

Dual Faces of IFN γ in Cancer Progression: A Role of PD-L1 Induction in the Determination of Pro- and Antitumor Immunity ^{CME}

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Abstract

IFN γ is a cytokine that plays a pivotal role in antitumor host immunity. IFN γ elicits potent antitumor immunity by inducing Th1 polarization, CTL activation, and dendritic cell tumoricidal activity. However, there are significant discrepancies in our understanding of the role of IFN γ as an antitumor cytokine. In certain circumstances, IFN γ obviously acts to induce tumor progression. IFN γ treatment has negatively affected patient outcomes in some clinical trials, while it has favorably affected outcomes in other trials. Several mechanisms, including IFN γ insensitivity and the downregulation of the MHC complex, have been regarded as the reasons for this discrepancy, but they do not fully explain it. We propose IFN γ -induced programmed cell death 1 ligand 1 (PD-L1) expression as a novel mechanism by which IFN γ impairs tumor immunity. When tumor cells

encounter CTLs in the local environment, they detect them via the high concentration of IFN γ secreted from CTLs, which induces PD-L1 expression in preparation for an immune attack. Thus, tumor cells acquire the capability to counterattack immune cells. These findings indicate that although IFN γ is thought to be a representative antitumor cytokine, it actually has dual roles: one as a hallmark of antitumor immunity and the other as an inducer of the immune escape phenomenon through various mechanisms, such as PD-L1 expression. In this context, the optimization of immunotherapy according to the local immune environment is important. Anti-PD-1/PD-L1 treatment may be particularly promising when efficient tumor immunity is present, but it is disturbed by PD-L1 expression. *Clin Cancer Res*; 22(10); 2329–34. ©2016 AACR.

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The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the basic mechanism of tumor immunity, especially of the role of IFN γ in the expression of PD-L1 in the local tumor environment.

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IFN γ as an Antitumor Cytokine in Cancer Biology and Tumor Immunity

Role of IFN γ in physiologic and tumor immunity

IFN γ is a multifunctional cytokine that is primarily secreted by activated T, natural killer cells (NK), and NK T cells. IFN γ plays a pivotal role in systemic and local immunity and is involved in almost all inflammatory responses. IFN γ is a key cytokine in the polarization of Th1 cells. The ability to secrete IFN γ is a hallmark

Translational Relevance

Recently, cancer immunotherapies, especially those using immune checkpoint inhibitors, such as anti-programmed cell death 1 ligand 1 (anti-PD-L1) or anti-PD-1 antibodies, are being focused on because of the efficacy they have shown in clinical trials. Nevertheless, they are effective in only a portion of patients with cancer, and it is necessary to personalize these treatments by selecting patients who will benefit from these immunotherapies. IFN γ is one of the representative immune-activating cytokines that has been tested in cancer immunotherapy, but its efficacy is still controversial. We investigated the role of PD-L1 expression in the local tumor environment and found that IFN γ plays a pivotal role in PD-L1 expression in cancer cells and the consequent immune escape by the tumor cells. Here, we focus on the dual aspects of IFN γ in tumor immunity and propose personalized immunotherapies according to the local immune status.

of Th1 cells, whereas the secretion of IL4 is a hallmark of Th2 cells. IFN γ secretion by NK cells and dendritic cells (DC) causes the local production of IL12 and thereby induces a Th1 response (1).

Th1 polarization typically induces the activation of CTL, NK cells, macrophages, and monocytes. These activations potentially serve as a defense against cancer. In this context, IFN γ is essentially regarded as an antitumor cytokine. It has been reported that the secretion of IFN γ by stimulated peripheral blood mononuclear cells (PBMC) is significantly reduced in patients with advanced cancer when compared with healthy controls (2). CD4⁺ Th1 (but not Th2) cells, Th17 cells, and regulatory T cells are capable of inducing the cytotoxic functions of DCs, and IFN γ is the major factor responsible for Th1-induced DC tumoricidal activity (3). IFN γ also acts as a CTL differentiation signal (4). IFN γ is essential to the induction of the proliferation of CTL precursors and their differentiation into CTLs (5). The IL12-induced regression of murine cancers was almost completely abrogated by the administration of an anti-IFN γ antibody (6).

Immune activation mechanisms of IFN γ

Although the biologic mechanism by which IFN γ exerts its antitumor effect is not fully understood, it is likely that the effect depends on multiple processes. IFN γ primarily activates the JAK-STAT pathways that lead to the induction of the expression of multiple genes. In cancer cells, the alterations in gene expression that are caused by IFN γ are presumably associated with increased immunogenicity, which thereby induces immune stimulation. The most typical example of this is the upregulation of MHC class I molecules by IFN γ (7). IFN γ -induced MHC class I expression has been shown to activate a tumor-specific immune response in a mouse model of prostate cancer (8). Sarcoma cells engineered to secrete IFN γ acquire sensitization to being killed by immune cells (9). The retrovirally mediated gene transfer of human IFN γ upregulates MHC antigen expression in human breast cancer and leukemia cell lines (7). The treatment of cervical carcinoma cells expressing low levels of class I and class II MHCs along with IFN γ results in the increased expression of these molecules and significantly

enhances the lysis of the tumor cells by specific CTLs (10). It has also been reported that IFN γ upregulates survivin and *lfi202* expression and induces the survival and proliferation of tumor-specific T cells (11).

Conflicting Data from Basic and Clinical Research on IFN γ Treatment

Negative effects of IFN γ on tumor inhibition

Although a large amount of data indicate that IFN γ acts as a key factor in anticancer immunity, there is also significant evidence demonstrating the opposite effect of this molecule. IFN γ -mediated hepatocarcinogenesis has been observed in mice treated with diethylnitrosamine (12). Suppressor of cytokine signaling-1 (SOCS1)-deficient mice spontaneously developed colorectal carcinomas in an IFN γ -dependent manner (13). IFN γ has been demonstrated to promote papilloma development (14). Mouse mammary adenocarcinomas transfected with the murine IFN γ gene give rise to progressive tumors (15). IFN γ induces lung colonization following intravenous inoculation with B16 melanoma cells, although this process also enhances MHC class I expression (16). These data clearly contrast with the aforementioned tumor-inhibiting effects of IFN γ .

Inconsistent clinical results regarding the effects of IFN γ

Reflecting the controversial results from basic research findings, the clinical data obtained in several trials are also inconsistent. In the relatively early studies on this topic, several reports suggested the efficacy of IFN γ for use in cancer treatment. The treatment of patients who had melanomas on their extremities using hyperthermic-isolated limb perfusion with melphalan, TNF, and IFN γ resulted in a 76% complete response rate (17). The inclusion of IFN γ in the first-line treatment of ovarian cancer resulted in an improvement in progression-free survival (18). In a prospective randomized study of patients with superficial transitional cell carcinomas who underwent transurethral tumor resection, prophylactic treatment with intravesicular IFN γ administration resulted in a better tumor-free rate compared with that of the nontreated group. Importantly, significant increases in T cells, Th cells, cytotoxic T cells, natural killer cells, and total leukocytes, as well as the numbers of B cells expressing intercellular adhesion molecule-1 and the total leukocytes expressing HLA-DR were observed following IFN γ treatment (19). In contrast, IFN γ treatment did not result in any difference in the outcomes of patients with metastatic renal cell carcinomas (20). No clinically meaningful benefit was observed in a controlled trial testing the use of IFN γ as a postoperative surgical adjuvant therapy for colon cancer (21). Furthermore, a phase III trial of IFN γ plus carboplatin/paclitaxel versus carboplatin/paclitaxel alone for treating advanced ovarian carcinomas was stopped early due to the significantly shorter overall survival (OS) time of the patients receiving IFN γ (22). Similarly, the time to progression and survival were inferior (although nonsignificantly) in patients treated with IFN γ compared with the outcomes of randomized control subjects in a trial including patients with small cell lung cancer with complete response following chemotherapy (23). These results indicate that the effects of IFN γ on tumor suppression are inconsistent and that IFN γ can even be detrimental depending upon the type of tumor and treatment protocol.

A Possible Mechanism Underlying the Controversial Effects of IFN γ in Tumor Immunity

IFN γ insensitivity and tumor development/progression

Insensitivity to IFN γ may contribute to tumor development and progression. Mutations in the IFN γ receptor lead to impaired IFN γ signal transduction. In an animal model, Meth A fibrosarcoma cells overexpressing a dominant-negative IFN γ receptor display enhanced tumorigenicity (24). Mice lacking sensitivity to IFN γ , such as IFN γ receptor-deficient mice, developed tumors more rapidly and with greater frequency than IFN γ -sensitive mice (25). Tumor escape variants that survive CTL adoptive immunotherapy exhibit decreased expression levels of the IFN γ receptor (26). In humans, IFN γ receptor α expression is lower in cases of infiltrating breast cancer than in cases of *in situ* tumors (27). Rare multiple cutaneous squamous cell carcinomas have been reported in a patient with an IFN γ receptor 2 deficiency (28). Functionally, the expression of the IFN γ receptor is downregulated by the overexpression of the activating protein (AP)-2 (29). The loss of the IFN γ receptor is an independent prognostic factor in ovarian cancer (30). These data all suggest that the lack of responsiveness of tumor cells to IFN γ signaling due to impairment of the IFN γ receptor results in cancer development and/or progression.

Even if the IFN γ receptor is normally expressed, the signal mediated by the receptor can be disrupted by various mechanisms. SOCS1 contributes to the attenuation of IFN γ signaling *in vivo* by binding to tyrosine-441 of the IFN γ receptor subunit 1 (31). The inhibitory effect of α GalCer on B16F10 lung metastases, of which IFN γ is known to be a critical mediator, is significantly more prominent in mice with mutations in tyrosine-441 of the IFN γ receptor subunit 1 (31). The IFN γ pathway has been demonstrated to be negatively regulated by IFN regulatory factor 2 in esophageal cancer (32).

MHC downregulation and the loss of immunogenicity

MHC molecule expression induced by IFN γ is a major mechanism involved in the immunostimulatory effect of IFN γ , as mentioned above. Therefore, an MHC deficiency and decreased immunogenicity are believed to be important consequences of IFN γ insensitivity. The downregulation of HLA class I molecules has been reported in various malignancies, including breast, cervical, colorectal, esophageal, gastric, ovarian, and renal cell carcinomas (33). However, the frequency of this downregulation varies significantly between tumor types. It can be as high as 48% in esophageal cancer but only 29% in ovarian cancer (34, 35). These findings suggest that MHC downregulation is not the only cause of immune escape by tumors. It has been shown in a uveal melanoma model that treatment with IFN γ boosted MHC class I presentation, but MHC class I-restricted CTL lysis was suppressed (36). Similarly, in human malignant melanomas, low-dose IFN γ treatment induced MHC expression, but this expression was not associated with a tumor response (37). A test using a sporadic tumor mouse model demonstrated that the tumors that develop in immunocompetent mice did not necessarily lose immunogenicity or escape from immunorecognition by T cells; instead, they induced tolerance accompanied by the expansion of anergic CD8⁺ T cells (38).

Induction of an immune-inhibitory microenvironment

If MHC downregulation is not the only cause of immune escape, what else could be a possible mechanism by which cancer fights against host immunity? One possibility is that IFN γ alters the immune microenvironment and consequently attenuates local tumor immunity. IFN γ is known to induce indoleamine 2,3-dioxygenase (IDO), which results in the induction of regulatory T cells (39). IFN γ has been reported to be essential for myeloid-derived suppressor cell (MDSC) development and its immunosuppressive function (40). Mundy-Bosse and colleagues demonstrated that the nitric oxide produced by MDSCs can reduce IFN γ responsiveness in immune cells such as CD4⁺, CD8⁺, and NK cells (41). Finally, we reported that IFN γ induces programmed cell death 1 (PD-1) ligand 1 (PD-L1) in cancer cells, as described below.

IFN γ Induces PD-L1 in Cancer Cells and Impairs Local Tumor Immunity

PD-L1 expression affects patient outcomes in various cancers

It has been reported that PD-L1 expression is associated with the prognosis of various types of malignant tumors. Meta-analyses of studies of non-small cell lung cancer, renal cell cancer, and gastrointestinal tract cancer have revealed that PD-L1 expression is associated with poor OS (42, 43). Wu and colleagues conducted a meta-analysis of 28 studies involving a total of 3,107 patients with solid tumors and concluded that the expression of PD-L1 is associated with lower survival rates in solid tumor patients (44). We also reported that PD-L1 expression is associated with a poor prognosis in patients with ovarian cancer (45). Although there are some variations in the clinical significance of PD-L1 expression in relation to tumor type, its expression is generally associated with poor outcomes for patients with cancer.

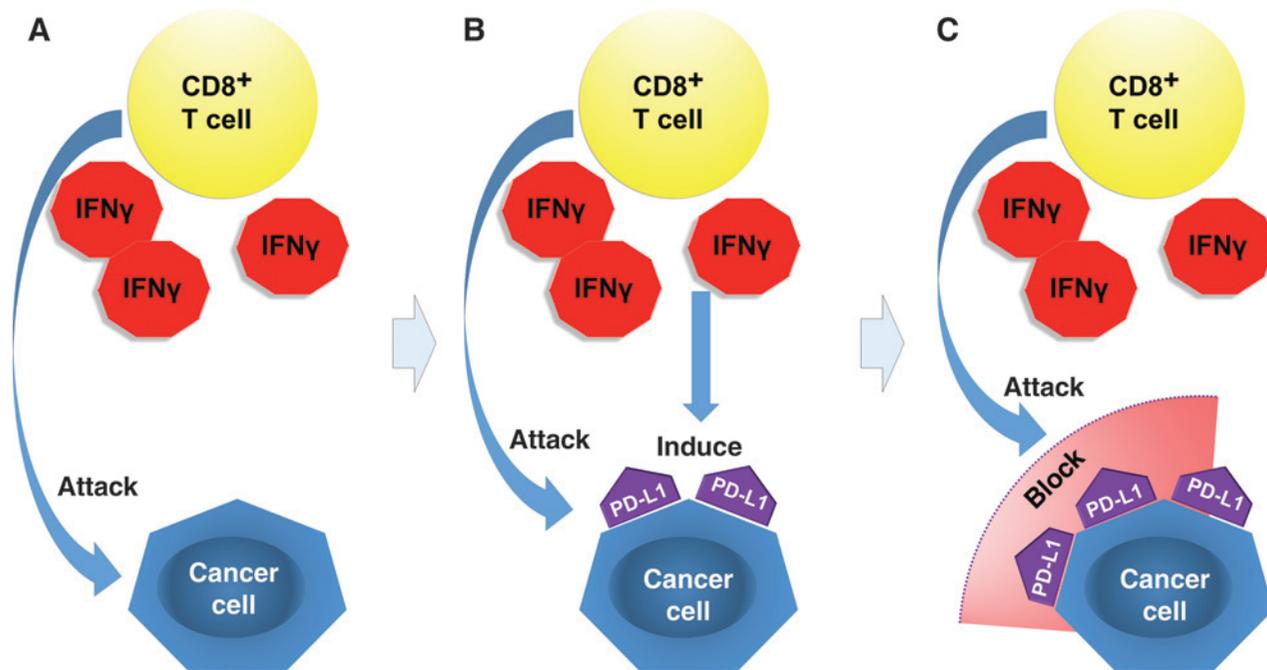
Anti-PD-L1/PD-1 therapy has been shown to be effective in clinical trials

Anti-PD-L1/PD-1 therapy is currently the focus of much attention in clinical oncology, and this therapy may change the conventional medical treatment strategy. Nivolumab and pembrolizumab are anti-PD-1 antibodies and have been approved by the FDA for the treatment of metastatic melanomas, and other chemicals, including anti-PD-L1 antibodies, have also been demonstrated to be effective in the treatment of various cancers, including malignant melanoma, non-small cell lung cancer, renal cell cancer, and hematologic malignancies (46). We have reported on the possible usefulness of nivolumab in treating ovarian cancer (47). These results suggest that PD-L1/PD-1 signaling plays not only an important biologic role but also an important clinical role in the treatment malignant tumors in terms of tumor immunity. However, how PD-L1 expression is induced and regulated in human cancers has not been clarified.

PD-L1 expression is induced by IFN γ secreted from T cells *in vitro*

Using an ovarian cancer model, we investigated the mechanism underlying PD-L1 expression (48). The expression of PD-L1 *in vitro* varied from high expression to no expression in human and mouse ovarian cancer cells as detected by flow cytometric analysis. However, in most of the human and mouse ovarian cancer cells, PD-L1 expression was strongly induced by IFN γ . Other cytokines, including IL2, IL6, and TGF β , did not induce PD-L1 expression *in vitro*. Next, we cocultured mouse ovarian cancer cells with

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**Figure 1.**

Induction of PD-L1 by IFN γ . A, IFN γ initially elicits antitumor cellular immunity by activating CD8⁺ cytotoxic T cells. B, however, IFN γ secreted from CD8⁺ T cells leads to the induction of the PD-L1 molecule on the surface of tumor cells. C, as a result, tumor cells become protected from cellular immune attack.

mouse CD8⁺ T cells recovered from the ascites of cancer-inoculated mice or with the supernatants of the ascites fluid. Notably, PD-L1 expression by the cancer cells was strongly induced by coculture with CD8⁺ T cells but not with the ascitic supernatant, which suggests that direct contact with T cells is necessary for the induction of PD-L1 (48). It is possible that paracrine exposure to the IFN γ secreted by T cells induces PD-L1.

PD-L1 expression is induced by IFN γ *in vivo* and attenuates local tumor immunity

We have demonstrated the correlation between PD-L1 expression and positive ascitic cytology in human ovarian cancer. Notably, when mouse ovarian cancer cells were inoculated in the mouse abdominal cavity and ascitic cancer cells were subsequently recovered, the expression of PD-L1 in the cancer cells was apparently elevated compared with expression in the cells cultured *in vitro* (48). On the basis of the *in vitro* findings, we speculated that direct contact with CD8⁺ T cells in the mouse abdominal cavity induced PD-L1 expression in the cancer cells via paracrine exposure to IFN γ . To test this hypothesis, the IFN γ receptor was knocked down in ovarian cancer cells using shRNA, and mice were intra-abdominally inoculated with these cells (49). The expression of PD-L1 by the IFN γ receptor–depleted cancer cells was reduced, which indicates that IFN γ also mediated PD-L1 expression *in vivo*. Consequently, CD8⁺ T-cell infiltration into the tumor site was significantly increased, and the survival of the mice was significantly improved compared with the mice inoculated with control mouse ovarian cancer cells, which suggests the recovery of antitumor immunity.

These findings indicate one of the mechanisms by which tumor cells escape immunity and survive despite an immunocompetent environment (Fig. 1). When tumor cells encounter T cells, they

detect them via the high concentration of IFN γ secreted from T cells, which induces PD-L1 expression on their surface in preparation for an immune attack. Consequently, local immune cells, especially tumor-specific CTLs, are paralyzed and become unable to attack the tumor cells. Thus, the IFN γ -dependent induction of PD-L1 could serve as a potent immune escape mechanism for cancer cells. This hypothesis is consistent with and partly explains the results of controversial clinical trials examining the efficacy of IFN γ treatment.

Future Directions for Cancer Immunotherapy Based on the Expression of PD-L1

IFN γ is thought to be a representative antitumor cytokine. However, IFN γ actually has dual roles: one as a hallmark of antitumor immunity and the other as an inducer of the immune escape phenomenon via PD-L1 expression. On the basis of these findings, we should consider the use of personalized immunotherapy according to the immune status of each case. For example, in cases with low IFN γ activity, active immunization either via IFN γ treatment or other methods, such as cancer vaccination, may be generally needed, and its further combination with anti-PD-L1/PD-1 therapy should be considered. In cases with high IFN γ activity and high PD-L1 expression, anti-PD-L1/PD-1 therapy alone is expected to be useful. We have shown that some chemotherapy reagents may induce PD-L1 expression in tumor cells (50). Therefore, during chemotherapy, using these drugs, the inclusion of anti-PD-L1/PD-1 therapy may augment the efficacy of the treatment. Although the actual immune condition of an individual patient might be complicated, a better understanding of tumor immunity, especially the effect of IFN γ in each case, should lead to the effective individualization of immunotherapy.

Collectively, an overview of the role of IFN γ in tumor immunity indicates that the local immune microenvironments of malignant tumors are complicated and variable. For effective future immunotherapy, a comprehensive understanding of local tumor immunity and the establishment of personalized treatments according to the evaluation of the immune status of each case appears to be necessary.

Authors' Contributions

Conception and design: M. Mandai, N. Matsumura, T. Baba
Development of methodology: M. Mandai, K. Abiko, T. Baba

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Hamanishi, K. Abiko, N. Matsumura
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Mandai, N. Matsumura, T. Baba
Writing, review, and/or revision of the manuscript: M. Mandai, T. Baba
Administrative, technical, or material support (i.e., reporting or organizing 626 data, constructing databases): J. Hamanishi, I. Konishi
Study supervision: I. Konishi

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Dual Faces of IFN γ in Cancer Progression: A Role of PD-L1 Induction in the Determination of Pro- and Antitumor Immunity

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