Class II components by IFN-γ.[185]

IFNs have also increased tumor-associated antigens such as carcinoembryonic antigen and TAG-72 on the membranes of tumor cells both *in vitro* and *in vivo*.[186] potentially thus facilitating antigen-specific T cell immunity as suggested by studies combining IFN-α with a CEA poxvirus vaccine.[187] In addition to MHC and tumor-associated antigens as ISGs that

can influence T cell function, other ISGs such as SECTM1 can serve as a co-stimulatory ligand for T cells after TCR activation.[188]

A number of ISGs function as chemoattractant to both lymphocytes and monocytes, recruiting these cells into tissues with induction by IFNs both *in vitro* and in patients.[189–191] These IFN-induced chemokines have included CCL5 (RANTES), CXCL10 (IP-10), CCL2 (MCP-1), CCL3 (MIP-1α), CXCL9 (MIG), and CXCL11(I-TAC).[23] STAT1 induction of chemokines CXCL9, CXCL10, CXCL11, and CXCL16 controlled recruitment of protective, antigen-specific Th1 cells into peripheral tissues.[192] Other ISG protein products, such as phospholipid scramblase 1 (PLSCR1), can provide macrophages with a signal for engulfment after tumor cell apoptosis.[193–195] PLSCR1 itself also may increase expression of other ISGs influencing apoptosis and other effects of IFNs.[193–195]

ISG15, a secreted protein induced by IFNs-α and IFN-β, induced IFN-γ synthesis by T cells and proliferation of NK and lymphokine-activated killer (LAK) cells.[196] A recently identified mutation in ISG15 secretion resulted in decreased production of IFN-γ by NK and T cells, impaired protective immunity to mycobacteria, and has resulted in new insights into the immunomodulatory functions of secreted ISG15.[197, 198] Four of the top 36 expressed genes in an expression array of melanoma cells (ISG15, USP18, UBE1L, UBE2L6) constitute part of a cascade of ubiquitin-related ISGs that can influence both innate immunity for malignant cells and cellular signaling.[199] Melanoma cells producing high levels of ISG15 were those able to induce e-cadherin expression on dendritic cells.[200] Conjugation of ISG15 to STAT1 and JAK1 and components of other signaling pathways (ERK1, phospholipase C, and heat shock proteins) suggest that regulation of ISG15 family molecules may have profound effects in the tumor microenvironment.[201–204] Consistent with this, an siRNA to the ISG, USP18, that deconjugates ISG15 from target proteins, increased expression of TRAIL and thus promoted apoptosis.[205] The functional effects of the ubiquitin-like ISGs may be explained by ISGylation and deISGylation stabilizing or altering binding of a target protein to its typical interaction partner at the protein-protein or protein-RNA interface.[198, 202, 206]

In contrast to immune augmenting effects, type I IFNs can also suppress T cell function through inhibition of secretion of IL-17.[207, 208] Reduced responsiveness in T cells to IFN-α and IFN-γ with decreases in pSTAT1 can result from myeloid-derived suppressor cells.[209] Possibly most important in suppressing T cell function in the tumor microenvironment is the protein, Programmed-cell Death-1 (PD-1), an inhibitory receptor on T-cells, activated in the tumor microenvironment by its ligands PD-L1 and PD-L2. PD-L1 secretion can be upregulated on tumor cells and tumor-associated stromal cells by IFNs-α and IFN-γ.[210–213] Upregulation of PD-L1, a ligand detrimental to host response, by IFN-γ was mediated at least in part by IRF1 transcription. Thus, while PD-L1, an ISG detrimental to host T cell response, other ISGs such as HLA components and CXCL10, have been essential mediators —again illustrating the research challenges for dissecting the importance of individual products of ISGs in the tumor microenvironment.

Inhibition of angiogenesis

IFNs inhibit angiogenesis both by inhibiting endothelial cells through increases and decreases of proteins mediating the angiogenic process. Inhibition of angiogenesis by IFNs occurred before antiproliferative effects on tumor cells and was identified *in vivo* within 24h of tumor cell inoculation.[214] IFN-sensitive and –resistant bladder carcinoma cells in mice after IFN-α had decreased tumor cell growth with reduced vascularization by suppression of the angiogenic cytokine, basic fibroblast growth factor (bFGF).[215] Knockout studies confirmed signaling through STAT1 as necessary for reduction by IFNs of bFGF signaling. [215] Compared with wild-type mice, IFNAR receptor knockout mice had increased angiogenesis and tumorigenesis.[216] In addition to bFGF, IFNs can inhibit other angiogenesis mediators such as VEGF by regulating VEGF promoter activity, in part at least mediated by a reduction in its promoter, HIF-1α, that was reduced by IFN-γ.[217, 218] Contributing to the reduction in VEGFA by IFN-γ may be a conformational change in VEGF-A RNA 3′ untranslated region to reduce VEGF-A translation through integration of hypoxia and STAT signaling.[219] In addition to IFN-γ, reductions in VEGF-A can also result from IFN-α2 in treated patients.[220] Furthermore, IL-8, a mediator of angiogenesis, was inhibited *in vitro* and *in vivo* by IFN-α2b and IFN-β.[221, 222]

Another ISG product family, the guanylate binding proteins (GBPs), a family seven human GTPases of the dynamin superfamily that are potently induced in part by IFNs, modulated proliferation and spreading of endothelial cells through matrix metalloproteases *in vitro*.[223–225] hGBP1 also inhibited proliferation of endothelial cells stimulated by VEGF or bFGF through its C-terminal alpha helices.[223, 226] Thus, induction of ISGs, such as GBP1 and others such as IFI16 and PML that function as angiostatic inhibitors, coupled with downregulation of other factors such as bFGF, VEGF, and IL8, may all contribute to inhibition of angiogenesis by IFNs.[225–228]

Endogenous Type I IFN signaling has a role as a negative regulator of angiogenesis, keeping the “angiogenic switch” in the off position. Indeed, mice lacking IFN-β (IFN-$\beta^{-/-}$) had faster growing melanomas and sarcomas with better developed blood vessels than did wild-type littermates.[229] These tumors from the IFN-$\beta^{-/-}$ mice had enhanced infiltration by a neutrophilic cell population consistent with myeloid-derived suppressor cells (MDSCs) and increased expressing of VEGF and matrix metalloproteinase 9. These finding thus further suggest that endogenous IFN-β may play an important role in regulating tumor-induced angiogenesis. Further supporting this was the finding that *in vitro* treatment of tumor-infiltrating neutrophils with low levels of IFN-β reduced expression of pro-angiogenic factors to normal levels.[229]

An essential part of the malignant process, the motility of transformed cells and their invasion of normal tissues, can be inhibited by several ISGs. One of these genes, highly induced by IFNs-α and IFN-β in most tissues, is MX1, the gene product of which is a GTPase that suppressed motility and invasiveness of prostate carcinoma and melanoma in both *in vitro* and *in vivo* assessments.[230] Another ISG product, schlafen 5, decreased melanoma cell invasiveness into three-dimensional collagen.[231] Also, the ISG protein, IFIT2 (p54), inhibited migration of oral squamous carcinomas *in vitro*, possibly through interaction

with cytokeratins.[232] Thus, both the necessary steps for regional and distant metastases, invasion and angiogenesis, are suppressed by IFNs and its ISG protein products.

Activation of apoptosis of cancer cells

At higher doses exogenous IFNs, however, can result in pro-apoptotic effects either directly or through induction of secreted ISGs such as TNF-alpha related apoptosis inducing ligand (TRAIL/Apo2L) or Fas ligand (FasL) by immune effector cells.[23, 233, 234] While expression may vary between cell types, pro-apoptotic, specific ISGs may be induced however only by a high dose of IFNs and/or last for short times because of IFN-induced negative regulators.[117] These pro-apoptotic ISGs include TRAIL, Fas/FasL, XIAP associated factor-1 (XAF-1), PKR, 2′ 5′ A oligoadenylate synthetase (OAS), ISG12 (IFI27) and ISG 6–16 (G1P3), death activating protein kinases (DAP kinase), phospholipid scramblase (PLSCR1), IRFs, and promyelocytic leukemia gene (PML). Among them, OAS, IFI27, and PLSCR1 have been identified as induced by U-ISGF3, suggesting that they might have dual role in regulating apoptosis.[117] While influences of concentration of IFNs and the kinetics of specific ISGs on apoptosis in cells of varied histologies are beyond the scope of this review, these are detailed in other reviews.[233, 234]

PERSPECTIVES AND CLINICAL IMPLICATIONS

The effects of IFNs in cancer biology are different depending on the levels of IFNs and the time of exposure to them (Figure 3). Either promoting or blocking IFN responses can be a good clinical strategy to cure cancers, depending on which effects of IFNs we need to target.

Good or bad IFNs

The ability of type I IFNs to induce pro-apoptotic and anti-proliferative responses in a variety of cell types has led logically to exploration of their potential as antitumor therapeutic agents. However, more recent studies have shown that constitutive exposure of cells to a low level of type I IFN leads to steady-state expression of the IRDS subset of ISGs and that, via detailed mechanisms that are still obscure, the IRDS proteins mediate phenotypes that are favorable to the tumor, including facilitation of EMT and metastasis, suppression of T cell toxicity and resistance to therapies that damage DNA[136] (Figure 4).

Endogenous interferons

IFNs might be produced constitutively in the tumor microenvironment by the tumor cells themselves, by the surrounding stroma, or by invading immune cells, especially macrophages and dendritic cells. It is also possible that the IRDS signature may be generated by additional mechanisms still to be discovered, including genetic factors (Figure 4). If IFNs in the tumor microenvironment are indeed responsible for the IRDS signature, a reasonable therapeutic strategy may be to inhibit transiently the ability of the tumor cells to respond to IFNs in advance of ionizing radiation therapy or chemotherapy. Such inhibition might be achieved by using antibodies against the type I IFN receptor, which has been successful in mice[235] or by using tyrosine kinase inhibitor of JAK1 and JAK2, which block responses to all known IFNs. JAK1/JAK2 inhibitors are already approved for clinical use in rheumatoid arthritis, psoriasis and other diseases.[236] In treating common cancers such as

prostate or breast, for example, it could be of major benefit to patients if down-regulation of the expression of the IRDS proteins in the tumor allowed a given clinical effect to be achieved with a lower dose of radiation or DNA damaging agents, thus reducing collateral damage. In coming years assessing these and other new insights into action of endogenous IFNs and ISGs in the tumor microenvironment should yield further improvements in patient outcomes.

Exogenous interferons

Although there have been some successes, except as a prototype for immune modulation and recombinant DNA pharmaceuticals, IFNs have not had much success as therapeutic agents in cancer. Our current realization that chronic exposure to type I IFN might be beneficial to tumors should be factored into the design of future trials. It may not be a good idea to prolong the exposure of tumors to exogenous IFNs, by using long-acting derivatives; a better strategy may be to use repeated pulses of short-acting IFNs in a protocol that minimizes down regulation and maximizes expression of the full set of ISGs, which encode many pro-apoptotic and anti-proliferative proteins. In other words, design the protocol to allow expression to subside of IFN-induced proteins, especially SOCS1, that suppress the expression of the full set of ISGs, but not the IRDS subset, following the first administration of IFN before giving a second dose. Additionally, when exogenous IFNs are to be combined with therapeutic regimens that cause DNA damage (ionizing radiation and many chemotherapeutic drugs), it is likely to be best to administer the drugs or radiation when the IRDS pattern of gene expression is minimal in the tumors, either immediately after administration of IFNs, when the full set of ISGs are still expressed, or long after, when expression of the IRDS proteins has subsided.

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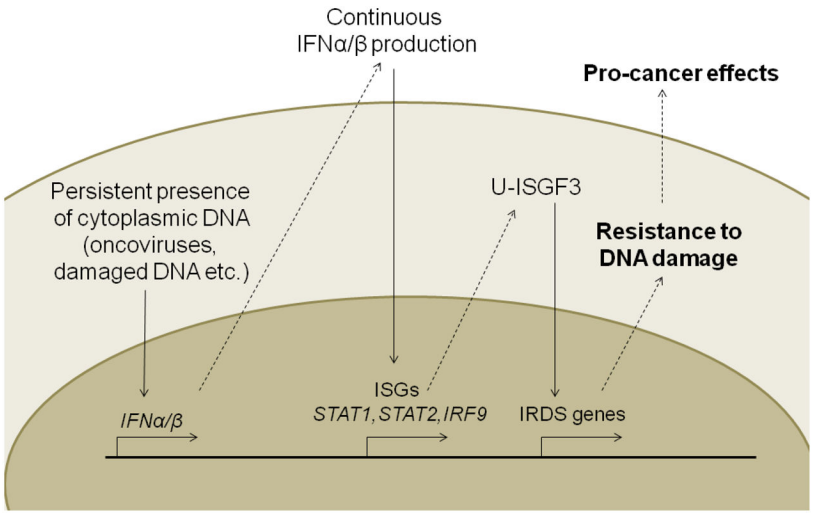

Figure 1. Causes and consequences of increased endogenous IFN production

Persistent infection with oncoviruses (DNA- or retroviruses) or exposure to DNA damaging agents (UV light, DNA damaging chemicals, etc.) leads to cytoplasmic DNA, which induces IFN-α/β production. Chronic exposure of cells to type I IFN increases the expression of ISGs, including *STAT1, STAT2, and IRF9*. U-ISGF3, formed by increased levels of unphosphorylated STAT1 and STAT2, and IRF9. U-ISGF3 selectively induces a subset of ISGs, the IRDS genes, leading to resistance to DNA damage. *U-ISGF3; unphosphorylated IFN stimulated gene factor 3, IRDS; IFN-related DNA damage resistance signature*

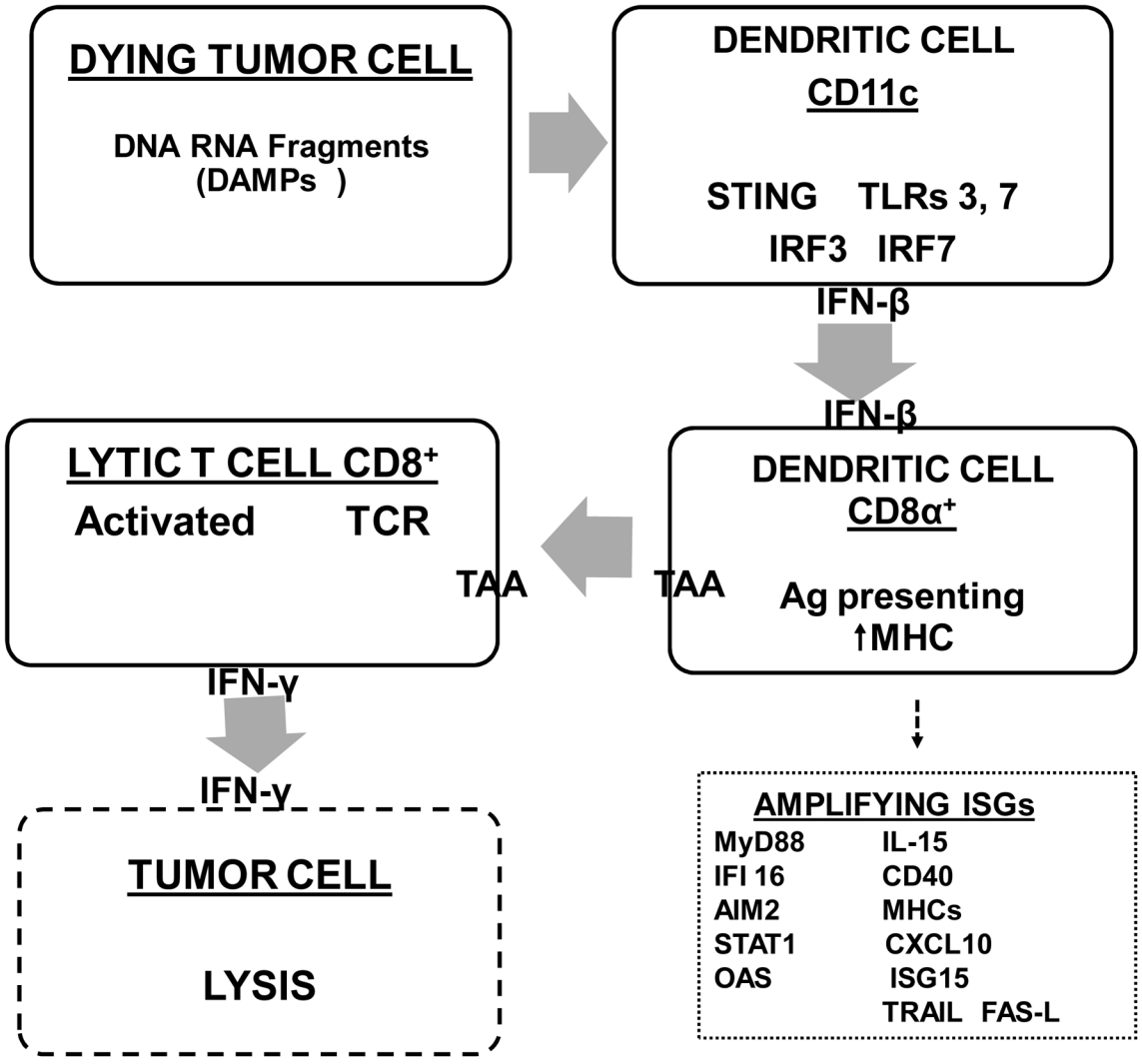

Figure 2. Assumed cascade of events in T cell activation resulting from triggering of IFN synthesis and secretion by release of nucleotide fragments into the microenvironment from dying tumor cells

Consistent with existing evidence detailed in the text (although not at all steps are yet completely confirmed), fragments of RNA and DNA are released into the microenvironment and processed through endosomal pathways of $CD11c^+$ plasmacytoid dendritic cells for secretion of IFN-β. Subsequent steps are activation of $CD8a^+$ dendritic cells, with presentation through MHC pathways of tumor-associated antigens (TAA) through the $CD8^+$ T cell receptor (TCR), and secretion of IFN-γ. [2,3] Various steps in the complete cascade, probably similar to but not necessarily identical to those resulting in constitutive IFN secretion and autoimmune diseases, are amplified by protein products of ISGs, A few examples are given.

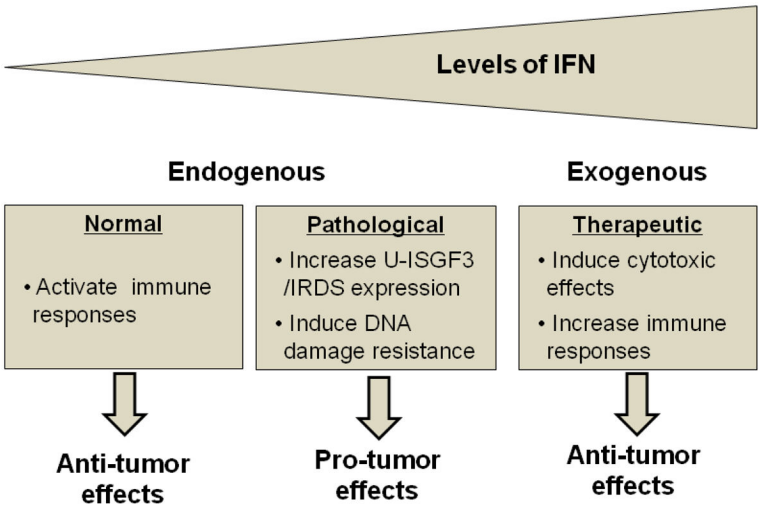

Figure 3. Effects of IFNs in tumor biology

The effects of IFNs are determined by the levels of IFNs and the duration of exposure to them. In normal conditions, very low levels of endogenous type I IFNs are constitutively expressed and activate immune responses, inhibiting tumor progression (left panel). In pathological conditions, the production of endogenous IFNs is increased, and chronic exposure to IFNs enhances the expression of the IRDS genes through U-ISGF3, resulting in enhanced resistance to DNA damage (middle panel). For therapeutic purposes, high levels of exogenous IFNs are used to increase the expression of cytotoxic genes as well as to stimulate anti-cancer immunity (right panel). *IRDS; IFN-related DNA damage resistance signature*

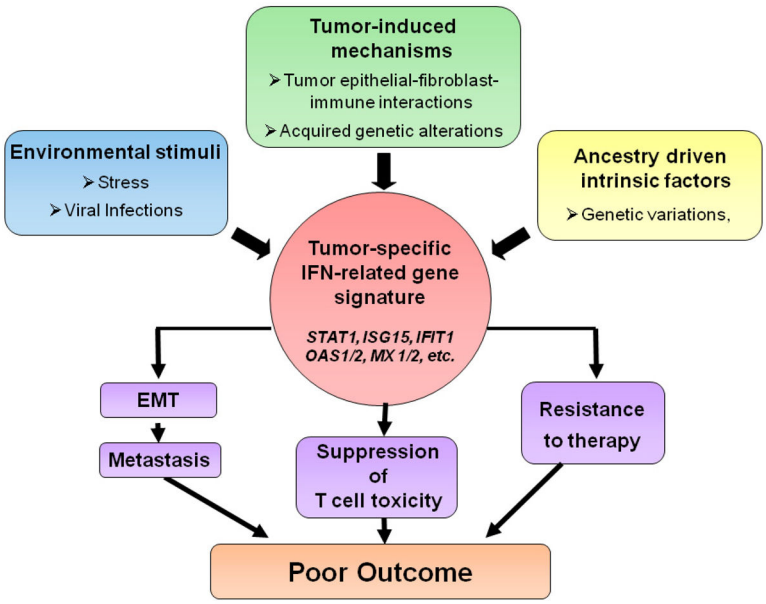

Figure 4. Potential origin and effects of the IRDS in tumor biology

Tumor-induced mechanisms, environmental stimuli, or ancestry-driven intrinsic factors may induce the IRDS in tumors. This signature may lead to poor outcomes by mechanisms that include EMT and consequently increased metastatic potential, suppression of T-cell toxicity, and resistance to therapy. *IRDS; IFN-related DNA damage resistance signature, EMT; epithelial to mesenchymal transition*

This figure and legend are modified from the original in the paper by Wallace et al[136] with the permission of Dr. Ambs.

Table 1

Receptors and Signaling Molecules in IFN Pathways

Receptors responding to pathogenic molecules
- Toll-like receptors (TLRs)
TLR3: dsRNA (poly I:C)
TLR4: LPS (paclitaxel)
TLR7/8: ssRNA (imiquimod)
TLR9: CpG DNA
- RIG-I, MDA5: dsRNA
- cGAS: cytoplasmic ss and dsDNA
Signaling molecules involved in IFN production
- TBK1, IKK
- IRF1, IRF2, IRF3, IRF5, IRF7, IRF8
- NF-κB, AP-1
- STING
Receptors responding to IFNs
- IFNAR1/ IFNAR2: type I IFNs
- IFNGR1/ IFNGR2: type II IFN
- IFNLR1/ IL-10R2: type III IFNs
Signaling molecules responding to IFNs
- JAK1, JAK2, TYK2
- STAT1, STAT2 (PY- and U-STATs)
- IRF9
- PI3K, MAPKs