The Interactions Between Cancer Stem Cells and the Innate Interferon Signaling Pathway

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Interferons (IFNs) form a family of cytokines with pleiotropic effects that modulate the immune response against multiple challenges like viral infections, autoimmune diseases, and cancer. While numerous anti-tumor activities have been described for IFNs, IFNs have also been associated with tumor growth and progression. The effect of IFNs on apoptosis, angiogenesis, tumor cell immunogenicity, and modulation of immune cells have been largely studied; however, less is known about their specific effects on cancer stem cells (CSCs). CSCs constitute a subpopulation of tumor cells endowed with stem-like properties including self-renewal, chemoresistance, tumorigenic capacity, and quiescence. This rare and unique subpopulation of cells is believed to be responsible for tumor maintenance, metastatic spread, and relapse. Thus, this review aims to summarize and discuss the current knowledge of the anti- and pro-CSCs effects of IFNs and also to highlight the need for further research on the interplay between IFNs and CSCs. Importantly, understanding this interplay will surely help to exploit the anti-tumor effects of IFNs, specifically those that target CSCs.

Keywords: interferons, cancer stem cells, immune response, plasticity, immunoediting, quiescence

INTRODUCTION

Interferons

Interferons (IFNs) constitute a family of cytokines first described in the late 1950s for their ability to trigger a very potent anti-viral response in cells (1). All IFNs are class II α-helical cytokines that are classified into three main types: IFN-I (mainly IFN-α and -β) (2), IFN-II (IFN-γ) (3), and IFN-III (IFN-λ) (4) and their canonical signaling consists of activation of the JAK/STAT pathway (5).

IFNs are fundamental players in the modulation of both innate and adaptive immune responses. Although they were first identified as molecules with a strong capability of inducing viral resistance in cells, many other activities have been discovered for this family of cytokines over the years, including their involvement in pathologies such as autoimmune diseases [e.g., systemic lupus erythematosus (6–9) and rheumatoid arthritis (8, 10, 11)] and cancer (discussed below). IFNs, regardless of the specific receptor they activate, are able to exert pleiotropic effects, suggesting a rich signaling network coupled to IFN stimulation and undoubtedly adds complexity to understanding its effects on cell function and its contributions to immune response regulation.
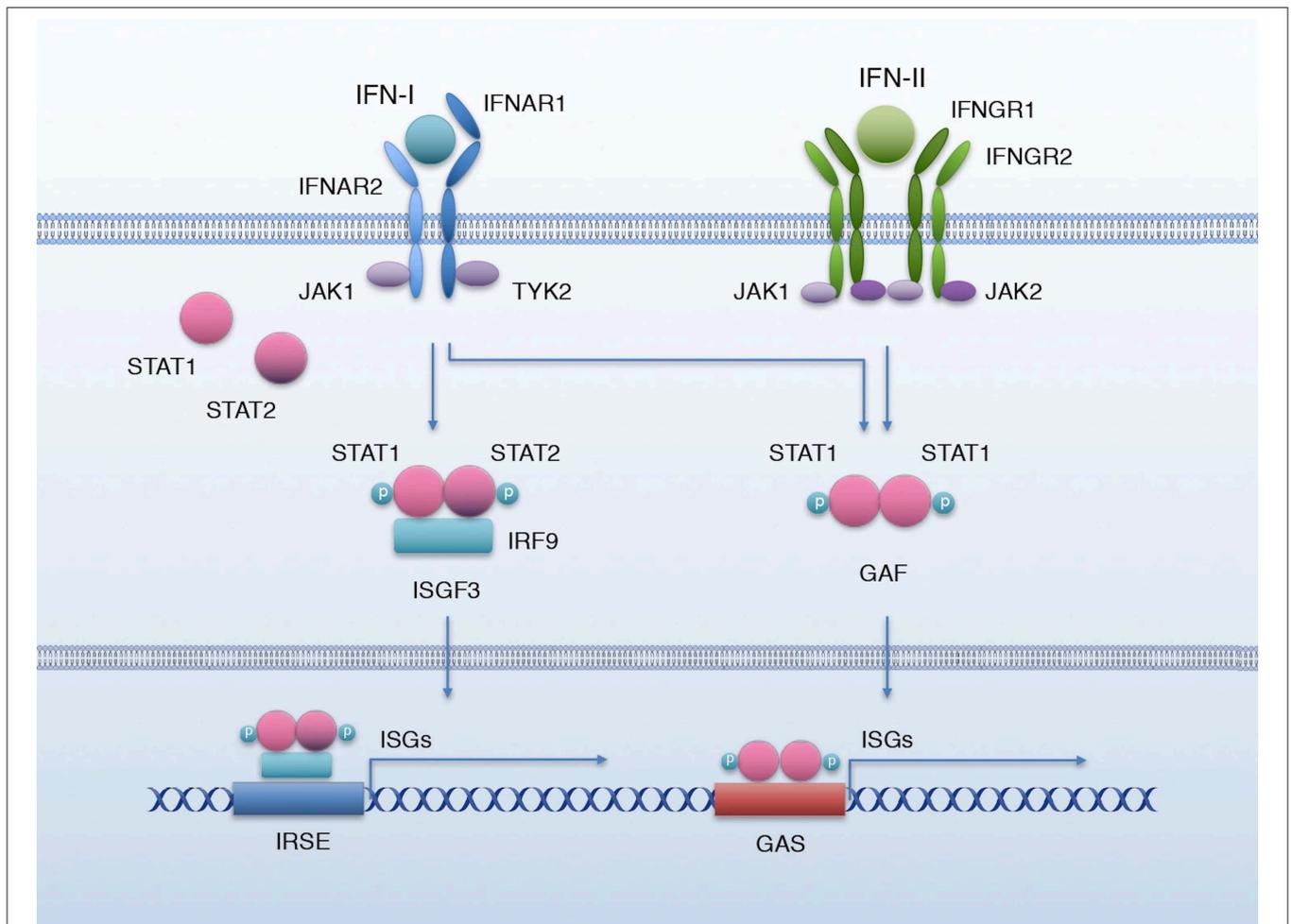
FIGURE 1 | IFN-I and IFN-II signaling. Canonical IFN-I and IFN-II signaling pathway. Binding of IFN-I to IFNAR activates JAK1 and TYK2 to phosphorylate STAT1 and STAT2, which associate with IRF9 to form the transcriptional complex ISGF3; ISGF3 translocates to the nucleus to bind the IRSE elements and activate the transcription of a battery of ISGs. IFN-II biding to its receptor IFNGR activates kinases JAK1 and JAK2, which phosphorylate STAT1; p-STAT1 forms a homodimer named GAF that translocates to the nucleus and activates the transcription of ISGs by binding GAS elements. IFN-I can also lead to the formation of GAF.

Type I Interferon (IFN-I)

IFN-I comprises multiple and diverse members; in mammals, 9 subtypes have been described: IFN-α (of which there are 13 known subtypes), IFN-β, -ε, -κ, -ω, -δ, -τ, -v, and -ζ; all of them except -δ and -τ exist in humans (12). The level of homology between these members can range from 20% to nearly 100% (2). However, they all signal through the same receptor, the IFN-α receptor (IFNAR). IFN-I binds a heterodimeric receptor formed by IFNAR1 and IFNAR2 chains, causing their constitutively associated Janus kinases TYK2 and JAK1, respectively, to activate and phosphorylate signal transducer and activator of transcription 1 (STAT1) and 2 (STAT2). pY-STAT1 and pY-STAT2 then form a heterodimer that associates IRF9 to form a transcriptional activator complex named IFN-stimulated gene factor 3 (ISGF3). ISGF3 translocates to the nucleus, where it binds interferon-stimulated response elements (IRSE) to activate the transcription of a battery of interferon-stimulated genes (ISGs) (**Figure 1**). However, IFN-I also activates other non-canonical

signaling pathways such as the MAPK (13, 14), PI3-Kinase (15–17), and NF-κB pathways (18, 19), as well as unphosphorylated STAT1 (U-STAT1) (5), that prolongs the expression of a subset of interferon-induced immune regulatory genes (20).

Regarding their immunomodulatory nature, IFN-I fulfills roles in both innate and adaptive immune responses, that include inducing cell-autonomous antiviral activity (21), stimulating immune cells, including natural killer (NK) (22–24) and T cells (25–29), and increasing antigen presentation by macrophages and dendritic cells (30), in order to help orchestrate an efficient immune response (5).

Type II Interferon (IFN-II)

IFN-II has only one member, IFN-γ, which is remarkably different from IFN-I in structure and has a different receptor, but was originally grouped in the IFN family due to its ability to trigger an antiviral response (31). Like other IFNs, IFN-γ also activates the JAK/STAT signaling pathway, through

IFNGR. This receiver is formed by two chains: IFNGR1 and IFNGR2. Binding of IFN-γ to its receptor activates the associated Janus kinases JAK1 and JAK2, respectively to IFNGR-1 and−2, to phosphorylate STAT1. pY-STAT1 forms homodimers, also known as interferon gamma-activated factor (GAF), that translocate to the nucleus to activate the transcription of a set of ISGs by binding the interferon-activated sites (GAS) (5) (**Figure 1**). Nonetheless, like IFN-I, IFN-γ can also activate other non-canonical signaling pathways such as MAPK (32, 33), PI3-Kinase (32, 33), and NF-κB (34, 35) and U-STAT1 (5, 20).

Functionally, IFN-γ also importantly contributes to the development of innate and adaptive immune responses, targeting mainly macrophages (36–39) and T cells (40–42). IFN-γ signaling induces the expression of many transcription factors, that can amplify the IFN response (5). Importantly, IFN-γ has a substantial role in modulating macrophage activation, as it upregulates the expression of gene products with microbicidal activity (43–46) and interacts with other cytokines and signaling molecules to enhance or antagonize their effect (47–50). Also, IFN-γ is capable of modulating helper T cell (Th) responses (51–53) and promoting class switching in B cells (54, 55). In addition, IFN-γ modulates the activity and recruitment of NK cells (56, 57). Interestingly, IFN-γ has been reported to either promote or repress NK cell-mediated lysis of tumor cells derived from diverse pediatric tumor cell lines (58). Treatment of the tumor cell lines with IFN-γ induced differential upregulation of MHC-class I and ICAM-I, which seemed to determine tumor cells' resistance or sensitivity, respectively, to NK cell-mediated lysis.

Type III Interferon (IFN-III)
Finally, interferon type III or IFN-λ is the latest class to be described, and it also shares the same antiviral functions as that of type I IFNs (2). The focus of this review will be on the effect that type I and type II IFNs have on cancer stem cells (CSCs) in different cancer entities.

Interferons in Cancer
Decades of research have demonstrated that IFNs are able to display a wide range of anti-tumor activities, including induction of apoptosis, inhibition of angiogenesis and proliferation, cell terminal differentiation and immune regulation. At the level of tumor cell survival, IFNs can induce tumor cell apoptosis through various mechanisms, such as the TRAIL pathway (59, 60), via CD95/Fas (61, 62) and the activation of pro-apoptotic members of the Bcl-2 family [reviewed by Kotredes and Gamero (63)]. Likewise, IFNs can impede tumor expansion by inducing cell cycle arrest. IFNs can up- or down-regulate CDK inhibitors and c-Myc expression, respectively, to inflict an anti-proliferative effect on tumor cells, amongst other mechanisms (64–67). However, IFNs have other indirect forms of fighting tumors, such as inducing oxygen and nutrients supply deprivation of tumor cells by suppressing angiogenesis, thus creating a hypoxic and acidic microenvironment. IFNs are also able to elicit inhibition of angiogenesis by downregulating the expression of potent angiogenic factors in endothelial and stromal cells, including IL-8, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and

in tumor cells, such as fibroblast growth factors (FGFs) (68–72). Furthermore, angiogenesis inhibition can result from IFN-mediated impairment of proliferation and migration of endothelial cells (70, 71, 73, 74).

Importantly, as already mentioned, IFNs are key regulators of the immune response against tumors. IFN-α, -β, and -γ are able to directly upregulate the expression of surface tumor-associated antigens (75, 76) via augmentation of MHC I class and MHC II class molecules (77), thus increasing the immunogenicity of tumor cells and making them more vulnerable to identification and subsequent destruction by the immune system. Indirect/unspecific immunoregulatory effects of IFNs encompass activation of dendritic cells to cross-present tumor antigens to T cells (78), promotion of full CD8+ maturation necessary for them to elicit their cytotoxic effects (29, 79, 80), prevention of the proliferation of T regulatory cells, as well as enhancement of T helper cell function (81, 82) and promotion of macrophage polarization toward an M1-like pro-inflammatory state instead of the M2 pro-tumoral state (83), thus eluding their immunosuppressive effect (83, 84), amongst other mechanisms (85).

Alternatively, pro-tumoral properties have also been described for IFNs. While classically considered as pro-apoptotic agents, it has been shown that IFN-α/β activate the NF-κB pathway, inducing cell survival and protecting tumor cells against apoptotic stimuli in a variety of cancer types (86, 87). Also, IFNs can upregulate survival factors that protect cells against apoptotic stimuli, including MCL1, increased in myeloma presumably via STAT3 (88), and G1P3, which has been reported to promote tumor cell survival and contribute to poor outcome of patients in estrogen-receptor positive breast cancer (89). IFNs can also act as proliferative stimuli (90). For example, IFITM1 is an IFN-induced protein whose expression was shown to enhance lung cancer cell proliferation *in vitro* and tumor growth *in vivo* (91). In addition, IFITM1 expression was reported to promote invasion in head and neck cancer (92). Interestingly, IFN-α has been reported to induce endothelial cell proliferation, thus fomenting angiogenesis (93). One of the most recognized pro-tumoral activities of IFNs is the induction or overexpression of a subset of ISGs in distinct cancers, identified as an IFN-related DNA damage-resistant signature (IRDS), that confers tumor cell resistance to therapy (94, 95). Also, high expression of IRDS genes has been shown to promote tumor growth and metastasis (92, 96). Another major role of IFNs in cancer is immunomodulation and, in this regard, IFNs have been shown to promote immunoevasion via upregulation of the expression of MHC I class molecules, thus decreasing sensitivity to NK cells (97), downregulation of tumor-associated antigen presentation (98, 99), upregulation of the cytotoxic T cell inhibitor PDL-1 in tumor cells (100, 101), and promotion of a tumorigenic TME milieu (102).

Interferons as Anticancer Therapy
Intensive research focused on IFNs' anti-tumor activities finally led to the approval of IFN-α by the FDA as the first cancer immunotherapy in 1986 (103). In spite of being

discovered for their anti-viral activities, IFN-α2a and IFN-α2b have been used as anticancer therapeutic agents across multiple cancer types, including hairy cell leukemia, chronic myelogenous leukemia (CML) (104), AIDS-related Kaposi's sarcoma, follicular lymphoma, multiple myeloma, melanoma, condyloma acuminate, hepatocellular carcinoma (HCC), and cervical intraepithelial neoplasms (105, 106). IFN-β use as an anticancer drug is still under study, although ongoing phase III trials for melanoma (107, 108) and for glioma (109) and glioblastoma (110) are being conducted with promising results. However, IFN-β treatment studies in metastatic breast cancer have not been as successful (111). IFN-γ has also been explored as a therapy for cancer, showing some contrasting results. While IFN-γ treatment has proved to increase survival in ovarian cancer (112) and prevent recurrence in bladder cancer (113), it did not achieve the same results in other malignancies such as melanoma (114), leukemia (115), colorectal (116), and pancreatic cancers (117). Unfavorably, other preclinical studies have shown how IFN-γ upregulation leads to increased metastasis in melanoma (97) and breast cancer (118). It is worth noting that IFN treatment presents adverse side-effects ranging from a flu-like syndrome consisting of fever, chills, headache, myalgia, arthralgia, anorexia and fatigue (119), to neuropsychiatric symptoms, being depression a frequent disorder with a prevalence of 30–70% (120). These adverse effects are dose-limiting and may lead to treatment cessation in severe or longstanding treatment cases.

CSC Model

Cancer stem cells (CSCs) constitute a subpopulation of tumor cells endowed with stem-like properties such as tumorigenesis, metastatic dissemination potential, chemoresistance, and relapse (121). Nowadays, the most accepted CSC model proposes that, on the one hand, CSCs remain in a de-differentiated state, maintain their pluripotency and have unlimited self-renewal capacity. However, on the other hand, they can also differentiate into all possible cancer cell states that form a continuum, thus building the tumor hierarchy and giving rise to intratumoral heterogeneity (122). These unique abilities define CSCs as the sole drivers of tumorigenesis and tumor maintenance, and subsequently the cell entity that drives metastatic spread.

CSCs are pluripotent due to the reactivation of embryonal signaling pathways, such as Sonic Hedgehog (SHH), WNT, NOTCH, and Bone Morphogenetic Protein (BMP) (123). Other classical pluripotent genes expressed by these cells include *KLF4* (124), *NANOG* (125), *OCT3/4* (125, 126), *SOX2* (125–127), and the NODAL/ACTIVIN axis (128). CSCs are also characterized by the expression of stem-like markers, some of which are associated with a cancer type and some of which are more broadly expressed. Some of the most commonly used stem-like markers to identify CSCs are CD24, CD44, CD133, ALDH1, and CXCR4 (129–131). However, not every CSC express the same stem-like markers, the latter being due to the heterogeneity that exists within the CSC population. Genetically and/or epigenetically diverse CSC subpopulations possess different characteristics, that allow them to or preclude them from adapting to challenging situations such as nutrient deprivation, hypoxia, chemotherapy, or immune pressure. This unequal fitness of each CSC subpopulation drives either their clonal expansion or retreat (121), thus driving tumor evolution.

CSCs maintenance is supported by specific niches within the tumor. Importantly, interaction with the TME is crucial for CSC niche formation. A dynamic communication and influence occur between CSCs and the TME, thus assembling a balanced loop of reciprocal modeling. Of note, CSCs represent only a small percentage of the total number of tumor cells, but they are dispersedly located within different CSC niches and present distinct phenotypes. While some niches are spatially distinct (e.g., hypoxic and perivascular regions), others are defined by cellular interactions (e.g., immune niche). These tumor ecology dynamics have been elegantly described and reviewed by Prager et al. (132).

Implicit in this model is the idea/concept of CSC plasticity. Classically, the cellular populations with the ability to differentiate or transition into different lineages (e.g., hematopoietic stem cells) possess phenotypic plasticity. However, we now know this is not a unidirectional process, and that progenitor, transient and differentiated cells are able to regain stem-like properties that drives them to a pluripotent state (121). The latter is greatly influenced by stem cell niche factors. In this same way, CSC niches provide the needed signals for more differentiated cells to activate their plasticity and go back to a stem-like state if necessary. From a clinical perspective, not only CSC targeting but also CSC niche elimination would be necessary for complete cancer eradication.

EMT is a crucial process for activating plasticity and stemness. Between the pure epithelial (E) and pure mesenchymal (M) states, there is a spectrum of intermediate conditions, being the hybrid E/M state, with both epithelial and mesenchymal features, the state that represents the population of cells with the highest plasticity and stemness, increased therapy resistance, tumor-initiating capacity and metastatic potential (133). Importantly, these E/M hybrids with stem-like properties are able to form clusters, with increased apoptosis-resistance, that enter into the bloodstream where they collectively migrate to distant sites and colonize them more successfully than pure mesenchymal-state motile tumor cells (134, 135). As part of CSC plasticity, these cells are also able to enter a state of reversible quiescence, that is actively maintained. Quiescence protects CSCs from cell-cycle targeted therapies and grants them long-term survival through activation of environmental stress adaptive responses, including metabolic reprogramming and mechanisms that favor genomic integrity protection. In addition, these cells present high tumorigenic potential (136). Quiescent CSCs can exist within the tumor, as a subpopulation that does not contribute to tumor growth but that is greatly resistant to adverse conditions and can reactivate and re-enter the cell cycle when in the presence of certain ques or when more favorable conditions are achieved (137). They can also appear as disseminated dormant tumor cells, that are maintained in a non-proliferating state for long periods of time and can reactivate driving relapse and metastasis (136).

Chemoresistance is another hallmark of CSCs (138, 139). CSCs are invulnerable to conventional anticancer therapies, as they have an intrinsic chemo- and radio-resistant profile that enables their survival and clonal expansion over those cells

unable to resist therapeutic pressures. Expression of drug efflux pumps, such as ABCG2 and MDR1, not only allows CSCs to evade the lethal impact of chemotherapy (140), but these pumps also seem to promote stem-like capacities via facilitating the clearance of endogenous anti-tumorigenic molecules from the cell while redirecting pro-tumorigenic molecules to the cell's surface receptors (141). Other common mechanisms of chemoresistance are ALDH activity, expression of pro-survival BCL-2 protein family members and activation of several signaling pathways involved in chemo- and radio-resistance, including MYC and AKT1 (142).

Without a doubt, CSCs represent a population of highly complex tumor cells with unique properties that are responsible for tumor progression, chemoresistance, dormancy, and metastasis. At the same time, these cells are divided into unique subpopulations whose nature is driven/influenced by CSC niches, thus promoting different phenotypes (i.e., plasticity). With this in mind, the only way to successfully eradicate cancer would be to eliminate CSCs and simultaneously target the cues that promote CSC maintenance/plasticity or the source of those cues (i.e., CSCs niches).

It is well-known that IFNs can exert many different anti-tumor effects that negatively affect tumor viability, but less is known about their specific impact on CSCs. In fact, the few studies that have tested the relationship between IFNs and CSCs have yielded opposite and contradictory conclusions, showing both pro and anti-tumor activity. Thus, this review will try to set the story straight by discussing this complex relationship and provided data to support both sides.

STEMNESS AND TUMORIGENIC POTENTIAL

Interferon Type I

A recent study by Castiello et al. (143) showed how IFNAR1 silencing had a significant impact on the CSC subset in an HER2/neu transgenic mouse model (neuT) of breast cancer. Loss of functional IFNAR1 not only resulted in earlier onset and increased tumor multiplicity, but also in the presentation of a gene expression profile associated with aggressive human breast cancer. In line with these results, IFNAR$^{-/-}$ tumors showed an enrichment in the ALDH1$^+$ CSC compartment, which demonstrated a greater self-renewal capacity *in vitro* and tumorigenic potential *in vivo*. These results clearly propose IFN-I as a negative regulator of stemness in breast cancer tumor cells. Accordingly, Doherty et al. (144) obtained similar conclusions when studying the role of IFN-β on triple-negative breast cancer (TNBC) CSCs, using an *in vitro* model of primary human mammary epithelial cells (HMEC) virally transduced with transforming factors. Within transformed cells, a subpopulation of mesenchymal-like cells with CSCs properties emerged (Mes/CSC), while the remaining cells maintained an epithelial phenotype and did not present such properties (Ep/non-CSC). Regarding IFN signaling, Mes/CSCs presented a basal repression of numerous ISGs, while Ep/non-CSCs had an IFN gene expression signature. Inhibition of ISG expression

was attributed to upregulation of unphosphorylated ISG3F (U-ISG3F) in Mes/CSCs, which is part of the alternative IFN-I signaling pathway, although the origin of its activation remains unclear. In order to test whether IFN-β was able to reactivate the canonical IFN pathway, Mes/CSCs and Ep/non-CSCs were treated with IFN-β and CSCs properties were tested *in vitro*, showing a reversion of the CSC status of Mes/CSC cells. Moreover, IFN-β reactivated the expression of ISGs in Mes/CSCs by upregulating P-ISG3F. Therefore, activation of the canonical IFN-I pathway by IFN-β inhibited the stem-like capacities of Mes/CSCs in this model.

In support of this, Yuki et al. (145) had previously reported IFN-β to reduce proliferation, self-renewal capacity, and tumorigenesis in human glioma-initiating cells (GICs) by inducing their terminal differentiation into oligodendrocytes via STAT3 activation. Treatment of patient tumor-derived cells with IFN-β induced the phosphorylation and subsequent activation of STAT3, leading to a cell-cycle arrest in G0/G1, decreased clonogenic capacity, reduction of the expression of stem markers and, importantly, terminal differentiation of the GICs into oligodendrocytes. Significantly, STAT3 had been previously linked to gliogenesis by Bonni et al. (146) and Rajan and McKay (147), who described how Ciliary Neurotrophic Factor (CNTF)-mediated activation of STAT3 promoted the differentiation of cortical precursor cells and multipotent stem cells of the central nervous system, respectively, into astrocytes. More recently, STAT3 activation has been linked to regulation of human neural stem cell differentiation (148) and to promotion of the differentiation of NG2 cells (oligodendrocytes progenitors) into oligodendrocytes after a contusive spinal cord injury (149). Likewise, STAT3 has been shown to mediate IL-6-induced neuroendocrine differentiation in prostate cancer cells (150). This pro-differentiating role for STAT3 contradicts previous work describing its role in promoting CSCs traits among different cancer types (151–155), thus highlighting the importance of the tumor context. Illustrating this complex regulation, another study underscored the role of IFN-I as a repressor of glioblastoma stem-like cells (GSCs), as it appeared to inhibit the proliferation and self-renewal capacity of GSCs. However, the authors claim that IFN-I also inhibits the ability of GSCs to differentiate into astrocytes, since it only induces a transient activation of STAT3, while induction of astrocytic differentiation results from sustained activation of STAT3 (156).

Another interesting study tested the effects of IFN-β produced intracellularly on lung cancer murine cells (LL), avoiding external treatment of cells with the recombinant cytokine (157). For that purpose, LL cells were transduced with the mouse *ifn-b* (rBV/IFN-β) gene using a baculovirus vector (BV) and subjected to several tumor-specific assays. rBV/IFN-β cells showed a lower proliferation rate and, importantly, decreased anchorage-independent growth (i.e., CSC self-renewal), compared to control cells. Consistent with these results, a reduction in the tumorigenic and metastatic capacity of rBV/IFN-β cells was observed, strengthening the link between IFN-β and inhibition of stem-like capacities.

IFN-α has also been reported to specifically target the side population (SP) of ovarian cancer cells, a subset of cells endowed

with stem-like properties (i.e., CSCs) (158). In an attempt to exploit the anti-tumor effects of IFN-α, ovarian PDXs were subjected to gene therapy with IFN-α, and results showed a marked increase in survival rate in those PDXs bearing a high proportion of SP cells compared to those containing a low proportion, indicating that IFN-α specifically and negatively affects the CSC compartment. Accordingly, treatment of isolated SP cells with IFN-α resulted in decreased proliferation and self-renewal capacity of these cells and in a dramatic change in their transcriptional profile, compared to non-SP cells. Moreover, these findings were tested in CRC and Daoy medulloblastoma cells with similar results, indicating that this negative regulation of the CSC compartment could be extended to other cancer types.

In contrast to the CSC inhibitory role of IFN-I described above, other studies have come to different conclusions. For example, Ma et al. (159) revealed that IFN-α fostered stem-like properties in oral squamous cell carcinoma (OSCC) cells. Treatment of implanted tumor xenografts with IFN-α resulted in increased expression of stemness markers and tumor growth. Similar results at the level of stemness markers and increased self-renewal capacity were also observed *in vitro* with OSCC cells treated with IFN-α.

More recently, a robust link between death receptor CD95/Fas, IFN-I-dependent activation of STAT1 and stemness in different cancer types has been described by Qadir et al. (160). CD95 is an apoptosis-inducing death receptor, although it can also participate in a variety of tumor promoting activities. In fact, chronic stimulation of CD95 in tumor cells has been reported to increase the number of CSCs in breast cancer (161). In this work, the authors observed that long-term stimulation of CD95 in tumor cells led to type IFN-I production and secretion, and subsequent activation of the IFN-I pathway. In MCF-7 breast cancer cells, activation of the IFN-I pathway resulted in increased expression of stem-like markers. Moreover, cell sorting of MCF-7 breast cancer cells using the stem marker CD44 revealed that CD44$^+$ cells had higher levels of STAT1 expression than CD44$^-$ cells. In addition, treatment with IFNα/β induced/increased ALDH1 activity and self-renewal capacity. To further confirm the role of IFN-I as a driver of stemness, IFN-β pre-treated cells were used in a limiting dilution assay (LDA), which revealed the ability of IFN-β to enhance tumorigenic potential *in vivo*. These findings are not limited to one cancer type, as the authors were able to show similar results for GBM and squamous cell carcinoma (SSC). Interestingly, knocking-down STAT1 resulted in abrogation of STAT2 and STAT3 phosphorylation, concomitant with a loss of IFN-I-induced stem-like properties, suggesting the involvement of STAT2 and STAT3 activation in mediating the observed CSCs promoting effects of IFN-I in a STAT1-dependent manner. Overall, this thorough study strongly suggests IFN-I as a cancer stemness driver in breast cancer, SCC and GBM, involving activation of STAT1, STAT2, and STAT3.

In line with this, IFN-β has also been linked to tumor stemness promotion in pancreatic ductal adenocarcinoma (PDAC). Sainz et al. (162) described an intimate communication between tumor-associated macrophages (TAMs) and pancreatic CSCs in primary tumor tissues and derived cultures. Interestingly, PDAC cells polarized resident TAMs toward an M2 phenotype, which

in turn actively secreted high levels of ISG15, an interferon-stimulated gene. ISG15 can act as a free molecule—intracellularly or in the tumor milieu—and it can also conjugate to proteins as a ubiquitin-like modifier through a process known as ISGylation (163). In this work, TAM-secreted ISG15 was found to enhance the stem-like properties of PDAC CSCs *in vivo* and *in vitro*, promoting their self-renewal, tumorigenic, chemoresistant and migratory capacities, in addition to higher levels of intracellular ISGylation, which have also been related to CSC promotion in nasopharyngeal carcinoma (164). Strikingly, TAMs secreted ISG15 in response to IFN-β secretion by pancreatic CSCs, thus establishing an intricate communication between CSCs and TAMs that resulted in reinforcement of stem-like properties in pancreatic CSCs. The fact that tumor cells (or CSCs) can secrete IFNs is not a novel concept. In 2011 Tsai et al. (165) described that ZR-75-1 breast cancer cells secreted elevated levels of IFN-β, which in turn contributed to Ras transformation. In addition, sarcoma, melanoma and leukemia tumor cells have been described to secrete IFN-α in response to doxorubicin treatment (166). Moreover, inflammatory breast cancer (IBC) cells have been reported to secrete high levels of IFN-α to the TME milieu, which contributed to increase its pro-tumorigenic character (102, 167). In addition to an IFN-α-secreting phenotype, IBC cells showed an upregulation of the IFN-α signaling pathway. Interestingly, Monsurrò et al. (168) identified two molecular phenotypes of PDAC based on differential expression of ISGs; the "anti-viral state" phenotype was characterized by increased resistance to oncolytic viral infection and was associated with activation of hypoxia pathways and increase of HLA proteins expression.

Interferon Type II

Regarding IFN-II, a study by Ni et al. (169) investigated the impact of IFN-γ on a specific subpopulation of quiescent colon CSCs (i.e., Label-retaining cancer cells or LRCCs), isolated from primary colon tumors based on PKH26/67 high staining. This work revealed that IFN-γ selectively targeted LRCCs due to their overexpression of IFNGR, compared to non-LRCCs. The authors showed that IFN-γ treatment of LRCCs greatly inhibited their self-renewal and tumorigenic capacities and induced apoptosis, while non-LRCCs were less affected. Therefore, in this context and in this model system, IFN-γ was proposed as a selective anti-CSC agent.

Another relevant study by Song et al. (170) explored the connection between endogenous IFN-γ levels and tumor stemness in a cohort of non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC), CRC and HCC patients. Strikingly, the study revealed that low-IFN-γ levels in tumor interstitial fluid (TIF) strongly correlated with poor prognosis, TNM tumor staging, brain metastasis and chemoresistance. In line with this, NSCLC, ESCC, CRC, and HCC patients with low TIF-IFN-γ levels showed higher CD133 and Vimentin expression, as well as increased tumor stemness-related and EMT-related gene expression. *In vitro* treatment of NSCLC cell lines with high and low doses of IFN-γ revealed that low dose treatments increased the self-renewal capacity and expression of stem-like makers. In line with this observation, *in vivo* treatment of NSCLC-derived cell lines with a low IFN-γ

dose resulted in higher frequency of CD133^{+} cells compared with those treated with a high IFN-γ dose, indicating an enrichment in the CSC compartment due to low IFN-γ stimulation. Dissection of the signaling cascade behind these effects revealed that low IFN-γ treatment of NSCLC cell lines induced I-CAM expression, which activated the PI3K-Akt-Notch1 axis leading to increased stemness. On the other hand, high IFN-γ doses induced apoptosis via the JAK1/STAT1/caspases pathway. This work not only illustrates the complex regulation of IFN signaling, but it also describes the opposing effects that can be achieved with the very same molecule using different dosing strategies. In addition, the results of this study are likely applicable to the immunoediting process, in which infiltrated effector T-cells and NK cells initially produce high levels of IFN-γ in the TME, resulting in tumor cell apoptosis. However, this initial immune response wave can eventually lead to T-cell and NK cell exhaustion and dysfunctional activity (171, 172), thus decreasing IFN-γ production and generating an IFN-γ-low TME with tumor stemness promoting capacity. Importantly, such a scenario could also occur during the earlier stages of tumor development in so-called "cold tumors" that are poorly infiltrated with immune cells. Interestingly, however, this study may also help to resolve the contradictory pro- and anti-tumor effects described above for both IFN-I and IFN-II, which may be the result of the doses of IFNs used across the different studies.

Very recently, Matteucci et al. (173) described and reviewed the pivotal role of human endogenous retrovirus (HERVs) activation in the promotion and maintenance of pluripotency and stem-like properties in melanoma CSCs. The authors also highlight the correlation between HERVs activation and aggressiveness features across several types of cancer. In this line, in the same year Cañadas et al. (174) described a very interesting interplay between IFN-γ and a particular subtype of HERVs named Stimulated 3 prime antisense retroviral coding sequences (SPARCS), which are located in the 3′ untranslated region of IFN-γ-inducible genes. Strikingly, IFN-γ induces the activation of SPARCS-containing genes—many of which are involved in innate immune regulation—resulting in the promotion of a more aggressive mesenchymal-like state of SCLC cells and in the production of cytosolic dsRNA through the bi-directional transcription of target genes. In turn, dsRNA can be sensed via the RIG-I/MAVS or the cGAS/STING pathways, which induce the production of IFNs, thus creating a positive feedback loop. Of note, IFN-γ induced the overexpression of PD-L1, which correlated with high baseline expression of the stem-like marker CD44. Moreover, deletion of *MAVS* significantly reduced the tumorigenic capacity of SCLC tumor cells. In summary, this work highlights the role of IFN-γ in activating the transcription of SPARCS and its impact on SCLC cells phenotype and opens the door to considering IFN-γ-induced SPARCS activation as a regulator of stem-like features in SCLC tumor cells.

INVASION, MIGRATION, AND METASTASIS

Interferon Type I

In ovarian cancer, Li et al. observed that IFI27, an IFN-α inducible protein, was upregulated in patient tumor tissue samples, compared to their paired healthy controls, and correlated with poor disease-free survival. The authors subsequently found IFI27 to not only be a driver of stemness (175), but this IFN-induced protein could also promote EMT, resulting in increased migration and invasion. It is well-known that EMT is one of the driving biological processes of stemness in tumor cells (176, 177), and in this work the authors make a very unique connection between EMT induction by an IFN-α stimulated gene and acquisition of stem-like properties such as increased self-renewal and drug resistance. In accordance with this observation, Zhu et al. (178) also described IFN-α as a promoter of stemness in PDAC. In an attempt to unveil possible differences of the effects of IFN-α on CSCs and non-CSCs, two PDAC cell lines with opposing stem markers levels were used: MiaPaca (low levels) and Panc1 (high levels). The authors showed in their study how IFN-α treatment of both PDAC cell lines reduced cell viability and proliferation *in vitro*, while simultaneously increasing the expression of CSCs cell surface markers, suggesting IFN-α induces a CSC enrichment, likely via killing off non-CSCs. In order to confirm these results *in vivo*, an orthotopic PDAC mouse model was used. While administration of IFN-α to mice reduced tumor volume in comparison to the control group, CSCs markers were significantly upregulated, suggesting again an enrichment in CSCs. Along these lines, IFN-α-treated mice presented more colon metastases compared to the non-IFN-treated control group. In summary, these results suggest that IFN-α treatment of PDAC cells leads to elimination of the tumor bulk cells resulting in an enrichment of the CSC compartment, concomitant with a boost in metastatic spread. However, based on the concept of plasticity, it is also feasible that non-CSCs converted into CSCs, contributing to the enrichment of the CSC population.

Interferon Type II

In head and neck squamous cell carcinomas (HNSCC), as in many other cancer types, the CXCL12/CXCR4 axis is involved in metastatic dissemination (179). As metastasis formation is one of the hallmarks of CSCs, CXCR4 is often used as a stem-like marker for the identification of CSCs with enhanced metastatic capacity (180). In this respect, Katayama et al. (181) performed a study to determine the effects of IFN-γ on CXCR4 expression and function in several HNSCC cell lines. Histological analysis of primary tumors and metastases from a cohort of 56 patients revealed high levels of CXCR4 in tumor cells, but not in healthy head and neck tissue, which correlated with poor prognosis. In addition, CXCL12 expression was barely detectable in the primary tumor stromal tissue, but was strongly expressed in metastatic lymph node stroma, illustrating the CXCR4/CXCL12 axis as a highly plausible mechanism for metastatic spread in this cancer. In this study, the authors aimed to regulate CXCR4 levels in HNSCC cell lines using IFN-γ as an inhibitor, since IFN-γ had been previously shown to downregulate expression of CXCR4 in immune cells like neutrophils (182). Interestingly, they discovered that IFN-γ treatment induced a downregulation of CXCR4, and this downregulation translated into an inhibition in the migratory and invasive capacities of HNSCC cells, as well as CXCR4/CXCL12 axis-mediated cell proliferation. Thus, these

authors proposed IFN-γ as a modulator of CXCR4 functional expression and as an inhibitor of HNSCC cell migration induced by this receptor.

Interestingly, during the late 1980's, multiple studies explored the relationship between IFN-γ and metastasis in mice. Firstly, Taniguchi et al. (97) observed that treatment of H-2-deficient non-metastatic B16 melanoma cells with physiological doses of IFN-γ (1–10 U/ml) was sufficient to decrease cell growth *in vitro* and, surprisingly, to increase the lung-colonizing potential of these cells *in vivo*. Treatment with IFN-β was also able to induce the same metastatic phenotype, although a 1,000-fold higher concentration was required to observe similar effects. Investigating the mechanisms behind this IFN-γ-mediated or -enhanced metastasis, it appeared that IFN-γ induced a higher expression of surface H-2, that enabled tumor cells to resist NK-mediated killing. Other studies published in the very same year supported the main concept of Taniguchi et al.'s. work but in melanoma and colon cancer (183–186). More recent studies have also reported the capacity of IFN-γ to promote invasion and metastasis (187), and to act as a double-edge sword in cancer (188, 189). These results suggest that local endogenous IFN-γ released in the TME may play a pivotal role in modulating tumor cells' sensitivity to innate and adaptive immune cells and therefore in their capacity to colonize other organs and metastasize. Again, as shown by Song et al. above, the concentration of IFN-γ at a specific given time during the evolution of the tumor may be critical for IFN-γ to act as a pro- or anti-metastatic/invasive factor.

DORMANCY

Interferon Type I

It is generally recognized that tumor cell dormancy represents a major obstacle when it comes to effectively treating cancer, as dormant cells are more chemoresistant and upon treatment cessation, these cells can drive tumor relapse. In a recent study, Liu et al. (190) dissected the impact of IFN-β in melanoma CSCs, establishing a previously unknown association with dormancy. In this work, murine and human implanted tumors in mice were treated *in vivo* with IFN-β. Subsequent analysis of isolated single tumor cells revealed that IFN-β treated tumors had a higher proportion of G_0/G_1 cells, which were not senescent. In fact, sorting cells using the CSC cell surface marker CD133 revealed that while IFN-β treatment did not reduced the CD133^{+} CSC compartment, IFN-β did induce cell cycle arrest in CD133^{+} and not in CD133^{−} cells, suggesting a specific effect of IFN-β on CSCs. Interestingly, both murine and human CD133^{+} "tumor repopulating cell" (TRC)-derived tumors showed halted growth when treated with IFN-β and a quick re-growth after IFN-β withdrawal, indicating that IFN-β induces a reversible dormancy in melanoma cells. Further studies *in vitro* supported these findings. Specifically, IFN-β treatment of CD133^{+} murine and human melanoma cells in soft 3D fibrin gels induced G_0/G_1 cell cycle arrest, expression of dormancy markers, decreased glucose consumption and higher resistance to chemotherapy, many of these features being hallmarks of CSCs. Consistently, IFN-β was not able to induce dormancy in 2D-cultured cells, which are

conditions that favor cell differentiation over CSC enrichment. Moreover, knocking-down either STAT1 or STAT2 abolished the IFN-β-mediated quiescence induction in melanoma cells, confirming IFN-β as the driver of dormancy in these cells. Finally, a thorough study of the signaling pathway responsible for this effect underlined the IDO/Kyn/AhR cascade and serine-phosphorylation of STAT3 as the effectors, providing new insights into tumor dormancy mechanisms associated with IFNs.

Interferon Type II

A similar approach to the Liu et al. (190) study was conducted by the same group using IFN-γ (191), and similar results at the level of stemness promotion were obtained in murine TRCs (i.e., stem cell-like cancer cells that can repopulate tumors). Again, the authors showed that IFN-γ treatment resulted in IDO1/AhR-dependent p27 induction, that prevented STAT1 signaling, suppressing cell death and inducing tumor cell-dormancy in murine TRCs. Importantly, a similar effect with IFN-γ was also shown in human melanoma, breast cancer and HCC cell lines, again through the IDO/AhR/p27 pathway. While Liu et al. dissected the molecular signaling pathway behind IFN-γ-mediated tumor cell-dormancy, Farrar et al. (192) discovered in 1999 that IFN-γ produced by CD8^{+} T cells played a major role in inducing tumor cell dormancy *in vivo*; however, the authors did not dissect the mechanism of action. In their study, a model of tumor dormancy was used, in which a murine B cell lymphoma (BCL_1) implanted in immunocompetent mice previously immunized with the BCL_1-derived Ig to orchestrate an anti-Id immune response could be induced into a dormant state. Adoptive transfer of Id-immune CD8^{+} T cells into SCID mice administered with α-BCL_1-Ig, concomitant with α-IFN-γ antibodies, resulted in complete abrogation of the induction and maintenance of tumor dormancy. These results indicated that endogenous production of IFN-γ by CD8^{+} T cells, in collaboration with humoral immunity, induced and maintained tumor cell dormancy *in vivo*. In line with this, Kmieciak et al. (193) reported 4 years later that CD8^{+} T cell-produced IFN-γ was able to induce apoptosis in those tumor cells expressing high levels of IFNGR, while those expressing low levels entered into a quiescent state. In addition, relapsed tumor-cells presented increased expression of cell surface stem-like markers and higher tumorigenic capacity *in vivo*, thus connecting IFN-γ stimulation in a subset of tumor cells with a quiescent phenotype and a subsequent enrichment in the CSC compartment after tumor regrowth.

DISCUSSION

The regulation of IFN signaling has been extensively investigated, and yet there are still many aspects that are not fully understood and many questions remain unresolved. An example is the question of how IFN-α and -β are able to exert different effects on cells while signaling through the same receptor—IFNAR—via the JAK/STAT pathway. We now know that IFN stimulation and subsequent downstream effects are highly dependent on the cell type, IFN dose and the cell surface-receptor density in the stimulated cell. Likewise, factors behind the regulation of IFN
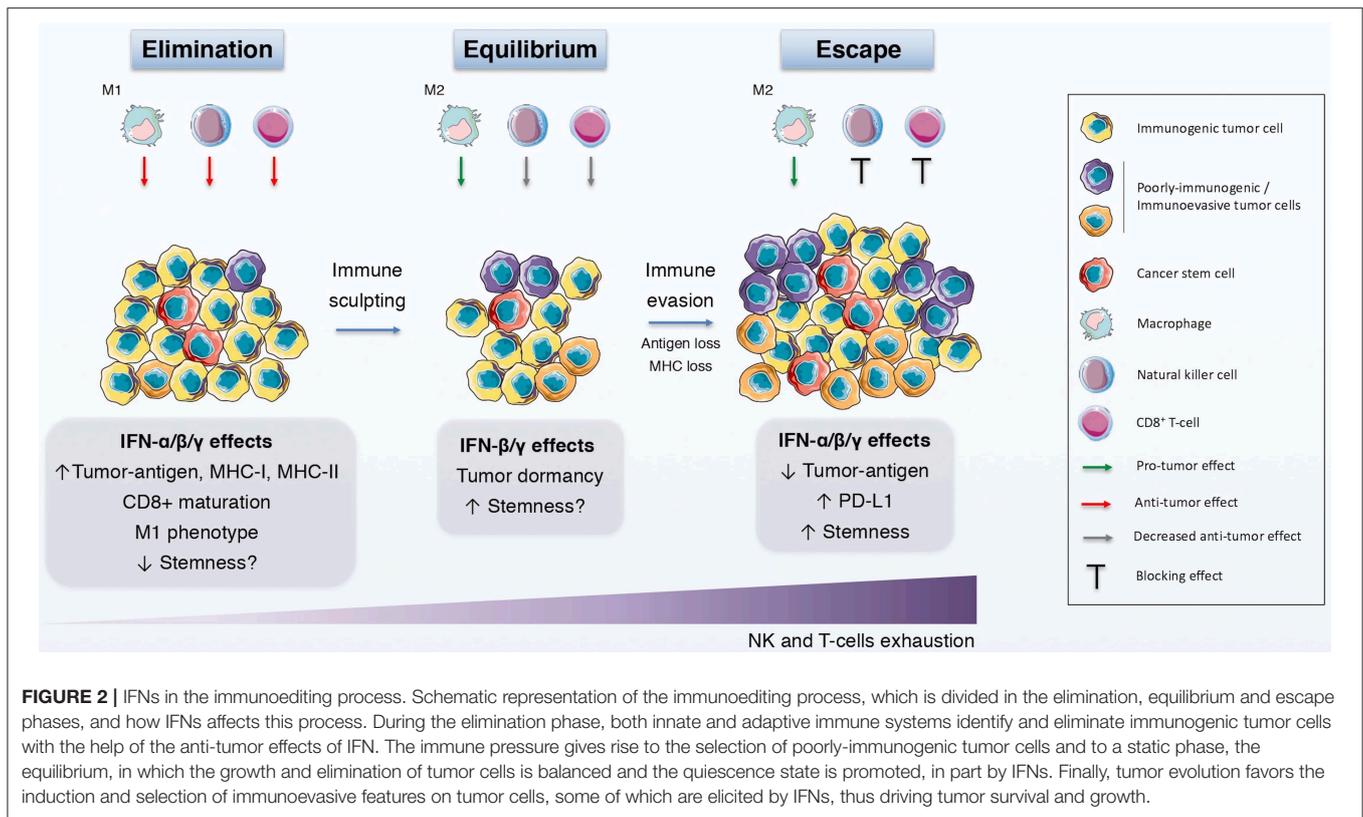
FIGURE 2 | IFNs in the immunoediting process. Schematic representation of the immunoediting process, which is divided in the elimination, equilibrium and escape phases, and how IFNs affects this process. During the elimination phase, both innate and adaptive immune systems identify and eliminate immunogenic tumor cells with the help of the anti-tumor effects of IFN. The immune pressure gives rise to the selection of poorly-immunogenic tumor cells and to a static phase, the equilibrium, in which the growth and elimination of tumor cells is balanced and the quiescence state is promoted, in part by IFNs. Finally, tumor evolution favors the induction and selection of immunoevasive features on tumor cells, some of which are elicited by IFNs, thus driving tumor survival and growth.

TABLE 1 | Anti- and pro-CSC effects of IFN-I and IFN-II.

Anti-CSC effects	Pro-CSC effects
IFN-I	
Decreased expression of stem-like markers and/or pluripotency genes (1–3)	Increased expression of stem-like markers and/or pluripotency genes (4–6)
Reduced self-renewal capacity (1, 2, 7–10)	Increased self-renewal capacity (4–6)
Reduced tumorigenic potential (1, 7, 9)	Increased tumorigenic potential (5, 6)
Reduced proliferation (7, 9, 10)	Chemoresistance (6)
Reduced metastatic potential (9)	Increased migratory/invasive and/or metastatic capacities (3, 6)
	Induction of dormancy (11)
IFN-II	
Reduced self-renewal capacity (14)	Increased self-renewal capacity (12, 15)
Reduced tumorigenic potential (14)	Increased tumorigenic potential (13)
Reduced migratory/invasive capacities (16)	Activation of EMT and/or migration/invasion (12, 15)
	Increased expression of stem-like markers and/or pluripotency genes (12, 13)
	Increased metastatic potential (15, 17–22)
	Chemoresistance (15)
	Induction of dormancy (23–25)

receptor presentation and IFN secretion levels are numerous and vary (2). This scenario highlights the importance of the cellular and environmental context in which a cell is stimulated

by IFNs, and CSCs are no exception. Thus, more research is needed to fully characterize and dissect the factors that mediate the different responses of distinct CSCs to IFNs, described in this review. While we have put forth several possible explanations, including IFN dosing, more studies are still needed. Nevertheless, it is highly likely that what we will discover are cell-type specific effects. For example, regarding IFNs and dormancy, it is known that IFN-α is able to activate dormant hematopoietic stem cells (HSCs), inducing them to proliferate and making them more vulnerable to anti-cycling therapies such as 5-fluorouracil (194); however, while CSCs share many common features with normal stem cells, they also possess an aberrant malignant behavior based in part on a very different signaling circuitry. Thus, the very same stimulus can have completely different effects on normal- and cancer- stem cells. This is certainly the case with respect to the dormancy-specific studies described in this manuscript, which demonstrate that IFN-β and -γ are dormancy drivers (190–193). To complicate the matter further, acute exposure of HSCs to IFN-I has been shown to induce quiescence exit and promote proliferation; however, far from leading to HSC pool exhaustion, chronic exposure to IFN-I reestablished the HSC quiescent state and induced protection from the killing effects of IFN-I (195). These findings highlight the importance of advancing research focused on IFN pathway regulation, since IFNs (specially IFN-α) have been proposed as "awakening" agents for dormant CSCs. Despite these findings described for HSC, it is yet to be demonstrated whether acute and chronic exposure of other CSCs to IFN-I induces the same effects as those described

for HSCs, but caution should be taken when exploring the therapeutic effects of IFNs on CSCs, specifically at the level of dormancy.

Finally and more interestingly, the concept of immunoediting might prove beneficial to further explain the contradictory conclusions regarding the effect of IFNs on CSCs (196) (**Figure 2**) (**Table 1**). Briefly, cancer immunoediting refers to a complex interplay between tumor cells and the host immune system that can be divided into three phases: elimination (immunosurveillance), equilibrium (quiescent state) and escape (immunoevasion) [reviewed by McCoach and Bivona (197)]. Thus, depending on the molecular and functional traits of a CSC subset at a certain time during tumor progression, IFNs would be able to boost or shut down that subpopulation. Although knowledge of how CSCs participate in cancer immunoediting is now expanding (198, 199), less is known about the role of IFNs in that interplay. Exploring this field would surely contribute significantly to a better understanding of the dynamics and relationship that exists between IFNs and CSCs.

In conclusion, IFNs comprise a family of cytokines with pleiotropic effects, and among the many effects attributed to IFNs and their signaling pathways, growing evidence now validates a unique role for these cytokines in CSC biology. IFNs are able to display both pro- and anti-CSCs effects, depending on the context, including synergistic effects with other cytokines. For this reason, further research is needed in order to build a more comprehensive perspective of these contradictory roles with the hope of being able to exploit the anti-tumor effects of IFNs and at the same time downregulate their pro-CSCs capabilities as a means of targeting CSCs to improve cancer patient overall survival.

AUTHOR CONTRIBUTIONS

BS and LM-H developed the idea and edited the text. LM-H wrote the manuscript. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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