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REVIEW

Double-edged effects of interferons on the regulation of cancer-immunity cycle

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ABSTRACT

Interferons (IFNs) are a large family of pleiotropic cytokines that regulate both innate and adaptive immunity and show anti-cancer effects in various cancer types. Moreover, it was revealed that IFN signaling plays critical roles in the success of cancer therapy strategies, thereby enhancing their therapeutic effects. However, IFNs have minimal or even adverse effects on cancer eradication, and mediate cancer immune escape in some instances. Thus, IFNs have a double-edged effect on the cancer immune response. Recent studies suggest that IFNs regulate each step of the cancer immunity-cycle, consisting of cancer antigen release, presentation of antigens and activation of T cells, trafficking and infiltration of effector T cells into the tumor microenvironment, and recognition and killing of cancer cells, which contributes to our understanding of the mechanisms of IFNs in regulating cancer immunity. In this review, we focus on IFNs and cancer immunity and elaborate on the roles of IFNs in regulating the cancer-immunity cycle.

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Introduction

The fact that inactive viruses interfere with the amplification of live viruses was established by the end of the 1940s, although the mechanism underlying this phenomenon was unknown.[1] In 1957, Isaacs and Lindenmann found that incubation of heat-inactivated influenza virus with the chorioallantoic membrane of chick embryos induced the production of a new factor interfering with the amplification of live influenza virus in the membrane. They named this new factor interferon (IFN).[2] At the beginning of the 1960s, chicken interferon (IFN-β) was purified.[3] Soon after purification of IFN-β, Wheelock discovered a novel virus-inhibitor (IFN-γ) produced by human leukocytes similar as chick embryo interferon in 1965.[4] It is now known that IFNs are a large family of cytokines.

Although IFNs were originally identified as potent anti-viral factors, they were also recognized to regulate immune responses and inhibit cancers. Before IFNs were purified, scientists employed unpurified interferon to treat various types of cancer in mice and patients.[5] Since interferon possesses anti-viral effects and virus infection is associated with some malignancies (for example, Rous sarcoma virus cause Rous sarcoma), researchers began to use IFNs to treat virus-induced tumors in animal models in the mid-1960s and observed therapeutic effects on these tumors.[3,5] The first clinical trial using IFN to treat cancer was initiated in 1971 in osteosarcoma,[6] and now IFNs have been used to treat various types of cancer in the clinic, including melanoma, hairy cell leukemia, and renal cell carcinoma.[7] However, IFN treatment has minimal or even adverse effects in some instances,[8] which suggests that IFNs play a complicated role in the cancer immune response.

Recently, immune checkpoint blockage (ICB) has been demonstrated to be a promising strategy to treat cancer,[9] and IFN signaling seems to be critical to successful ICB therapy.[10–12] Moreover, IFNs enhance the therapeutic sensitivity of ICBs in various cancer types.[13–17] These studies suggest that IFN signaling plays an important role in cancer immunotherapy. In this review, we focus on IFNs and cancer immunity, and elaborate on the roles of IFNs in regulating the cancer-immunity cycle.

IFNs and IFN-induced signaling

IFNs are divided into three subtypes based on their cognate receptors and sequence identity. IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω belong to type I IFNs that bind to the IFNα/β receptor composed of IFNAR1 and IFNAR2. Type I IFN receptors are expressed in most cell types in the body. IFNAR1 is absolutely necessary for type I IFN signaling,[18] whereas IFNAR2 has various isoforms with different effects on this signaling pathway. In humans, the longest IFNAR2c isoform and the soluble IFNAR2a isoform (lacking the transmembrane domain) activate this signaling.[19–22] The shorter IFNAR2b isoform inhibits this signaling by acting as a dominant-negative regulator.[23] IFN-γ is the only member of type II IFN and binds to the IFN-γ receptor composed of IFNGR1 and IFNGR2.

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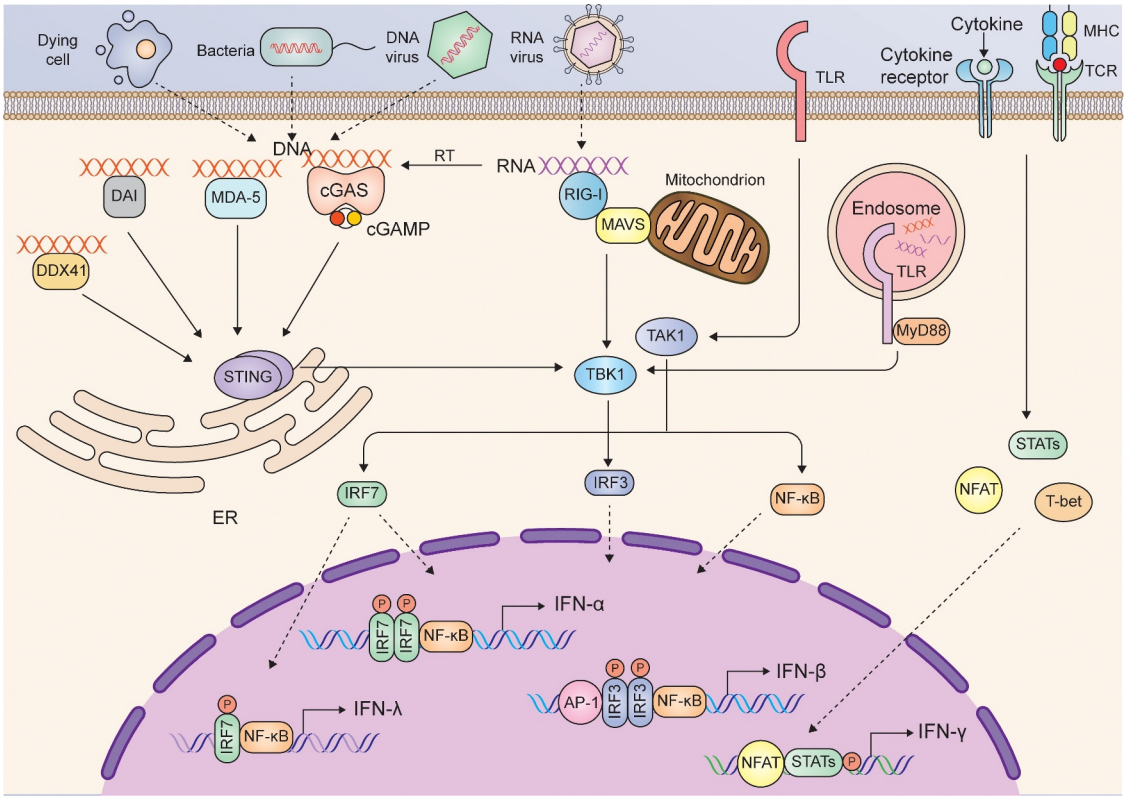

Figure 1. Signaling pathways in the induction of IFNs.

IFNGR1 recognizes and binds to IFN-γ, and IFNGR2 is responsible for signal transduction. Both subunits of IFNGR are ubiquitously expressed in all mammalian cells.[24,25] The type III IFNs consist of IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B), and IFN-λ4, and this type of IFN binds to the heterodimeric receptor composed of IFNLR1 (also known as IL28RA) and IL10RB.[19] Although the expression of IL10RB is widely expressed in many cell types, the expression of IFNLR1 is usually restricted in epithelial cells and absent in some immune cells, such as human NK cells; thus, the actions of type III IFNs may be restricted spatially.[26,27]

There are many intracellular and extracellular stimuli that trigger the production of type I IFNs. Typically, upon infection with microbes or exposure to damaged cellular components, danger-associated molecular patterns (DAMPs) can be recognized by pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), cyclic GMP-AMP synthase (cGAS), MDA-5, DAI, RIG-I like receptors, and DDX41in the cell membrane or cytoplasm. After recognizing and binding with DAMPs, these PRRs are activated and interact with adaptor proteins and activate kinases to phosphorylate NF-κB, IFN regulatory factor 3 (IRF3), and activating protein 1 (AP-1), which translocate into the nucleus and induce the expression of IFN-β in most cell types in the body[28] (Figure 1). The production of IFN-α requires the transcription factor IRF7 rather than IRF3, and IFN-α is primarily expressed by plasmacytoid dendritic cells (DCs) because of the constitutive expression of IRF7.[29] The less-studied members of type I IFNs (IFN-ε, IFN-κ and IFN-ω) seem to be secreted in a tissue-specific manner in response to various stimuli.[19] Similar to type I IFNs, the stimuli and source of type III IFNs are broad, and most cell types in the body produce IFN-λ.[26] In contrast to type I and type III IFNs, the resource of IFN-γ is restricted in immune cells, such as T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, DCs, and macrophages.[30–37] Many cytokines, such as IL-1, IL-2, IL-12, IL-15, IL-18, IL-21, IL-23, IL-27, IFN-α/β and TNF-α, can induce IFN-γ secretion in various types of immune cells.[38] For example, IL-12 alone or combined with other cytokines (such as IL-18) or combined with T cell receptor (TCR) and MHCII-Ag peptide complexes induce IFN-γ secretion in lymphoid cells mediated by signal transducer and activator of transcription 4 (STAT4) or nuclear factor of activated T cells (NFAT).[31,39–41] In addition to cytokines, bacterial infection (such as mycobacteria or Legionella) or stimulation with the components of bacteria (such as lipopolysaccharide) induces IFN-γ production in macrophages and DCs via unclear mechanisms.[34]

The functions of the three types of IFNs seem to be redundant, and the canonical signaling induced by different IFNs is also similar; in particular, type I and type III IFNs induce the same signaling. Upon binding to their ligands, IFNAR or IFNLR activates the constitutively interacting kinases JAK1 and TYK2. Activated JAK1 and TYK2 phosphorylate STAT1 and STAT2 and induce heterodimerization of STAT1 and STAT2 or homodimerization of STAT1, and then form a trimeric complex known as IFN-stimulated gene factor 3 (ISGF3) by interacting with IRF9. ISGF3 enters the nucleus and binds IFN-stimulated response elements (ISREs) to induce the expression of type I and type III IFN target genes. Unlike IFNAR and IFNLR, IFNGR binds to IFN-γ and activates JAK1 and JAK2. Activated JAK1 and JAK2 cause phosphorylation and homodimerization of STAT1, which translocates into the

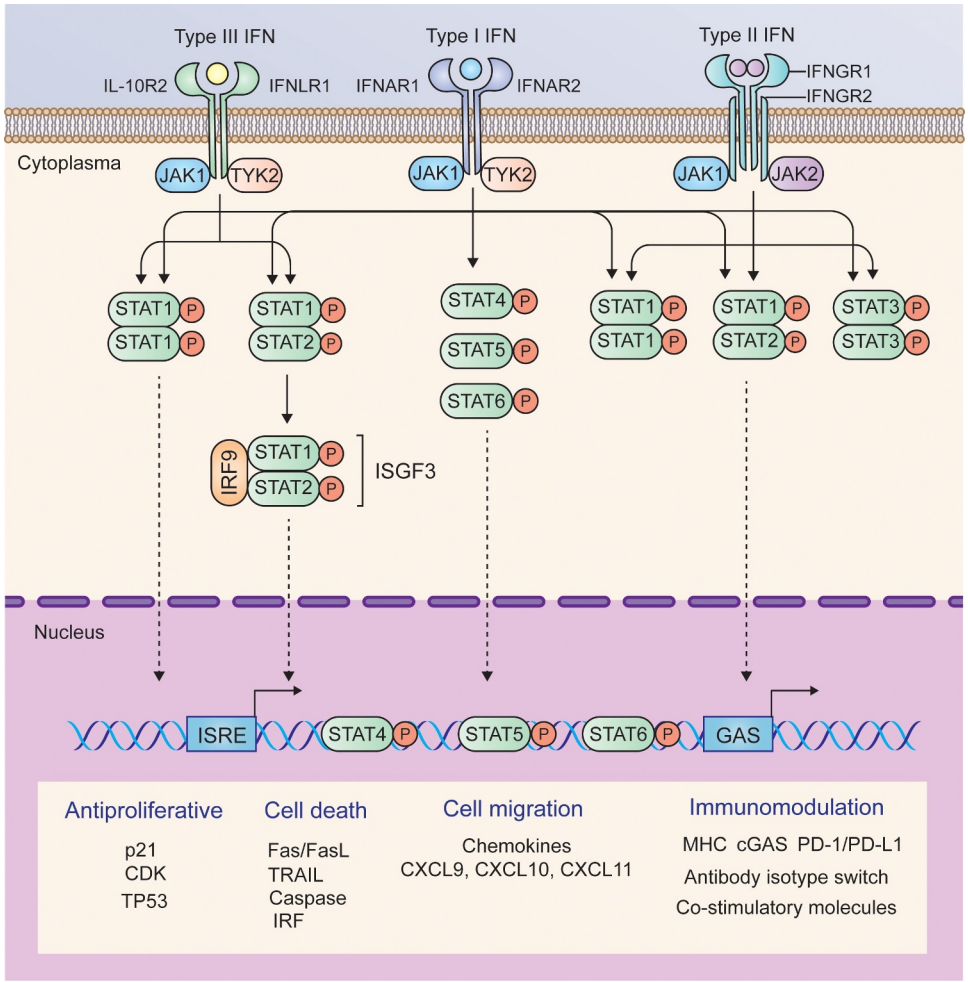

Figure 2. Signaling pathways and major target genes induced by IFNs.

nucleus and binds IFN-γ-activating sites (GASs) to induce the transcription of IFN-γ target genes.[25] The signaling pathways and major target genes induced by the three types of IFNs are summarized in Figure 2.

The implication of IFNs in cancer therapy

Given that the induction of IFNs is largely triggered by multiple DAMPs and the activation of IFN signaling pathway exhibits cell intrinsic (anti-proliferation and inducing cell death) and extrinsic (immunomodulation) anti-cancer activity, it seems reasonable to conclude that IFNs play a critical role in the successes of conventional cancer therapeutic strategies. Indeed, IFNs alone or strategies of stimulating IFN production, and combined using IFNs and other cancer therapies have been demonstrated to be effective to treat various malignancies. Additionally, it has also been revealed that deficiency of IFN signaling is one of the most important reasons for the resistance or failure of common cancer therapeutic strategies.

Firstly, the efficient type I IFN signaling was recognized as a footstone closely related to the success of conventional cancer therapeutic strategies, such as chemotherapy, radiotherapy and immunotherapy.[42] Sistigu et al. demonstrated that cancericidal effects of anthracyclines rely on cancer cell autonomously producing type I IFN induced by the activation of toll-like receptor 3 (TLR3).[43] Chemotherapeutic drug cyclophosphamide was revealed to modulate the transcriptional prolife of peripheral blood mononuclear cells (PBMCs) in patients with hematologic malignancies and induce a type I IFN associated sterile inflammation, which contributes to cancer cell elimination.[44–46] Apart from chemotherapy, the efficacy of radiotherapy was also highly entwined with the activation of type I IFN signaling.[47,48] Both studies in mouse models of melanoma and colorectal carcinoma indicated that radiotherapy induces the production of type I IFN in myeloid cells and thus attributes to the generation of tumor infiltrating DC with enhanced ability to prime T cells.[47,48] Additionally, both type I IFN (IFN-α and IFN-β) and type II IFN have been reported to enhance the efficacy of anti-PD1 or anti-PD-L1 in various cancer types, such as melanoma and pancreatic cancer.[13–17]

Secondly, various IFN stimulating strategies based on targeting PRRs have been developed to treat cancer, and accumulating evidence indicate that PRR agonists synergize with other therapy approaches and attribute to a better therapeutic efficacy. Deng et al. found that the administration of STING agonist (2′3′ cGAMP, 10μg) synergized with radiation (20 Gy) and significantly boost anti-cancer immune response in murine colon cancer bearing mouse models.[48] Ghaffari et al. also showed that STING agonist (2′3′-c-di-AM, 4 mg/kg i.p.) combined with anti-PD-1 antibody, greatly promotes IFN

response and the expression of MHC class II genes and subsequently amplifies the therapeutic efficacy of carboplatin in the murine model of high-grade serous ovarian cancer.[49] Recently, Márquez-Rodaet al. found that intratumoral injection of a nanoplexed form of polyinosinic:polycytidylic acid (poly I:C), a TLR3 agonist called BO-112, in combination with PD-1 blockade therapy, significantly promotes infiltration of $CD8^+$ T cells and increases the expression of genes associated with T cell cytotoxic activity.[50] Moreover, BO-112 is also found to restore the efficacy of T cell-based adoptive cell therapy (ACT) through increasing MHC class I expression of type I and type II IFN deficient melanoma cells in an IFN- and Nlrc5-independent manner.[51] Beside, a very recent study indicated that STING agonist (DMXAA or cGAMP) helps to subvert the immunosuppressive TME, thereby promotes CAR T cell trafficking and persistence in breast cancer.[52] In general, the PRRs in cancer cells or surrounding non-cancer cells (including infiltrated immune cells) senses DAMPs or directly activated by their agonists to induce the production of IFNs, which subsequently boost anti-cancer immune response to eradicate cancer cells. Therefore, positive feedback between cancericidal strategies and IFN-based anti-cancer immunity exists in the process of killing cancer cells.

Thirdly, accumulating evidence indicated that deficiency of IFN signaling is one of the most important reasons for the immune dysfunction and even the resistance or failure of common cancer therapeutic strategies. For example, the efficacy of immune checkpoint blockade therapy was significantly reduced on STING knockout mice bearing B16-SIY melanoma, because the loss of STING signaling impaired the tumor-cell-derived DNA triggered production of type I IFN and thus failed to activate DCs.[53] Ghosh et al. showed that mutant p53 mediates apoptosis resistance and immune evasion of cancer cells through interacting with TBK1 and then preventing the formation of TBK1/STING/IRF3 complex and finally impairing the expression of IFN-β.[54] An early study indicated that the expression of interferon-stimulated genes (ISGs) was impaired in the lymphocytes from patients with breast cancer, melanoma, and gastrointestinal cancer, which indicates that defect in IFN signaling in lymphocyte may represent a common cancer-associated mechanism of immune dysfunction.[55] Similarly, it was showen that the downstream targets of IFN-γ were downregulated in different melanoma cell lines with the disappointing response to immunotherapies, suggesting downregulation of IFN-γ signaling is common in melanoma and potentially predicts the response to immunotherapy.[56] It has been elucidated recently that JAK1 defeated melanoma B16 cells were insensitive to T cell-based adoptive cell therapy (ACT) due to the incompetence in both type I and II IFN signaling.[51] Similarly, loss-of-function mutations in JAK1/2 has also been revealed to be responsible for the primary and acquired resistance to anti-PD-1 blockage in melanoma and colon cancer carcinoma.[12] Christopher et al. demonstrated that effective antitumor responses to anti-PD-1 blockage required DCs to produce IL-12 upon sensing IFN-γ released from T cells, in turn DC derived IL-12 activates T effector cells, whereas IFN-γ deficiency impaired the anti-PD-1 efficiency.[10]

In summary, it is a promising strategy to use IFNs alone or combined with therapeutic strategies to treat cancer. Preclinical studies have indicated that IFNs are competent in provoking cancer immunity in different cancer types (Table 1). Consistent with the results of preclinical studies, a number of clinical studies have also confirmed the efficiency of IFNs in the management of various types of cancer (Table 2). However, it should be mentioned that different types of IFNs may be suitable for the treatment of different types of cancer.[25]

Although the positive roles of IFNs in cancer therapy have been well recognized, IFNs occasionally have been noticed to induce the acquisition of therapy resistance through mediating cancer immune escape by affecting both immune cells and nonimmune cells in the tumor microvironment.[91] For instance, Jacquelot et al. reported that sustained type I IFN activation induce the up-regulation of programmed cell death ligand 1 (PD-L1) in both tumor and DCs and then enhance the expression of nitric oxide synthase 2 (NOS2), which is related to the accumulation of Treg and myeloid cells in the TME, finally lead to the resistance to programmed cell death 1 (PD-1) blockade.[92] Consistently, type I IFN also upregulates the expression of *NOS2* and *PD-L1* gene in PBMCs from melanoma patients.[92] Type I IFN singling also induce radiation resistance by promoting the recruitment of immunosuppressive myeloid cells via the CCR2 pathway.[93] In addition, several studies indicated that the overexpression of a subset of ISGs known as interferon-related DNA damage resistance signature (IRDS) reduced the sensitivity of tumor cells to genotoxic therapy strategies *in vitro*.[94,95]Another similar study showed that tumor cells taken up the stroma-cell-derived exosomes containing non-coding RNA and repeat/transposable elements, enhanced STAT1-drived expression of IRDS and the activation of NOTH3. And the cooperation of STAT1 and NOTH3 triggered the accumulation of therapy resistant tumor-initiating cells and tumor recurrence.[96]

Conclusively, more effort should be paid to further understand the mechanisms by which IFNs regulate cancer immunity and how they are involved in other cancer therapies in order to conceive optimal and efficient therapeutic strategies for cancer management, and it may reduce therapeutic resistance of IFN-based therapy by adjusting the dosage and administration duration or combination with other therapeutic approaches.

IFNs regulate the cancer-immunity cycle

Cancer growth is determined by the balance between cell proliferation and cell death. Neoantigens resulting from gene mutation or overexpression of oncogenes in cancer cells are released after cell death, captured, and then presented to T cells by antigen-presenting cells (APCs), such as DCs and macrophages, which cause the activation of effector T cells. The activated effector T cells traffic and infiltrate into tumor tissues, where they recognize and kill cancer cells with the same tumor antigens, resulting in the release of more antigens. This cyclic process is defined as the cancer immunity cycle.[97] Current studies suggest that IFNs regulate each step of the cancer immunity cycle (Figure 3), contributing to our understanding of the mechanisms by which IFNs regulate cancer immunity.

Table 1. Pre-clinical studies of IFNs in cancer treatment.

Cancer type	Treatment information	Biological roles	Reference
Melanoma	IFN-α, 5-Aza-2 -deoxycitidine and DNA vaccine	Improve vaccine efficacy and correlate with changes in chemokine gene expression and $CD8^+$ TIL infiltration. Reduce tumor burden and increase median survival.	57
Melanoma	PEG-IFN-α	Reduce tumor weight. Inhibit proliferation but promote apoptosis of tumor cells.	58
Melanoma	IFN-α and dacarbazine	Reduce tumor hypoxia, downregulate G-protein signaling-5 (RGS5) expression, and increase mature pericyte coverage. Inhibit tumor growth by normalizing tumor vasculature.	59
Melanoma	IFN-α-2b and thalidomide	Decrease mean vessel count of tumors and suppress angiogenesis.	60
Colorectal cancer	IFN-α	Suppress CCL17 expression in tumors and thus decrease the trafficking of Treg.	61
Colorectal cancer	Dendritic cell-based immunotherapy and IFN-α	Suppress outgrowth of tumors and induce potent antitumor cellular immune responses.	62
Renal cell carcinoma	IFN-α-incorporated Hyaluronic acid-tyramine hydrogel and sorafenib	Inhibit proliferation of tumors by inducing apoptosis and suppress angiogenesis.	63
Renal cell carcinoma	PEG-IFN-α2b and 5-FU	Augment IFN-induced anti-proliferative effects with the induction of cell apoptosis.	64
Mesothelioma	IFN-α or combination with β-carotene or alpha-difluoromethylornithine (DFMO)	Stimulate effects on immune cells by inhibiting TGF-β generation.	65
Pancreatic cancer	IFN-α and doxorubicin	Inhibit tumor cells growth in vivo and activate cytotoxicity of NK cells and CTLs, by increasing the expression of MHC I and NKG2D ligands on tumor cells.	66
Prostate cancer	PEG-IFN-α and docetaxel	Inhibit neoplastic angiogenesis by inducing a decrease in the local production of proangiogenic molecules by tumor cells and increasing apoptosis of tumor associated endothelial cells.	67
Colon cancer	IFN-β	Repress the growth of colon cancer in the peritoneal cavity and liver.	68
Melanoma	IFN-β	Activate neutrophils and alter tumor associated neutrophils (TAN) polarization toward anti-tumor N1 in mice and patients.	69
Glioblastoma	IFN-β and temozolomide	Promote tumor cell death, eliminate invasive tumors, activate microglia surrounding the tumors, and increase long-term survival.	70
Prostate cancer	IFN-β	Increase the natural killer cell activity and reduce tumor volume.	71
Neuroblastoma	IFN-β	Delay tumor growth, stabilize vessel, enhance antitumor efficacy by improving intratumoral delivery of systemically administered topotecan (TPT).	72 73
Lymphoma	IFN-α/β	Increase the survival time of ESb-immunized mice rechallenged with ESb cells and inhibit the development of lymphoma cell metastases.	74
Melanoma	Salmonella typhimurium expressing recombinant IFN-γ	Inhibit tumor growth and prolong the survival of C57BL/6 mice bearing B16F10 melanoma.	75
Cervical cancer	IFN-γ	Induce the resolution of cervical intraepithelial lesions and high-risk HPV DNA clearance in vivo.	76
Breast cancer	IFN-γ-endostatin-based gene-radiotherapy	Activate IFN-γ-stimulated CTL and NK cells, and enhance the endostatin-induced anti-angiogenic activity.	77
Ovarian cancer	IL-4-Pseudomonas exotoxin and IFN-α and IFN-γ	Increase overall survival of mice with human ovarian cancer xenograft and increase ovarian cancer cell death in vitro and in vivo.	78
Glioblastoma	hTERT-siRNA and IFN-γ	Inhibit angiogenesis and tumor progression through the downregulation of molecules involved in these processes.	79
Lung cancer	Hyperthermia and IFN-γ	Suppress the basal, the heat shock-induced and the cisplatin-induced expression of Hsp27 in tumor cells and suppress tumor growth in vivo.	80
Oral squamous carcinoma	Hyperthermia and IFN-γ	Suppress the basal, the heat shock-induced and the cisplatin-induced expression of Hsp27 in tumor cells and suppress tumor growth in vivo.	80
Pancreatic cancer	Anti-PD1 therapy combined with IFN-γ	Suppress tumor-derived CXCL8 and inhibit the tumor trafficking of $CXCR2^+$ $CD68^+$ macrophages by blocking the CXCL8-CXCR2 axis to enhance anti-PD1 efficacy.	17
Colon cancer	IFN-γ and ATG5-targeted inhibition	Decrease tumor incidence rate and enhance the antitumor efficacy.	81
Colon adenocarcinoma	GM-CSF and IFN-γ	Exhibit tumor formation delay, induce a systemic immune response and indicate a dual role for T and NK cells in mediating the anti-tumor activity.	82
Hepatocellular carcinoma	IFN-α and PEG-IFN-λ1	Obtain highest antitumor efficacy at the tumor site that was associated with infiltration of NK cells into TME. Suppress tumor growth, inhibit HBsAg production and induce tumor cell apoptosis.	83 84 85
Melanoma	IFN-λ	Induce both tumor apoptosis and NK cell-mediated immunological tumor destruction through innate immune responses.	86
Melanoma	Ad-IFN-λ2 orAd-IFN-λ1	Increase the number of infiltrating $CD8^+$ T cells into the tumors.	87
Colon cancer	IFN-λ	Inhibit metastatic tumor formation through innate immune responses.	86
Colon adenocarcinoma	rhIFN-λ1	Inhibit the proliferation of tumor cells in a dose-dependent manner, activate the STATs and induce apoptosis of tumor cells.	88
Lung adenocarcinoma	Ad-mIFN-λ2	Inhibit tumor cell growth through inducing apoptosis of tumor cell and regulating cell immune response.	89
Lung cancer	IFN-λ2	Suppress tumor cell growth and induce cell death.	90

IFNs directly induce cell death and promote release of tumor antigens

It has long been believed that only IFN-γ directly induces malignant cell death, whereas the other types of IFNs exert their anti-cancer effects by regulating the activity of host immune cells, such as DCs, NK cells and cytotoxic T lymphocytes (CTLs).[25,98] Recent studies have shown that all types of IFNs have direct pro-apoptotic effects.

Both IFN-α and IFN-β regulate intrinsic and extrinsic apoptotic pathways.[99,100] Mechanistically, IFN-α and IFN-β induce the transcription of the *TP53* gene, inhibit proliferation, and induce apoptosis of cancer cells.[101] Moreover, they also directly

induce the production of pro-apoptotic factors, such as TRAIL and FAS[102,103] and enhance their pro-apoptotic effects in various malignant cell types.[104,105] Additionally, IRF family members are well-known ISGs induced by type I IFNs.[25] Most members of the IRF family, such as IRF1, IRF3, and IRF5, have been documented to induce cell death in various malignant tumor types.[106–108] Although the pro-cytotoxic effects of type III and other members of type I IFNs are currently not well studied, considering that the ISGs induced by them are almost same, it is reasonable to deduce that most members of type I and type III IFNs could directly induce malignant cell death. As expected, several recent studies have shown that type III IFNs, such as IFN-λ1, IFN-λ2, and IFN-λ4, induce cell death in various malignant tumor types.[90,109–112]

The pro-apoptotic effects of IFN-γ have been well documented and intensively reviewed previously.[113–115] Like type I and type III IFNs, IFN-γ also induces the transcription of pro-apoptosis genes, such as TRAIL, FAS, FAS ligand, and caspase-8.[116–119] Moreover, it can promote apoptosis of malignant cells by inducing endoplasmic reticulum stress and reactive oxygen species (ROS).[120] Apart from apoptosis, IFN-γ also induces ferroptosis in cancer cells. It was recently reported that IFN-γ secreted by activated $CD8^+$ T cells enhanced the ferroptosis of cancer cells by inhibiting the expression of SLC3A2 and SLC7A11, which disturbed the uptake of cysteine and thus resulted in lipid peroxidation and consequent ferroptosis of cancer cells.[121] Additionally, IFN-γ has been reported to induce ETosis in lung cancer cells.[122,123] ETosis is a suicidal process in which the cell extrudes its intracellular DNA and histones to generate an extracellular reticular structure. This event is a special type of cell death that usually occurs in neutrophils and mast cells.[124] IFN-γ can induce oxidative stress and the upregulation of ROS, which promotes mimic ETosis in lung malignant cells.[122] Additionally, IFN-γ treatment was also found to induce caspase-mediated DNA damage and further activate ATR/ATM-regulated peptidyl arginine deiminase 4 (PAD4) mediated histone 3 citrullination, triggering mimic ETosis in A549 human lung cancer cells.[123]

IFNs promote the tumor-antigen presentation

DCs are typically antigen-presenting cells that process and present antigens to T cells. Generally, endogenous antigens (such as synthesized virus antigens) are presented to $CD8^+$ T cells in a class I MHC-dependent manner, whereas the exogenous antigens are presented to $CD4^+$ T cells in a class II MHC dependent manner by DCs. Tumor-antigens are acquired and processed by DCs and presented to $CD8^+$ T cells with the help of Th1 $CD4^+$ T cells.[125] It has been demonstrated that all types of IFNs promote the tumor-antigen presentation process of DCs.

The effects of IFNs on the differentiation and maturation of DCs have been investigated as early as 1998 when the type I IFNs, such as IFN-α and IFN-β, were first identified to be not only necessary for the differentiation,[126,127] but also facilitate the maturation and activation of DCs.[128,129] Based on these findings, IFN-α or IFN-β has been developed as one of the standard components of cytokine cocktails inducing maturation of DCs.[130] In 2011, Diamond et al. revealed that type I IFNs were essential for tumor-specific antigen presentation of DCs, because the lack of IFNAR1 in DCs resulted in defects of antigen cross-presentation to $CD8^+$ T cells.[131] Moreover, DCs treated with IFN-α2b or IFN-α5 showed enhanced adhesion to cultured lymphatic endothelial cells, indicating that IFN-α is favor of the adhesion and transmigration of DCs.[132] Various studies have consistently demonstrated that the activation of IFN-β-producing signaling pathways also facilitate the process of tumor-antigen presentation of DCs. For example, TLR agonists, such as lipopolysaccharide (LPS) and polyinosinic: polycytidylic acid (poly I:C), are known to stimulate the maturation of DCs via activation of the TLR signal transduction pathway.[133,134] Additionally, STING agonists have been reported to promote the infiltration of DCs into the TME and enhance the antigen-presentation ability of DCs through the STING-TBK1 signaling pathway.[97,135,136]

It has been long believed that the major function of NK, NKT, and γδ T cells was to lyse virus-infected or transformed cells through the cytolytic effect of IFN-γ. However, recent studies have shown that these IFN-γ-producing innate lymphocytes also facilitate the antigen-presentation of DCs.[137] A study comparing the efficiency of several clinical grade DC maturation cocktails demonstrated that LPS plus IFN-γ is more potent in inducing the maturation of DCs compared with the gold standard cocktails based on IFN-α and other cytokines.[138] Moreover, it has been demonstrated that IFN-γ produced by $CD4^+$ T cells in the TME induces the expression of class I and class II MHC molecules and stimulates the production of antigen processing machinery by APCs, which enhances the antigen-presentation to T cells in a class I or class II restricted manner.[139–141] One recent study also confirmed that short-term (less than 48 h) exposure to LPS and IFN-γ promotes the maturation of DCs; however, long-term exposure to LPS and IFN-γ inhibits the functions of DCs and even induces apoptosis of DCs.[142] This study suggests that long-term exposure to inflammation may result in the exhaustion of DCs in the cancer tissue microenvironment.

Some type III IFN members have also been reported to regulate the maturation of DCs. For example, IFN-λ1 has been shown to induce the maturation of DCs, break immune tolerance and potentially contribute to clearance of hepatitis B virus (HBV) by the immune system.[143,144] However, no study has investigated and compared the effect and efficiency of type III IFNs on promoting maturation of DCs in the TME.

Apart from the modulation of DCs, IFN signaling also plays a critical role in the crosstalks between innate immune cells and DCs. In the TME, tumor derived cGAMP was taken up or transferred to the endothelial cells, DCs or macrophages via some specific transporters,[145–147] which triggers the production of type I IFN. Afterward, secreted type I IFN promotes the infiltration of innate cytolytic cells, such as NK cells. And activated NK cells by the ligands on cancer cells will perform their cytotoxic function to promote the release of tumor antigen and concomitantly secrete several chemoattractants, such as XCL1, CCL5[148] or FLT3LG,[149] which mediate the recruitment of conventional dendritic cells (cDC), a type of DCs specialized in cross-presentation. IFNs are also important in NK-dependent DC maturation. An early research found that the interaction between NK cells and DCs lead to the

Table 2. Clinical trials of IFNs in cancer treatment.

NCT number	Cancer type	Study title	Sponsor/Collaborator	Status	Phase
NCT00004122	Bladder Cancer	BCG plus interferon α-2b in treating patients with bladder cancer	Roswell Park Cancer Institute and National Cancer Institute (NCI)	Completed	II
NCT00227656	Breast Cancer	Capecitabine and pegylated interferon α-2a in treating patients with recurrent or progressive brain metastases due to breast cancer	M.D. Anderson Cancer Center and National Cancer Institute (NCI)	Terminated	II
NCT03112590	Breast Cancer	Phase I-II study of interferon-γ in patients with HER-2 positive breast cancer	H. Lee Moffitt Cancer Center and Research Institute and Horizon Pharma Ireland, Ltd., Dublin Ireland	Active, not recruiting	II
NCT00276536	Breast Cancer	Interferon α in treating patients with Stage IV solid tumors, lymphoma, or myeloma	The Cleveland Clinic and National Cancer Institute (NCI)	Completed	I
NCT00138151	Cervical Cancer	Isotretinoin, interferon α-2b, and paclitaxel in Stage IV, recurrent, or persistent cervical cancer	University of Medicine and Dentistry of New Jersey, National Cancer Institute (NCI) and Rutgers, The State University of New Jersey	Terminated	II
NCT03403634	Colorectal Cancer	Celecoxib, recombinant interferon α-2b, and rintatolimod in treating patients with colorectal cancer metastatic to the liver	Roswell Park Cancer Institute and National Cancer Institute (NCI)	Active, not recruiting	II
NCT00786643	Colorectal Cancer	Study of interferon γ in metastatic colorectal carcinoma	Accelerated Community Oncology Research Network and InterMune	Completed	II
NCT00085384	Fallopian Tube Cancer	PEG-interferon α-2b in treating patients with platinum-resistant ovarian epithelial, peritoneal, or fallopian tube cancer	M.D. Anderson Cancer Center	Terminated	II
NCT00276523	Head and Neck Cancer	PEG-interferon α-2b in treating patients with Stage II, Stage III, or Stage IV head and neck cancer that can be removed by surgery	M.D. Anderson Cancer Center and National Cancer Institute (NCI)	Completed	II
NCT00054561	Head and Neck Cancer	Isotretinoin, interferon α, and vitamin E in treating patients with Stage III or Stage IV head and neck cancer	Eastern Cooperative Oncology Group and National Cancer Institute (NCI)	Completed	III
NCT00873236	Kidney Cancer	MRI scans of blood vessel changes caused by bevacizumab alone or given together with interferon α-2a in treating patients with Stage III or Stage IV kidney cancer	Mount Vernon Cancer Center at Mount Vernon Hospital and National Cancer Institute (NCI)	Unknown	II
NCT00278174	Kidney Cancer	IFN-α-1b in renal cancer with metastatic kidney cancer	Case Comprehensive Cancer Center and National Cancer Institute (NCI)	Completed	II
NCT00003542	Kidney Cancer	Interferon α in treating patients with advanced kidney cancer	Memorial Sloan Kettering Cancer Center and National Cancer Institute (NCI)	Completed	II
NCT00045279	Kidney Cancer	PEG-interferon α-2b in treating patients with metastatic kidney cancer	Memorial Sloan Kettering Cancer Center and National Cancer Institute (NCI)	Completed	II
NCT00003656	Kidney Cancer	Tretinoin plus interferon α in treating patients with metastatic kidney cancer	Weill Medical College of Cornell University	Completed	II
NCT00467077	Kidney Cancer	Gefitinib and PEG-interferon α-2b in treating patients with unresectable or metastatic kidney cancer	California Cancer Consortium and National Cancer Institute (NCI)	Terminated	II
NCT00589550	Kidney Cancer	PEG-interferon α-2b and sorafenib in treating patients with unresectable or metastatic kidney cancer	Thomas Olencki and Schering-Plow and Ohio State University Comprehensive Cancer Center	Terminated	I
NCT00101114	Kidney Cancer	Sorafenib and interferon α in treating patients with metastatic or unresectable kidney cancer	National Cancer Institute (NCI)	Completed	II
NCT01158534	Kidney Cancer	Celecoxib and recombinant interferon α-2b in metastatic kidney cancer who have undergone surgery	Case Comprehensive Cancer Center	Completed	II
NCT00090870	Kidney Cancer	PEG-interferon α-2b, sargramostim, and thalidomide in treating patients with metastatic kidney cancer	Medical University of South Carolina	Terminated	II
NCT00006384	Kidney Cancer	SU5416 and interferon α-2b in treating patients with unresectable or metastatic kidney cancer	City of Hope Medical Center and National Cancer Institute (NCI)	Completed	II
NCT00059813	Kidney Cancer	Oblimersen and interferon α in treating patients with metastatic renal cell cancer	National Cancer Institute (NCI)	Completed	II
NCT00045370	Kidney Cancer	Chemotherapy and biological therapy in treating patients with locally advanced or metastatic kidney cancer	Memorial Sloan Kettering Cancer Center and National Cancer Institute (NCI)	Completed	I
NCT00416871	Kidney Cancer	Interleukin-2 and interferon in treating patients with metastatic kidney cancer	Center Leon Berard	Completed	III
NCT00004244	Kidney Cancer	Interleukin-12 and interferon α in treating patients with metastatic kidney cancer or malignant melanoma	National Cancer Institute (NCI) and The Cleveland Clinic	Completed	I
NCT00053807	Kidney Cancer	Interleukin-2, interferon α, and fluorouracil compared with observation in treating patients who have undergone surgery for kidney cancer	European Organization for Research and Treatment of Cancer – EORTC and University of Glasgow	Completed	III
NCT00085436	Kidney Cancer	DC vaccine combined with IL-2 and IFNα-2a in treating patients with mRCC	Dartmouth-Hitchcock Medical Center and National Cancer Institute (NCI)	Completed	II
NCT00006006	Liver Cancer	Thalidomide plus interferon α in treating patients with progressive liver cancer that cannot be surgically removed	National Cancer Institute	Completed	II
NCT00471484	Liver Cancer	Combination chemotherapy and interferon α-2b in treating patients with nonmetastatic liver cancer that cannot be removed by surgery	National Cancer Center, Singapore and National Cancer Institute (NCI)	Unknown	II

(*Continued*)

Table 2. (Continued).

NCT number	Cancer type	Study title	Sponsor/Collaborator	Status	Phase
NCT00062010	Lung Cancer	Interferon α, isotretinoin, and paclitaxel in treating patients with recurrent small cell lung cancer	Eastern Cooperative Oncology Group	Completed	II
NCT00002470	Lung Cancer	Fluorouracil plus interferon α in treating patients with advanced metastatic carcinoid tumors	Mid-Atlantic Oncology Program and Cancer Biotherapy Research Group and National Cancer Institute (NCI)	Completed	II
NCT00004016	Melanoma	Interferon γ in treating patients with recurrent or metastatic melanoma or other solid tumors	University of Rochester and National Cancer Institute (NCI)	Completed	I
NCT00085384	Ovarian Cancer	PEG-interferon α-2b in treating patients with platinum-resistant ovarian epithelial, peritoneal, or fallopian tube cancer	National Cancer Institute (NCI)	Terminated	II
NCT02530047	Ovarian Cancer	Mesenchymal stem cells (MSC) for ovarian cancer	M.D. Anderson Cancer Center	Completed	I
NCT00002734	Ovarian Cancer	Radiolabeled monoclonal antibody, paclitaxel, and interferon α in treating patients with recurrent ovarian cancer	National Cancer Institute (NCI)	Completed	I
NCT02948426	Ovarian Cancer	Intraperitoneal infusion of autologous monocytes with sylatron (Peginterferon α-2b) and actimmune (Interferon γ-1b) in women with recurrent or refractory ovarian cancer, fallopian tube cancer or primary peritoneal cancer	National Cancer Institute (NCI) and National Institutes of Health Clinical Center (CC)	Completed	I
NCT00047632	Ovarian Cancer	Safety and efficacy of interferon γ-1b plus chemotherapy for ovarian and peritoneal cancer	InterMune	Terminated	III
NCT00082862	Pancreatic Cancer	Cisplatin, metronomic low-dose interferon α, gemcitabine, and fever-range whole-body hyperthermia in treating patients with inoperable or metastatic pancreatic cancer	The University of Texas Health Science Center, Houston and National Cancer Institute (NCI)	Unknown	II
NCT00068575	Pancreatic Cancer	Chemotherapy, interferon α, and radiation therapy in treating patients who have undergone surgery for pancreatic cancer	M.D. Anderson Cancer Center and National Cancer Institute (NCI) and Schering-Plow	Completed	II
NCT00059826	Pancreatic Cancer	Adjuvant chemoradiotherapy and interferon α in treating patients with resected pancreatic cancer	Alliance for Clinical Trials in Oncology and National Cancer Institute (NCI)	Completed	II
NCT00176527	Prostate Cancer	Isotretinoin, interferon α-2b, docetaxel, and estramustine in treating patients with metastatic prostate cancer that did not respond to hormone therapy	University of Medicine and Dentistry of New Jersey and National Cancer Institute (NCI) and Rutgers, The State University of New Jersey	Terminated	II
NCT00002637	Prostate Cancer	Biological therapy in treating patients with prostate cancer	Memorial Sloan Kettering Cancer Center	Completed	II
NCT01060501	Rectal Cancer	Modulation of adjuvant 5-FU by folinic acid and interferon-α in colon cancer	University of Ulm	Completed	III
NCT01658813	Renal Cell Cancer Metastatic	5-Fluorouracil followed by interferon-α-2b in previously-treated metastatic gastrointestinal, kidney, or lung cancer	Western Regional Medical Center	Completed	II
NCT01658813	Non Small Cell Lung Cancer Metastatic	5-Fluorouracil followed by interferon-α-2b in previously-treated metastatic gastrointestinal, kidney, or lung cancer	Western Regional Medical Center	Completed	II

engagement of NKp30, which further induces the production of TNF-α and IFN-γ from NK cells, and these cytokines will promote the maturation of DCs.[150]

IFNs promote the priming and activation of t cells

DCs not only process and present antigens to T cells, but also prime and activate T cells by providing cytokines that are essential for the activation of naïve T cells; thus, DCs also play important roles in their priming and activation. As early as 2002, it was demonstrated that IFN-α was essential for DCs to stimulate naïve T-cell proliferation based on the observation that the lack of IFNAR1 in DCs or blocking IFN-α with neutralizing antibody impaired the ability of DCs from bone marrow to stimulate T cell priming.[129] Similarly, Longhi et al. also revealed that the systemic type I IFN signaling pathway is required for DCs to induce a $CD4^+$ Th1 immune response *in vivo*.[133] Additionally, IFN-γ is one of the most important cytokines for inducing Th1 polarization. NK cells interact with DCs and then assist the polarization of Th1 cells in an IFN-γ-dependent manner.[151] Moreover, Type III IFNs also facilitate Th1 polarization. A study indicated that naïve and memory human $CD4^+$ T cells express IL-28AR (IFNLR1) and preclude the expression of Th2 cytokines (IL-4 and IL-13) in these cells.[152] Consistent with this study, IFN-λ1 was also found to reduce IL-13 secretion but enhance IFN-γ secretion in human PBMCs following mitogen stimulation (Con-A).[153] Hence, IFN-λ could modulate Th1/Th2 balance by elevating Th1 cytokines but restricting the production of Th2 cytokines,[154,155] which contributes to T cell priming and cancer elimination.

Type I IFNs not only promote the priming of T cells, but also prolong the survival and augment the proliferation of activated T cells through the cell-intrinsic type I IFN signaling pathway. Marrack et al. first reported in 1999 that IFN-α/β plays an important role in maintaining the vitality of T cells *in vitro*.[156] It was then revealed that type I IFN directly stimulated the clonal expansion and effector differentiation of $CD8^+$ T cells *in vitro* and *in vivo*, because IFNAR expression by T cells was necessary for this process.[157,158] In addition to type I IFN, Zimmerman et al. demonstrated that IFN-γ also promoted the survival and proliferation of tumor-specific T cells by upregulating the expression of survivin and Ifi202.[159]

IFNs promote trafficking and infiltration of t cells

Trafficking and infiltration of T cells is one of the key steps in the anti-cancer response of T cells. T cells must traffic toward the tumor site and undergo extravasation before they recognize and eliminate tumor cells. This process is largely dependent on multiple chemokines, including CCL2, CCL3, CCL4, CCL5, CXCL9, and CXCL10. These chemokines are important signaling molecules that recruit T cells in the TME.[160] IFNs are pleiotropic cytokines that promote multiple types of cells to produce chemokines that attract and recruit T cells in the TME. Padovan et al. found that IFN-α stimulates the secretion of CXCL9 and CXCL10 in monocyte-derived DCs and consequently promotes the infiltration of $CD8^+$ T cells.[161] IFN-β promotes the expression of CCL5 and CXCR3 in melanoma cells and augments $CD8^+$ T cell recruitment into the tumor.[14] IFN-γ has been reported to promote the production of CXCL10 in melanoma cells,[162] which enhances the production of CCL5 in fibroblasts, a common component cell type in the TME.[163]

Intact endothelial cells are also very important for T cell infiltration by providing an adhesion face. Moreover, endothelial cells were recently identified as the main source of type I IFNs in the TME to stimulate the infiltration of $CD8^+$ T cells into the TME.[164] IFNs can also affect the functions of endothelial cells and promote T cell infiltration. For example, type I IFN is found to promote the synthesis of CCL5 in endothelial cells.[165] In addition, treatment of endothelial cells with IFN-γ can selectively augment the migration of Th1 cells, the subtype of T cells that promotes cellular immunity.[166]

Apart from endothelial cells, tumor vasculature also plays a crucial role in the process of trafficking and infiltration of T cells. However, IFNs, as anti-angiogenic cytokines,[167] may restrict the construction of vessels in the TME and thus make it difficult for T cell trafficking. Hence, it is necessary to evaluate the net effect of IFN treatment on the trafficking and infiltration of T cells during cancer management.

IFNs enhance the recognition and killing of cancer cells by effector cells

The coordination between antigen peptide-class I MHC molecules and TCR provides initial and essential signals for T cell-mediated elimination of cancer cells.[168] IFNs have been shown to enhance the recognition of cancer cells by T cells by boosting these crucial signals. An early study indicated that IFN-α increased the surface expression of tumor-associated antigens in breast cancer and colon cancer cells.[169] Moreover, IFNs can promote the expression of MHC class I molecules on cancer cells, which contributes to tumor antigen peptide presentation and recognition by T cells.[66,76,86,170,171] Additionally, IFNs also elevate the expression of adhesion molecules to stabilize the interaction between T cells and target cells. It was demonstrated that IFN-γ not only induces the expression of MHC, but also stimulates the expression of adhesion molecule ICAM-1 in human bladder carcinoma cells.[172]

Activated T cells kill target cancer cells either through the release of perforin and granzyme or by enhancing the expression of tumor necrosis factor (TNF) family proteins, including FasL (CD95L), TRIAL, and mTNF, to induce apoptosis of target cells.[173–175] IFNs promote the expression of these molecules involved in the cytotoxic effects of T cells. Type I IFN was found to promote the expression of the activation marker CD69 and contribute to increase the cytotoxicity of γδ T cells against leukemia cells.[176] Several studies have demonstrated that IFN-γ increases the expression of perforin, granzyme B, CD95, CD95 ligand, and TRAIL in effector T cells, thereby promotes cancer cell death.[177–179] Type III IFNs also increase the cytotoxic effect of T cells. It has been reported that IFN-λ3 stimulation significantly enhanced the co-expression of CD107a and granzyme B, and increased the release of perforin in CTLs of macaques.[180]

In addition to T cells, NK cells and NKT cells are also significant effector cells killing cancer cells, and IFNs enhance the cytotoxicity of these effector cells. A study has

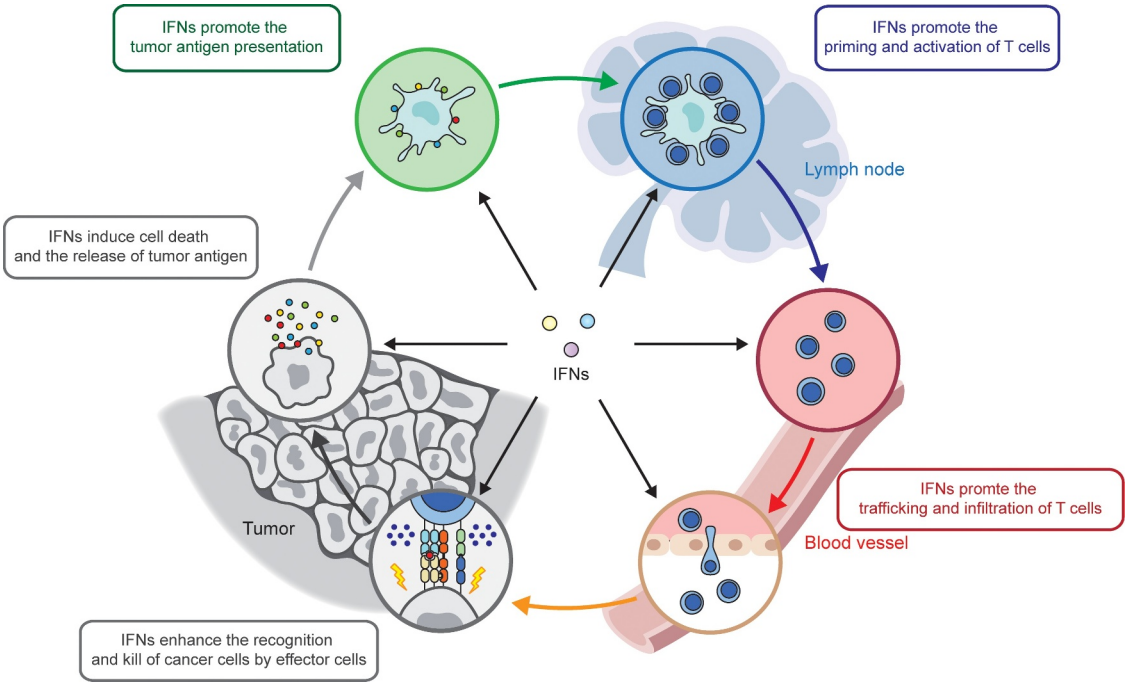

Figure 3. IFNs regulate each step of cancer-immunity cycle.

demonstrated that *IFNR2*$^{-/-}$NK cells showed significantly compromised cytotoxicity against RMA-S MSCV compared with WT NK cells, suggesting type I IFNs play a pivotal role in the killing of cancer cells by NK cells.[181] Moreover, combined with perforin, IFN-γ is also important for the successful rejection of MHC class I-deficient RMA-S-CD80 tumor cells by NK cells.[182] Additionally, IFN-α and TLR ligands are reported to directly modulate the function of NKT cells by promoting the secretion of cytotoxic cytokines, such as TNF-α and IFN-γ.[183] A recent study found that IFN-α treatment (1000 IU/mL, 18h) also induce the elevated expression of CD69 and perforin of NK cells and NKT cells from melanoma patients.[184]

Both NK cells and macrophages also kill cancer cells through the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC), which mainly depends on the binding of the Fc fragment of IgG antibodies and their coordinated receptor FcγR located on effector cells.[185] IFN-α has been reported to induce ADCC against B16 melanoma cells *in vivo*.[186] IFN-β also contributes to enhancing the sensitivity of lung cancer cells to ADCC.[187] IFN-γ is a predominant activator of macrophages,[188] and thus promotes killing of cancer cells via ADCC.[187] Mechanistically, type I IFNs and IFN-γ could promote antibody isotype switching into IgG.[189,190] The regulation of class switch recombination is largely dependent on germline (GL) transcription, which means that distinct cytokines determine the isotypes of antibodies synthesized by B cells by inducing different transcription factors targeting various cytokine-responsive elements accompanied by GL promoters.[191] STAT1 and T-bet, induced by IFN signaling,[192,193] are both important transcriptional activators for IgG germline transcription.[194–196] Additionally, IFN-γ has also been found to enhance the transcription of the Fc receptor for IgG,[197,198] which may also contribute to ADCC.

IFNs negatively regulate anti-cancer immunity

Activation of the immune response usually triggers negative feedback mechanisms and suppresses immune responses to maintain immune homeostasis. As expected, although most studies suggest that IFNs competently facilitate anti-tumor immune response, increasing evidence indicates that IFNs also negatively regulate anti-tumor immunity by either stimulating the expression of immunosuppressive molecules or recruiting the infiltration of immune-suppressive cells into the TME (Figure 4).

Numerous studies have indicated that IFN-γ induces the expression of PD-1 and PD-L1 in cancer cells. For example, IFN-γ promoted the expression of PD-L1 in pancreatic cancer.[199] IFN-γ secreted by tumor-infiltrating lymphocytes has been found to stimulate the expression of PD-L1 in human melanocytic lesions.[200] Mechanistically, IFN-γ secreted by tumor-associated macrophages was reported to induce PD-L1 elevation through the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway and the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway.[201] IFN-γ is also reported to stimulate the expression of PD-L1 in melanoma in a P53 related JAK2 dependent manner.[202] Apart from PD-1 and PD-L1, the expression of CTLA-4 was also found to be upregulated by IFN-γ signaling in melanoma cells and melanocytes.[203] Moreover, tryptophan-metabolizing enzyme indoleamine-2,3-dioxygenase (IDO), a potent negative regulator of anti-cancer immunity, was also reported to be induced by IFN-γ secreted by $CD8^+$ T cells in the TME, which suppresses anti-cancer immunity in a melanoma model.[204]

Additionally, IFNs also induce the production of immunosuppressive cytokines. For example, IFN-β has been found to

induce the expression of IL-10 and IL-6 in DCs, which results in Th2-biased immune suppression.[205] Moreover, type I and type III IFNs enhance the expression of IL-10R on APCs and sensitize them to IL-10 stimulation, which negatively regulates the activity of IFNs on APCs through inhibiting TLR-induced IL-12 production.[206]

In addition to immune suppressive molecules and cytokines, IFNs also promote the infiltration of immune suppressive cells. Type I IFN has been found to be associated with myeloid-derived suppressor cell (MDSC) mobilization via the CCR2 pathway and leads to the radiation resistance in a mouse cancer model.[93] Besides, type I IFN contributes to induction of the infiltration of regulatory T cell (Treg) through upregulation of IL-10.[207] Whereas IFN-λ has also been reported to trigger the proliferation of FOXP3-expressing suppressor T cells by inducing tolerogenic DCs.[208] Additionally, the loss of E74-like transcription factor (Elf5) in a triple-negative breast cancer tumor model reduces the expression of an ubiquitin ligase named FBXW7, leads to the stabilization of IFN-γ receptor 1 (IFNGR1).[209] Then, the enhanced IFN-γ signaling promotes the infiltration of immunosuppressive neutrophils and the upregulation of PD-L1 expression.[209]

Finally, IFNs have an anti-angiogenic ability to constrain tumor growth. It is noteworthy that the diminishment of tumor vessels may also make it difficult for the trafficking and infiltration of T cells, and thus compromise anti-tumor immunity. However, this point needs to be validated by further experiments.

nonimmune effects of IFNs

IFNs, as cytokines, share several common characteristics of most cytokines. The receptors of one cytokine may be distributed on a variety of cell types. In addition, even a slight dose of cytokines may induce various biological effects due to the affinity between the cytokine and its corresponding receptor. This means that IFN administration in cancer treatment may contribute to unexpected severe side effects when the dosage is slightly higher than it should be. In fact, many nonimmune effects of IFN administration in patients have been reported, such as skin rash, flu-like symptoms, nephropathy, gastrointestinal discomfort, endocrine disorders, autoimmune diseases, and mental disorders.[210–215] Additionally, it has been revealed that IFNs participate in the regulation of cell cycle, cell differentiation, angiogenesis, and cancer development and progression.

IFNs can regulate the cell cycle by targeting cell cycle regulatory proteins or pathways related to the cell cycle. It has been reported that IFN-α restricts the cell cycle from G0 to S phase in prostate cancer cell lines by upregulating the expression of the cyclin-dependent kinase inhibitor p21.[216,217] Sangfelt et al. also found that IFN-α treatment caused the induction of a group of cyclin-dependent kinase inhibitors (CKIs), including p21, p15, and p27.[217] IFN-α also stalls the cell cycle by inhibiting cyclin D3 and cdc25A[218] or inhibiting cyclin E- and cyclin D1-dependent CDK2 kinase activity.[219] Additionally, Lu et al. proved that IFN-α constrains the growth of hematopoietic progenitor cells by activating the p38 mitogen-activated protein kinase pathway.[220] In addition to IFN-α, IFN-γ also induce the expression of p21WAF1 and thus contribute to cell cycle arrest in the prostate cancer cell line DU145.[221] Moreover, IFN-λ was also reported to induce G1 phase arrest in esophageal carcinoma cells.[222]

It has been known that IFNs promote the differentiation of some naïve cells, such as hematopoietic progenitor cells.[223,224] Recent studies showed that IFNs also promote the differentiation of various types of malignant cells. A study has elucidated that differentiation of mouse myeloid leukemic cells can be induced by IFN treatment.[225] IFN-β has been shown to induce terminal cellular differentiation or programmed cell death in non-small-cell lung cancer.[226] In addition, IFN-α alone or in combination with retinoic acid contribute to the differentiation of cervical carcinoma cell lines.[227] IFNs (IFN-α, IFN-β, and IFN-γ) also show anti-angiogenic effects,[166,228,229] and inhibition of angiogenesis is one of the important mechanisms involved in the anti-cancer effects of IFN. Mechanistically, IFNs inhibit the expression of pro-angiogenic factors, such as vascular endothelial growth factor and basic fibroblast growth factor.[230,231]

Finally, IFNs are involved in carcinogenesis and cancer progression by inducing inflammation, which is one of the hallmarks of cancer and closely intertwined with cancer development. IFN-γ is a pro-inflammatory cytokine and is associated with a group of inflammation-related diseases of the digestive tract, such as inflammatory bowel disease and ulcerative colitis,[232] which are important risk factors for colorectal cancer (CRC), a typical inflammation-related cancer. Kobelt et al. also demonstrated that IFN-γ, accompanied with TNF-α, promote the growth and metastasis of colon cancer cells (HCT 116) by enhancing the expression of the *MACC1* gene, a crucial oncogene involved in CRC metastasis.[233] In addition to CRC, IFN-γ also promotes metastasis of pancreatic cancer, another type of inflammation-related cancer. It has been reported that IFN-γ administration promotes epithelial-mesenchymal transition (EMT) of pancreatic cancer cells by enhancing the expression of vimentin and reducing the expression of E-cadherin in a dose-dependent manner.[199] However, in other studies, IFN-β and IFN-γ have been reported to suppress metastasis of human astroglioma and fibrosarcoma cell lines by suppressing the expression of matrix metalloproteinase 9 (MMP-9), the enzyme undermining ECM promoting malignant cell spreading.[234] These paradoxical results suggest that the effects of IFN-γ on cancer progression may be diverse in different cancer types.

Conclusions and perspectives

Since IFNs play a critical role in the immune responses, they have attracted great interest in the cancer immunotherapy. In this review, we elaborated on their effects at each step of the cancer-immunity cycle. Conclusively, IFNs potently regulate the cancer immunity and function at each step of the cancer-immunity cycle. However, the anti-cancer immune suppressive roles of IFNs are emerging and worthy of attention. Especially, it has been noticed that IFNs promote cancer progression in some cases by inducing cancer-associated inflammation.

It was believed that immune system both restricts and promotes cancer development and progression.[235] The double-edged roles of IFNs in the cancer immunity may be in

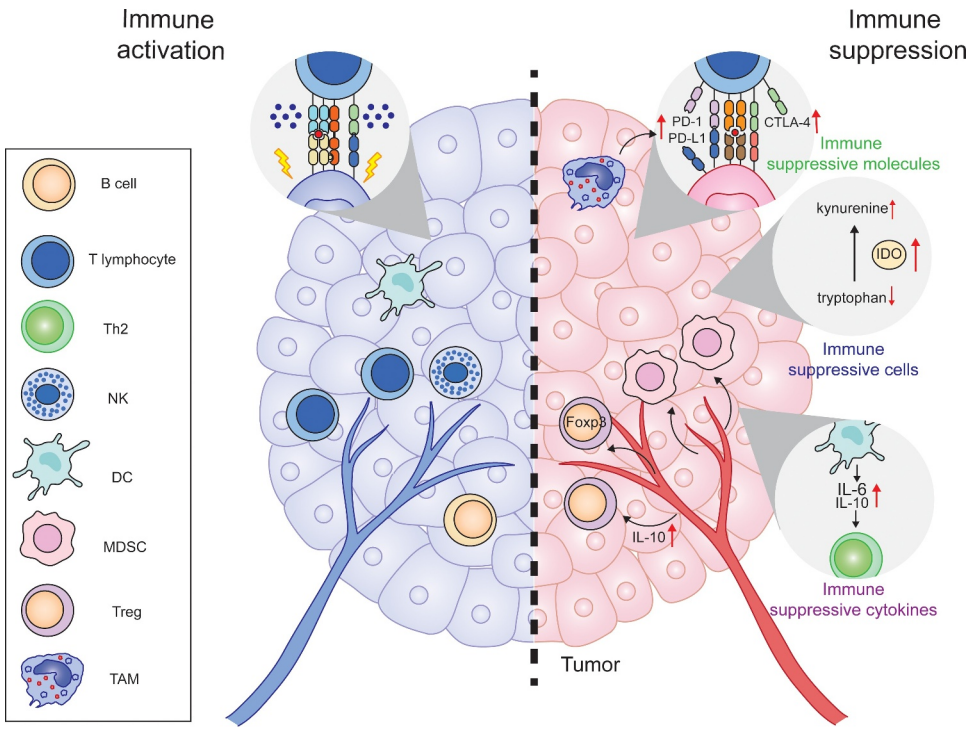

Figure 4. IFNs negatively regulate anti-tumor immunity.

accordance with the theory of cancer immunoediting, which consists of elimination, equilibrium, and escape.[236] IFNs play important roles in each phase of cancer immunoediting.[25] Since IFNs positively regulate each step of the cancer-immunity cycle, there is no doubt that IFNs contribute to the process of cancer elimination. IFNs may also be involved in immune equilibrium. It has been reported that IFN-γ can stimulate the expression of IL-7 in the gut epithelium,[237] which is an important cytokine that maintains memory $CD8^+$ T cells. In addition, tissue-resident memory $CD8^+$ T cells promote melanoma-immune equilibrium in the skin.[238] Thus, it can be postulated that IFN-γ may be associated with immune equilibrium in the anti-cancer immune response. In the last phase, IFNs facilitate the immune escape of cancer cells by upregulating immune suppressive molecules and promoting the infiltration of immune suppressive cells. For example, continuous exposure of leukemia cells to IFN-α caused a decrease in IFN-α-induced apoptosis due to the loss of STAT2.[239] Clarifying the phase-specific roles of IFNs in cancer immunity may be helpful to optimize stage-specific immunotherapy based on IFNs.

Conclusively, the double-edged effects of IFNs on the regulation of anti-cancer immune response embody the important philosophical tenet of traditional Chinese medicine: the theory of yin (negative regulation) and yang (positive regulation).[240] There are several factors influencing the yin and the yang of IFNs in cancer immunosurveillance and cancer immune escape. One is the duration of the IFN signaling in the TME. Generally, rapid activation of IFN signaling induces the acute inflammation and is beneficial to mobilize the immune system and eradiate cancer cells. However, the sustained or prolonged stimulation by IFN signaling causes the chronic inflammation, which is associated with immune aging and leads to inflammation-associated cancers.[228] Another is the effects of IFNs on different types of immune cells in the TME. As a family of pleiotropic cytokines, IFNs modulate the behaviors of both immune-activating cells (e.g. CTL, γ/δ T cell, DC, B cell) and immunosuppressive cells (e.g. MDSC, Treg, M2) (Figure 4).[19] In addition, the nature of ISGs also should with be taken into account for evaluating the yin and yang effect of IFNs on cancer immunity. ISGs are diverse, and some ISGs encode molecules involved in the regulation of cell death, danger signal sensing, and positively promoting immune response. Whereas some ISGs encode immune checkpoint blockade molecules and thus have the opposite effects and cause immune suppression.

Taken together, the activation of IFNs signaling has double-edged effects on anti-cancer immunity. Considering that IFNs induce the expression of immune suppressive molecules, such as PD1, PD-L1, CTLA4 and IDO, combining them with immune checkpoint blockage therapy is a promising strategy to enhance the therapeutic effect of IFNs in the clinic, and such translational studies combining use of IFNs with anti-PD-L1 or anti-PD-1 antibodies are emerging.[13–17]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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