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Interferon Gamma, MHC Class I Regulation and Immunotherapy

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Highlights

- Inactivation of the IFNγ signaling pathway downregulates MHC-I expression and impairs tumor antigen presentation.
- Recurrent immunotherapy failure observed in patients with IFNγ pathway deficiencies.
- IFNγ signaling pathway and MHC class I regulation require profound molecular understanding to mitigate resistance against cancer treatments.

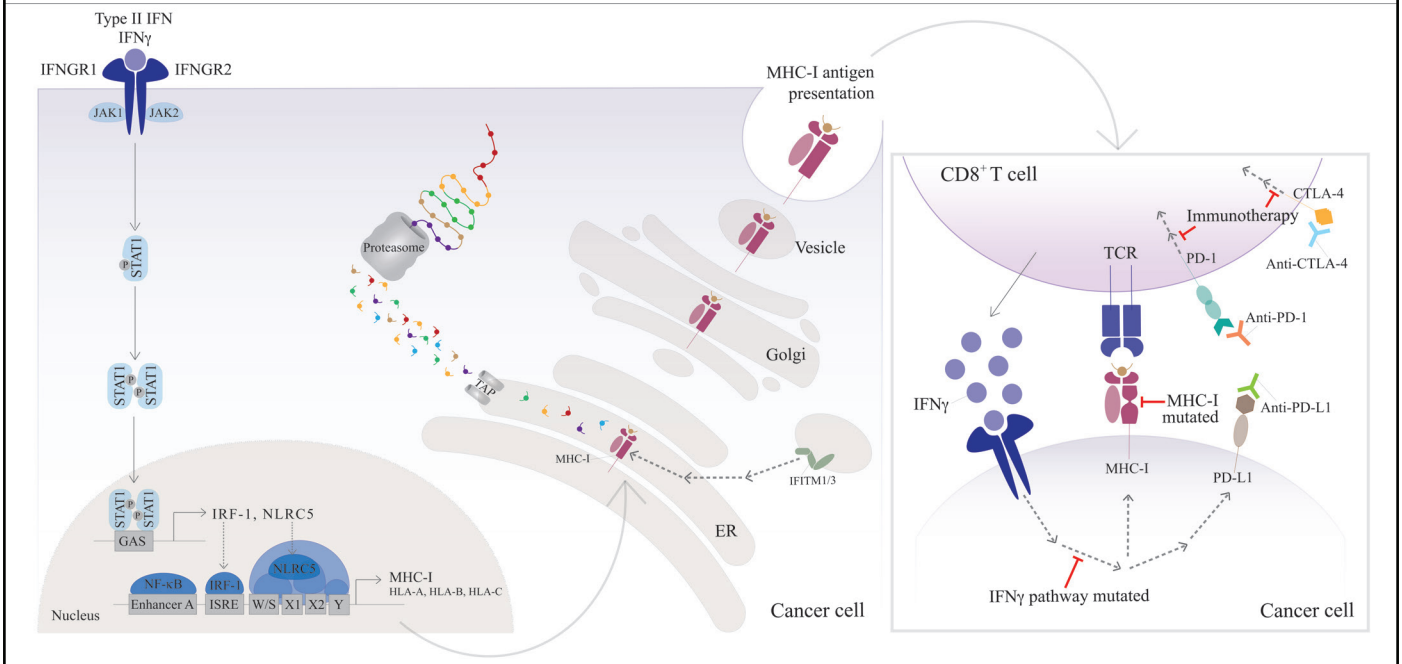
Abstract

The activation of endogenous IFNγ signaling pathway or the administration of recombinant IFNγ increases the expression of MHC-I. MHC-I molecules are core elements for antigen recognition in tumor cells. A better understanding of the regulation of their expression would contribute to counteracting tumor immune escape and enduring permanent tumor rejection. Efficient and functional expression of HLAs dramatically impacts the number of tumor-associated antigens presented to CTL for cell recognition. Many patients diagnosed with various types of cancer have inhibited the IFNγ signaling pathway. This review explores how anomalies associated with IFNγ signaling in tumor cells affect HLA-I expression, current immunotherapies association, and outcome. Globally, MHC-I lesions could be divided into reversible and permanent. Irreversible lesions cannot be recapitulated; hence, the patient will not respond to immunotherapies requiring MHC-I activity. However, gaining precise and systematic molecular knowledge improves tumor stratification, which could help predict which tumors will recover expression of MHC-I. Complementary IFNγ effectors can function as a compensatory mechanism that restores the expression of HLA-I proteins in tumors with deleterious IFNγ pathways. For those non-responsive patients with inactive IFNγ pathways, designing personalized approaches to recover HLA-I expression can make the tumor sensitive to immunotherapy, leading to a better outcome.

Keywords: MHC class I, HLA, IFNγ, Immunotherapy

Abbreviations: CTL: Cytotoxic T Lymphocytes; MHC: Major Histocompatibility Complex; HLA: Human Leukocyte Antigen; IFN: Interferon; JAK: Janus Kinase; STAT: Signal Transducer and Activator of Transcription; ISG: Interferon-Stimulated Genes; IRF: Interferon Regulatory Factor; ISGF: Interferon-Stimulated Gene Factor; GAF: Gamma-Interferon Activation Factor; GAS: Gamma- Interferon Activated Site; ISRE: Interferon-Sensitive Response Element; IRDS: Interferon-Related DNA Damage Resistant Signature; IFITM: Interferon-Induced Transmembrane; NLRC5: NOD-Like Receptor Family CARD Domain Containing 5; PRR: Pattern Recognition Receptor; dsRNA: Double-stranded RNA; LOH: Loss of the Heterozygosity; B2M: Beta-2-Microglobulin; APM: Antigen-Processing Machinery; IFNR: Interferon Receptor; HPV: Human-Papillomavirus; DNMTi: Histone Deacetylase Inhibitors; TAP: Transporter associated with Antigen Processing; LPM: Low-Molecular Mass Polypeptide; MECL: Multi-Catalytic Endopeptidase Complex-Like: DUX4: Double Homeobox 4; LNK: Lymphocyte Adapter Protein; PIN1: Peptidyl-Prolyl Cis-Trans Isomerase NIMA-Interacting 1

Graphical abstract



IFNγ Signaling Pathway

Malignant cells are highly adaptive to their microenvironment and develop complex and selective molecular strategies to promote cell survival. Thus, tumor development is a dynamic process sustained during the appearance of the disease, diagnosis, course of treatment, and remission. Furthermore, a decrease in the symptoms and absence of cancer-associated markers may not necessarily translate into the complete disappearance of cancer; dormant cells may remain in the organism causing a future relapse [1]. Hence, the importance of continuous characterization of key molecular abnormalities is desirable to design effective and personalized immunotherapies at all stages [2].

The central paradigm for cancer cell eradication requires effective tumor-derived peptide processing, presentation by MHC-I molecules, and optimal peptide recognition by the cytotoxic T lymphocytes (CTL) [3]. Unfortunately, a comprehensive understanding of the mechanisms behind cancer immunosurveillance is extremely complex. However, this review aims to unravel fundamental features involving the regulation of MHC class I by IFNγ associated with immunotherapy.

The canonical MHC-I (HLA-A, HLA-B, HLA-C) genes are induced by the exceedingly investigated IFN signaling [4]. IFNs are pleiotropic cytokines that rapidly activate the JAK-STAT signaling cascade and mediate the expression of many genes collectively known as interferon-stimulated genes (ISG) [5-11]. In humans, IFNs are classified into three different classes: type I (IFNα, IFNβ, IFNε, IFNκ, and IFNω), type II (IFNγ) and type III (IFNγ) [12-14]. The MHC class I molecules are induced by type I IFN and more efficiently by type II IFN [15-18].

The IFNγ signaling activates the homodimerization of p-STAT1, forming the GAF complex in the cytosol. In addition, p-STAT1 also forms a heterodimer with p-STAT2 and binds to IRF9, constituting the ISGF3 complex, representative of the type I IFN pathway [19,20]. Thus, this illustrates that despite unique receptors for each class of IFN, there is underlying crosstalk between IFNγ and type I IFN pathways. In the primary IFNγ response, the GAF complex translocates to the nucleus. It binds to the GAS sites present in the promoter of ISG genes, such as the transcription factors IRF1 and p48. Sequentially, IRF1 regulates the expression of many genes activated in the secondary response through DNA recognition with ISRE motifs. The p48 enhances the binding specificity between the ISRE boxes to the principal transactivator factor for type I IFN, ISGF3. The induction of MHC class I genes is driven by the binding of IRF1 to the ISRE element presented in the gene's promoter upon IFNγ stimulation [21-23]. More specifically, HLA-A is less responsive to IFNγ than the counterparts HLA-B and HLA-C due to changes in the structure of ISRE sequences [24-28].

IFNγ has numerous protective anti-cancer functions related to the activation of immune cells [29-31], promoting apoptosis [32-34], preventing angiogenesis [35], and inhibiting proliferative processes [36] occurring in cancer cells.

In contrast, this view is challenged when examining tumor resistance in chemotherapy and radiotherapy patients [37,38]. Throughout cancer treatment and in cancer development, chronic inflammation results in the sustained activation of the IFNγ pathway [39]. Conversely, consistent exposure to IFNγ constitutes an adverse effect promoting cell growth [40,41] and genomic instability [42], depleting immunogenic tumor-associated antigens [43], and exhausting CTL cell recognition [44]. The study of the gene expression in various cancer types has defined a subgroup of ISG genes called IFN-related DNA-damage signature (IRDS), responsible for chemotherapy and radiotherapy resistance [45-47]. Notoriously, HLA-B and HLA-G (non-classical MHC class I molecule) are induced by IRDS genes. However, the current understanding of the cellular mechanism behind the protective phenotype against radiotherapy and chemotherapy conferred by IRDS genes is insufficient. Nonetheless, a steady low dose of IFNγ initiates a turnover from phosphorylated to unphosphorylated STAT1 form that induces the expression of IRDS genes [48,49].

Moreover, multiple factors have been linked with altered IFNγ signaling, including the embryonic transcription factor double homeobox 4 (DUX4), which upregulation in cancer results in a decrease of JAK1/2 and STAT1 and reduces MHC class I and other genes of the antigen-presentation machinery (APM) [50]. In addition, DUX4-mediated suppression of MHC-I and antigen presentation has been associated with resistance to immune checkpoint blockade and promotion of cancer immune escape. The lymphocyte adapter protein (LNK) is another factor that induces the dephosphorylation of STAT1 and, consequently, negatively modulates IFNγ signaling [51]. A further example is a peptidyl-prolyl isomerase (Pin1) that has been shown to play a role in inducing ubiquitination and suppressing the interferon-regulatory factor 3 (IRF3). Increased Pin1 expression has been reported in many types of cancer and has been detected in cancer cells undergoing malignant transformation [52,53].

To increase the complexity of the MHC class I pathway, specific tumor cell subclones can acquire resistance by sabotaging the activation of the IFN pathway, which affects the optimal expression of MHC class I and leads to therapeutic failure. To overcome this event, we have proposed a novel role for the IFN-inducible IFITM1 (which is an IRDS component) and IFITM3 [54,55] mediating protein synthesis in the context of cancer. Our results suggest that IFITM1/3 stimulates the protein synthesis of MHC class I components, most significantly for HLA-B [56]. We hypothesize that the absence of IFITM1/3 expression could decrease MHC class I molecules, resulting in deficient processing of the antigen-presentation pathway and affecting the peptide recognition by CTL. Reduced MHC class I expression followed by malfunctions in recognizing tumor-associated peptides by the $CD8^+$ T cell leads to immune evasion, causing metastasis and lack of response to immunotherapy [57-62]. Our interpretation is consistent with the fact that deficient IFITM1/3 expression observed in cervical cancer specimens is more prone to metastasis [56]. With our work, we would like to expand the knowledge on the HLA regulation and draw interest in non-canonical cellular signaling (s) to activate the expression of MHC class I molecules. Alternative mechanisms are investigated in tumors defective on the IFN pathway to recapitulate the expression of MHC class I in an IFN-independent manner; for example, an increase of the transcriptional activator NLRC5 [63-65] restores the production of MHC class I. In addition to that, an intratumoral injection with the synthetic BO-112 (nanoplexed formulation of poly I:C) restores the pattern recognition receptor (PRR) pathway and activates dsRNA sensing to express MHC class I through the nuclear factor-kB (NF-kB) [66]. All in all, this phenomenon raises the question of whether alternative mechanism(s) responsible for potential tumor sensitivity could be caused (at least partially) by unexplored MHC class I mediators.

Regulation of MHC Class I in Cancer

MHC class I downregulation or total expression loss is frequently observed in malignant tumors [67]. In addition, it is considered a dominant mechanism was facilitating escape from cancer immune surveillance [68]. MHC class I processing and presentation on the cell surface is mediated at the genetic, epigenetic, transcriptional, and posttranscriptional levels. Garrido et al. distinguished two types of alterations in cancers that affect MHC class I expression depending on whether the change is reversible, classified as 'soft' mutation, or irreversible, referred to as 'hard' mutation [69].

Due to tumor genetic instability, various genetic variations can affect MHC class I expression patterns. These structural irreversible 'hard' aberrations can arise through deletions, mutations in chromosome sequences, and somatic recombination [70]. For instance, the loss of the heterozygosity (LOH) by deleting one allele of *HLA* class I or *B2M* genes is frequent in numerous types of tumors [71-74]. In particular, loss of MHC class I copy number has been described to occur in 17% out of 59 different cancer types analyzed [75]. Moreover, further studies showed a higher prevalence of LOH events in tumors with a higher mutational burden, thus, more prone to display mutated neoantigens [76]. In cancer immunotherapy, however, targeting irreversible alterations is hindered by technical limitations, whereas reversible events with the possibility of restoring gene expression provide potential target candidates for therapeutic approaches.

Tumor-driven reversible 'soft' defects can alter MHC class I expression by targeting components of the APM. For example, numerous studies conducted in several cancer types demonstrated reduced levels of transcription factors and regulators, namely NLRC5 [77-79], that consequently led to attenuated levels of MHC alpha chain (the heavy chain component of the MHC class I complex), B2M (the light chain component of the MHC class I complex). Moreover, other peptide-loading and processing machinery components

include the transporter associated with antigen processing (TAP), tapasin, endoplasmic reticulum aminopeptidase 1 (ERAP1) and immunoproteasome subunits.

Deficiencies in the activation of the IFNγ signaling pathway can cause MHC class I inhibition and leads to poor prognosis in patients with cancer. The complex regulatory system of MHC class I transcription consists of multiple components [80] that have been found altered in tumors [81-86]. For instance, loss of the interferon regulatory factor IRF1 in melanoma has been linked with the tumor resistance to immune checkpoint blockade (ICB) therapy [87]. Furthermore, loss of constitutive IRF2 expression is correlated with downregulation of MHC class I, TAP2, and ERAP1; consequently, tumors presenting this phenotype may evade immune detection and elimination [88].

Epigenetic mechanisms silencing MHC class I in tumors have been researched comprehensively as potential therapeutic targets. Hypermethylation of the regulatory elements of *MHC-I, B2M*, APM components, *NLRC5,* and elements of the IFN pathway has been described in several types of cancers such as sarcomas, gliomas, breast, lung, colon, thyroid, and human papillomavirus (HPV)-related cancers [89-93]. Nonetheless, suppression of MHC class I by DNA hypermethylation can be recovered with DNA methyltransferase inhibitors (DNMTi). Moreover, the induction of *MHC-I* genes silenced by histone deacetylation can be restored with histone deacetylase inhibitors (HDACi), leading to increased acetylation levels in melanoma and glioma [94,95]. Currently, there are several epigenetic inhibitors approved by the FDA for treatment or undergoing clinical trials that show an increase in the expression of IFN and genes associated with the MHC class I antigen presentation pathway in cancers both *in vitro* and *in vivo* [96-98].

MHC class I expression is mediated by IFN signaling (primarily by IFNγ) in response to inflammation. Several factors are involved in alterations of the IFNγ signaling, and subsequent MHC class I downregulation; defects in IFNGR1 receptors, mutations in the signaling factors JAK1, JAK2 and modification of downstream components of the IFNγ signaling cascade such as STAT1 and IRF1 have been associated with poor cancer prognosis [99-103]. To emphasize the role that IFNγ plays in regulating antigen presentation pathways, IFNγ also upregulates most components of the peptide-loading complex such as proteases or TAP transporters and three unique components of the immunoproteasome (LPM2, LPM7, and MECL) [104-106]. In addition, IFNγ affects the MHC class I peptidome repertoire presented on the cell surface [107-109].

In this regard, it has been observed an increased presence of mutated neoantigens in the displayed peptidome following MHC class I induction with IFNγ, thus, potentially stimulating T-cell response in the tumor microenvironment [110]. Despite extensive research, IFNγ clinical benefit remains unknown in cancer immunotherapy. In cancers classified with reduced MHC class I, IFNγ was reported to restore MHC class I expression through epigenetic modifications, increased histone acetylation, and DNA demethylation of TAP and immunoproteasome regulatory elements [111,112]. In addition, downregulation of IFNγ signaling has been correlated with resistance to ICB therapy and adoptive cell therapy in lung cancer and melanoma [99,113,114]. However, whether this process involved MHC class I expression remains to be elucidated. Nonetheless, upregulation of IFNγ signaling having a positive outcome on ICB was observed in cancer where IFNγ alterations are less common [115].

Multiple analyses such as immunohistochemistry, microarray, and RNA sequencing showed decreased MHC class I expression from 40% and up to 90% of lesions analyzed across various histological cancers types, including solid tumors [85,116-120] and hematopoietic tumors [121,122], often correlating with worse prognosis [123-125]. In fact, the detection of impaired MHC class I expression during immunotherapy has been identified as a mechanism for acquired resistance to ICB therapy [126-129]. Furthermore, to highlight its role in cancer promotion, the low MHC class I phenotype derived from melanoma metastases in patients undergoing immunotherapy was correlated with cancer progression while metastases regressed in the high MHC class I phenotype [130]. All in all, the complex and polymorphic nature of MHC class I genes coupled with cancer heterogeneity and discrepancies in published clinical data pose a challenge in understanding the precise mechanism behind MHC class I loss.

The Role of IFNγ in Immunotherapy

ICB therapies targeting the CTLA-4 and PD-1 inhibitory pathways are considered a breakthrough therapy for cancer treatment [131,132]. Checkpoint inhibitors have promised positive outcomes in immune responsive tumors, referred to as "hot" tumors, such as in melanoma and lung cancer. In contrast, "cold" tumors that will not activate a strong immune response can resist these immunotherapies by activating multiple mechanisms [133]. For instance, low expression of MHC-I molecules and a lack of tumor infiltrating lymphocytes (TIL). In addition, MHC-I molecules are very poorly present in various cancer lines; however, IFNγ can stimulate their expression [134,135]. Conversely, "cold" sarcomas treated with IFNγ enhance the expression of MHC-I and increase the infiltration and activation of cytotoxic T cells [136]. Furthermore, treatment with IFNγ upregulates the expression of PD-L1 [137-139], CTLA-4 [140], and IDO1[139,141] in tumor cells which will benefit ICB therapy.

Several clinical trials are ongoing with only IFNγ or combined with other drugs for various types of cancer. For example, patients with HER-2 positive breast cancer are treated with IFNγ, Paclitaxel, Trastuzumab, and Pertuzumab in a phase I-II

study (NCT03112590). Another clinical trial exclusively uses the recombinant IFNγ as an immunotherapy agent to treat soft tissue sarcoma (NCT01957709). A growing body of evidence shows that IFNγ interferes with the growth of cancer cells [142,143]. Hence, it is considered for a clinical trial in phase I to treat patients with recurrent metastatic melanoma or other solid tumors (NCT00004016). In addition, the recombinant IFNγ-1b form has also been considered alone or combined with Lexatumumab to treat children with various solids tumors (NCT00428272). Moreover, the chemotherapy drugs cyclophosphamide and cisplatin combined with IFNγ yielded a significant benefit in prolonging progression-free survival in patients with ovarian cancer [144].

Ionizing radiation and chemotherapeutical agents act more effectively with recombinant IFNγ [144-147]. Radiation in a murine colon adenocarcinoma model increases the peptide repertoire, the MHC-I presentation, and CTL recognition dose-dependent [148]. However, radiation has proven insufficient to cure some human cancers. The combination of IFNγ with radiation therapy has improved T cells activation and the immune system for a more effective response against colon cancer [146].

Furthermore, functional IFNγ signaling improves the response to PD-L1 inhibitor treatment. It increases the survival of patients affected with non-small cell lung cancer and urothelial cancer [149-151]. The combination of PD-1 and CTLA-4 blockers increases the infiltration and the production of IFNγ in effector T cells [152]. In fact, clinical trials conducted on patients with bladder cancer revealed that the treatment with anti-CTLA-4 antibody was directly associated with increased IFNγ-producing $CD4^{+}ICOShi$ (inducible co-stimulator) cells ratio effector to regulatory T cells [153].

Murine models have shown that inactivation of the IFN-pathway is a prevalent cause for resistance to ICB therapy failure [154,155]. Moreover, deficiencies in the IFN signaling inactivate MHC class I expression, and consequently, antigens are presented on the cell surface in a deficient manner [83,155]. Comparably, mutated B2M is recurrent in patients non-responsive to ICB therapy [129]. In addition, tumor resistance to ICB targeting PD-L1 and CTLA-4 co-receptors sustain the inflammatory response of the IFN signaling modifying STAT1, increasing ISG gene expression and activating T cell inhibitory receptors [156]. However, this adverse effect is mitigated by inhibiting the type I and type II IFN receptors in cancer cells.

Lack of response to the cancer treatment or uncomplete clearance of tumor cells is originated by factors intrinsic to the immune infiltrated cells and/or tumor cells [157]; the immune-related functions of IFNγ present a stimulatory and suppressive role in cancer [158]. How these dual antagonistic activities of IFNγ coexist is still under debate. Nonetheless, the implications of IFNγ in the cancer cell may diverge from the one exerted by the neighboring immune cell. Thus, the IFN regulation between cancer cells and immune cells is fundamental to define resistance or response to immunotherapy. In this regard, suppressing the IFNγ pathway diminishes the expression of ISG genes in tumor cells. However, higher production of IFNγ in exhausted T cells induces ISG genes [159]. Therefore, the homeostatic balance of the IFNγ is crucial for a favorable immunotherapeutic outcome. Thus, there is an urgent need to improve the predictive biomarkers for immune checkpoint inhibitors prior to treatment. Besides the various biomarkers based on gene expression profiling and RNA analysis, the ratio of the IFNγ signature to the immunosuppression signature better predicts the response to anti-PD-1 therapy in patients with melanoma [160].

Personalized cancer immunotherapies based on therapeutic vaccination and the transfer of TILs targeting tumor-specific neoantigens have shown promising clinical outcomes [161-163]. IFNγ has the potential to remodel the antigen presentation and MHC expressions in the tumor cells [107]. The effective activation of antigen-presenting cells (APCs) and its machinery by IFNγ signaling pathways promote the T cell functioning against the tumor cells. However, the loss of IFNγ inhibits the activation of T cells and allows tumor development and immunoediting [164]. Therefore, it is crucial to consider the role of IFNγ while developing the approach to identify tumor neoantigens. The identification of neoantigens is further limited by the low number of T cells recognizing a specific tumor antigen. Therefore, the development of NeoScreen as a neoantigen screening pipeline is valuable for selecting relevant and personalized targeted tumor antigens for further cancer vaccine and T cell therapy development [165].

Taking everything together, the complexity of the IFNγ reflects the need to study the state of the canonical and alternative IFNγ signaling pathways to design, understand and better predict the outcomes of IFNγ based therapy [166-168]. We would like to remark the need for more advanced analysis of the IFN pathway, novel non-canonical molecules, and the study of individual patient-associated immunopeptides presented in tumor cells to design combined personalized (immuno)therapies and predict with more confidence the responsiveness to anti-cancer treatment [127].

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Author Contributions

MGH: Conceptualization, original draft preparation, writing, reviewing, editing, funding acquisition. MP: conceptualization, original draft preparation, writing, reviewing. SK: conceptualization, original draft preparation, writing. TH: supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

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