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IFN-γ: A cytokine at the right time, is in the right place

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Abstract

Interferon gamma has long been studied as a critical mediator of tumor immunity. In recent years, the complexity of cellular interactions that take place in the tumor microenvironment has become better appreciated in the context of immunotherapy. While checkpoint inhibitors have dramatically improved remission rates in cancer treatment, IFN-γ and related effectors continue to be identified as strong predictors of treatment success. In this review, we provide an overview of the multiple immunosuppressive barriers that IFN-γ has to overcome to eliminate tumors, and potential avenues for modulating the immune response in favor of tumor rejection.

Keywords

Interferon gamma; Tumor microenvironment; IL-12; Immunotherapy; Immunosuppression

1. Introduction

In recent years, we have witnessed enormous growth in the application of immunotherapy to treat various malignancies. Extending from a standard of surgery, chemo- and radiation therapies, remarkable improvements in response rates have been observed through the application of various antibody [1,2] and cell based therapies [3–5]. A major contributing factor to the efficacy of these treatments is mediated by the secretion of cytokines which activate and instruct cells of the immune system, as well as exert direct cytotoxic effects on tumor cells themselves. It was a consequence of the highly potent effects exerted by cytokines that they were first explored as treatments for different malignancies. The earliest FDA approved cytokine treatment was recombinant Interleukin-2 (IL-2), which arose from clinical trials demonstrating responses in renal cell carcinoma (RCC) and metastatic melanoma [6]. However, despite promising responses, these therapies encountered severe toxicities which curbed their acceptance as a viable therapy. Indeed, given the broad cytokine-sensitivity of cells spread throughout the body, including cells of hematopoietic and non-hematopoietic origin, systemic administration of cytokines is not well tolerated due to acute [7,8] and chronic adverse events [9,10]. Recognizing the challenges of systemic toxicity, efforts were undertaken to localize the delivery of cytokines, and to better

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understand the immunological activity of cells found within the tumor [11,12]. It was appreciated early on, that a good correlation existed between the anti-tumor activity of tumor infiltrating lymphocytes (TILs), and their capacity to secrete IFN-γ [13–15]. In very early adoptive cell therapy trials, transfusion of *ex vivo* expanded TILs and treatment with systemic IL-2 produced regression of tumors, and this was suspected to be a function of IFN-γ secretion [13,16]. Attempts at exploiting the potency of IFN-γ have yielded conflicting results, with both anti- and pro-tumorigenic effects being observed. Unfortunately, intravenous or sub-cutaneous administration of IFN-γ has not improved the outcome of melanoma [17], renal cell carcinoma [18], leukemia [19], pancreatic carcinoma [20], breast cancer [21], and colon cancer [22].

2. IFN-gamma biology

Following its discovery in 1965 as a soluble antiviral factor released by phytohemagglutinin-stimulated PBMC [23], Interferon gamma (IFN-γ) became well known for its pleiotropic immunomodulatory effects on both innate and adaptive immunity. As a soluble homodimer [24], IFN-γ has been shown to be secreted primarily by activated lymphocytes such as CD4 and CD8 T cells [25,26], gamma delta T cells [27], as well as NK [28,29] and NK T cells [30]. Additional sources include B cells [31–34] and antigen presenting cells (macrophages [35], monocytes [36] and dendritic cells [37]). IFN-γ signals through a heterodimer of IFNgR1/2, whose expression is broadly distributed among hematopoietic and non-hematopoietic cells alike [38]. Signaling is tightly regulated through controlled expression of IFNgR2 with stable expression of IFNgR1 among different cells [39,40]. This differential regulation of receptor subunits is thought to influence the balance between the mitogenic and growth inhibitory effects of IFN-γ [41]. Numerous antitumor effects of IFN-γ have been described, and include the regulation of antigen presentation, promotion of inflammatory and chemotactic signals [42,43], activation and polarization of responding leukocytes, as well as direct antiproliferative [44–46] and anti-angiogenic effects [47] (Fig. 1). Induction of angiostatic chemokines, CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC) by IFN-γ block neovascularization and also recruit effector leukocytes [48–50]. IFN-γ also antagonizes suppressive cytokine expression (TGF-β, IL-10), and favors the induction of IL-12 expression in macrophages [51,52]. IFN-γ signaling is able to repress tumorigenic M2-differentiation of macrophages [53]. Proapoptotic effects have also been attributed to IFN-γ [54,55]. Induction of TRAIL and its cognate receptor, a potent mediator of apoptosis in tumor cells, is also upregulated by IFN-γ [56,57]. Direct induction of caspase-1 and −8 in tumor cells by IFN-γ is also an effective inducer of apoptosis [58,59]. Tumor cell apoptosis is also induced through upregulation of Fas and FasL [60,61]. Generation of reactive oxygen species and nitric oxide are potent cytotoxic effectors that are also regulated by IFN-γ [62,63].

Secretion of IFN-γ by tumor infiltrating lymphocytes (TILs) results in the upregulation of antigen presentation in dendritic cells and macrophages [42,64]. IFN-γ also upregulates specific components of the immunoproteasome thereby producing unique peptides for MHC-I presentation [65–67]. In macrophages and dendritic cells, IFN-γ upregulates MHC-II expression through activation of MHC class II transactivator (CIITA) [68,69]. Acting on APC, IFN-γ upregulates expression of costimulatory molecules and cytokines which are

necessary for activation of T cells [70]. In tumor cells, IFN-γ also induces the expression of MHC-I and STAT1 associated cyclin dependent kinase resulting in apoptosis of tumor cells and immune recognition [47,71]. Underscoring the requirement for IFN-γ in eliminating tumors, many studies have utilized various genetic and antibody blocking approaches to demonstrate both the direct [72,73] and indirect [74] aspects of IFN-γ-mediated tumor suppression.

Contrary to the many antitumorigenic effects exerted by IFN-γ, protumoral effects have also been observed. This activity is thought to occur primarily through a loss of IFN-γ signaling sensitivity, reduced antigen presentation [75] and induction of indolamine 2, 3-dioxygenase (IDO) [76] and checkpoint inhibitors [77]. Resistance to IFN-γ mediated cytotoxicity and cytostasis can be mediated by mutations in JAK-STAT signaling and antigen processing proteins [78–80]. A loss of IFN-γ signaling reduces MHC-I induction. Additionally, tumor-associated methylation of the IFN-γ promoter reduces MHC-I expression in tumors tissues [81]. The loss of IFN-γ responsiveness in tumors is associated with lower antigenicity [72]. Along with the aberrant expression of the coinhibitory molecule, PD-L1, in tumor tissues [82,83], its expression is also induced through exposure to IFN-γ [84,85]. Interestingly, the duration of IFN-γ exposure also dictates the responsiveness of tumors to immune suppression, with chronic exposure producing a loss of sensitivity known as “adaptive resistance” [77].

3. IL-12 biology

A major inducer of IFN-γ is IL-12, and the expression of both genes is coordinated (i.e. IL-12 induces IFN-γ, and IFN-γ induces IL-12). IL-12 exerts potent immunomodulatory effects of cells of innate and adaptive immunity. Secreted as a biologically active 70 kDa heterodimer, IL-12 is composed of disuphide linked alpha (p35) and beta (p40) subunits [86]. Binding to its cognate heterodimeric IL12RB1/2 receptor induces signaling via Jak-mediated phosphorylation of STAT4 [87,88]. Signaling through STAT4 induces the expression of IFN-γ [89] (Fig. 1). During the activation of naïve CD8 T cells, IL-12 provides a third signal, alongside TCR and CD28 costimulation which improves clonal expansion and cytolytic activity [90,91]. Proliferative responses to IL-12 can be influenced by induction of CD25, a necessary component of IL-2 signaling [92]. Other significant effects of IL-12 include the induction of T cell, NK and NK T cell cytolytic activity, and enhanced antigen presentation [93]. Many of the IL-12 mediated effects are exerted through inducible IFN-γ expression and the skewing of CD4 T cells to a Th1 phenotype [94,95]. Induction of IFN-γ in T cells initiates a positive feedback loop whereby IFN-γ sensitive APCs are primed to produce additional IL-12 [96]. Synergy between IL-12 and IL-18 has also been demonstrated to strongly induce IFN-γ in B cells [33,34]. IL-12, and other cytokines have been shown to enhance the CTL activity of T cells through increasing the sensitivity to weak or self antigens [97,98]. This has been one explanation for the development of autoimmunity developing during microbial infections, as there is often an abundance of IL-12 present at the site of infection [99]. IL-12 is mainly produced by APCs (dendritic cells, monocytes, macrophages and B cells) and can be activated by various TLR signals. This effect is currently being explored as a potential mechanism to boost anti-tumor immunity [100–103]. However, opposing effects have also been observed where TLR

ligands can promote a tolerogenic response in DCs through the upregulation of IL-10 and TGF-β [104]. Signals that inhibit IL-12 production include IL-10 and TGF-β, and these same signals also inhibit IFN-γ [105,106].

4. Tumor microenvironment

As our understanding of tumor immunology has advanced, we have appreciated that various malignancies exert profoundly suppressive cues toward anti-tumor immune cells [107–110] (Fig. 1). The tumor microenvironment, once formed, is a formidable obstacle for innate and adaptive immunity to overcome. Prominent barriers to elimination include the tumor promoted conditioning of immunosuppressive cells such as T_{reg}, MDSC and M2-macrophages, as well as limited antigen presentation, upregulation of T cell suppressive signals (e.g. PD-1/L1 and CTLA-4) and metabolic cues.

One prominent inhibitory molecule that is produced in tumors, and is associated with poor outcome, is IL-10, a potent anti-inflammatory cytokine [111,112]. Within the tumor microenvironment, tumor cells themselves have been shown to express IL-10 [113,114] in addition to infiltrating hematopoietic cells of myeloid [115] and lymphoid origin [116]. Regulatory CD4 T cells (T_{reg}) are also significant sources of IL-10 in tumors, and their presence in high proportion relative to CD8 T cells is indicative of poor prognosis [117–119]. Opposing effects of IL-10 have been observed, where a decrease in antigen presentation is detected in CD4 T cells [120,121] and macrophages, and a stimulatory effect is observed in CD8 T cells [122–125]. Cross-regulation between cytokines has been shown to exist between IL-10 and IFN-γ [126]. Depending on the timing and magnitude of expression, both cytokines can interfere with one another. IL-10 has been clearly shown to mitigate the effects of IFN-γ in antigen presentation through down regulation of MHC-II, costimulatory molecules and proteolytic enzymes [127–132]. This effect is mediated by interference with IFN-γ signaling through the Jak-STAT and NFkB transcriptional pathways [133,134]. In macrophages, IL-10 mediates downregulation of costimulatory molecules and MHC-II through the induction of March-1, an E3 ubiquitin ligase, which specifically targets these critical molecules for proteolytic degradation [135]. Mirrored in T cells, IL-10 also inhibits tyrosine phosphorylation and activation of CD28 [136]. IFN-γ exerts a strong antagonism towards IL-10 through transcriptional suppression [137]. Suppression of IL-10 in CpG-stimulated DCs was accompanied by a strong induction of IL-12 expression [138]. A number of studies have also provided evidence for the suppressive effect of IFN-γ towards T_{reg} stability [32,139,140].

Another contributor to tumor immunosuppression is myeloid derived suppressive cells (MDSC), which are activated through inflammatory processes and serve to dampen immune responses. MDSC secrete various immunosuppressive molecules including arginase (ARG1), iNOS-2, TGF-β, IL-10, COX2 and indoleamine 2, 3-dioxygenase (IDO) which sequesters tryptophan and decreases L-selectin expression on T cells [141–144] (Fig. 1). Of interest is the fact that IFN-γ induces many of these genes, thus it's actions enhance the host immune response but also damped the response if IFN-γ signaling is prolonged. Both arginase and iNOS2 utilize L-arginine as a substrate, and thus deplete its availability to T cells, which limits their functional capacity. Surface expression of ADAM17 on MDSC

cleaves L-selectin (CD62 L) and interferes with homing to lymph nodes [145]. Production of ROS can interfere directly with TCR activation and chemokine activity through protein nitration [146,147] (Fig. 1). In macrophages, nitration of STAT1 has also been suggested to limit IFN-γ inducible signaling [148]. Additionally, MDSC promote tumorigenesis through expression of VEGF, bFGF, Bv8 and MMP9 which have been shown to be angiogenic [149,150].

Tumor-associated macrophages are another significant leukocyte population commonly found in tumors, and can be generally defined by their pro- or anti-inflammatory function [151,152]. Pro-inflammatory M1-type macrophages can suppress tumor growth through production of IL-1, IL-6, IL-12, TNF-α and upregulation of antigen presentation and costimulatory molecule expression [153]. Their development is promoted by the presence of IFN-γ, GM-CSF or LPS [154]. In contrast, anti-inflammatory M2-type macrophages produce abundant IL-4, IL-10, TGF-β, prostaglandin E2 and VEGF which favor tumorigenesis. Environmental factors which influence the development of M2-type macrophages include tumor secreted IL-4, IL-13, IL-10 and M-CSF [152]. Additionally, their development is also favored by exposure to lactic acid and contact with apoptotic cells or damage-associated molecular patterns (DAMPs) which are distributed through tumor tissue [155,156]. The presence of M2-type macrophages is correlated with poor prognosis in a variety of malignancies [157,158].

Co-inhibitory molecules are normally upregulated on activated T cells following stimulation. These signals serve to limit excessive inflammation, and exert negative feedback. In animals lacking co-inhibitory molecules, or during administration of checkpoint inhibitors in the clinic, autoimmune-like pathologies have been documented [159]. However, in tumors, these regulatory mechanisms limit the development of a robust response. Consequently, a number of co-inhibitory signaling molecules (PD-1/-L1, CTLA-4 and others) have been investigated in the context of boosting anti-tumoral immunity [160,161]. The expression of these markers correlates well with the degree of unresponsiveness. PD-1 is expressed on the surface of activated T cells, and directly attenuates CD28-mediated signaling through the recruitment of phosphatases to TCR-proximal signaling complexes [162] (Fig. 1). CTLA-4 is also upregulated on the surface of activated T cells, but interferes with CD28 costimulation through distinct mechanisms from PD-1 [162,163]. During chronic viral infection, or in tumors, where persistent exposure to antigen can occur, the degree to which T cells are stimulated with antigen, corresponds with their loss of functional capacity [164]. Continual TCR signaling leads to a reduced rate of remethylation at the PD-1 locus, thereby reinforcing expression and potentiating inhibitory effects [165]. A progressive loss of proliferative capacity and IL-2 production by T cells is followed by a failure to produce TNF-α and IFN-γ. This process, termed exhaustion, is not a terminal cell fate, and can be reversed in vivo through the blockade of co-inhibitory receptors [161,166]. Indeed, FDA-approved monoclonal antibodies directed against PD-1, PD-L1 or CTLA-4 have proven effective at interfering with the immunosuppressive effects that are exerted by tumor tissues on cytotoxic T cells [167]. Additional co-inhibitory receptors such as Lag-3, Tim-3, BTLA, CD160 and 2B4 are being explored in clinical and pre-clinical development [168,169].

Another hallmark of the tumor microenvironment is dysregulated metabolism, where glucose is utilized through aerobic glycolysis instead of oxidative phosphorylation. This process, known as the Warburg effect, produces considerable secreted lactate (lactic acid) which signals though GPR81 on surrounding tumor cells to induce PD-L1 expression [170] (Fig. 1). Lactate also strongly inhibits the expression of cytolytic effectors granzyme B and IFN-γ in CD8 T cells [171]. Additionally, given the rapid consumption of glucose by tumor cells, it's reduced availability limits T cell function [172]. This metabolic restriction is sensed by the metabolic enzyme and RNA binding protein, GAPDH, which, in turn, binds to the AU-rich regions of the 3′ UTR of IFN-γ transcripts and reduces expression [173]. Interestingly, glucose deprivation exerts a stronger inhibitory effect on IFN-γ expression than IL-2 [174].

5. Overcoming immunosuppression

With increasing usage of checkpoint inhibitors, our understanding of their mechanistic role in facilitating immune-mediated tumor clearance is becoming better understood. Certainly, an IFN-γ-associated gene signature was shown to be necessary for clinical benefit during PD-L1 blockade [175]. In a recent structural study of IFNγR activation, Mendoza et al. identified synthetic IFN-γ mimetics that were able to specifically activate signaling to upregulate MHC-I expression in tumor cell lines, without upregulating the immunosuppressive molecule, PD-L1 [176]. This decoupling of immunostimulatory and immunosuppressive effects certainly opens exciting possibilities for development. A recent study by Garris et al. highlighted the critical function of PD-1 blockade in enabling the amplification of IL-12 and IFN-γ reciprocal regulation to permit an effective anti-tumoral response [177]. In the context of adoptive T cell therapy, *ex vivo* activation and expansion of T cells in the presence of IL-12 has improved CTL activity [178–180]. This effect has been attributed to dampening the negative regulatory effects exerted by IFN-γ. Specifically, a reduction of PD-1 expression in T cells limited the suppressive effects of IFN-γ-inducible PD-L1 expression in tumor tissues. Additionally, a decrease in IFN-γR2 expression on expanded T cells also reduced the negative autocrine effects of IFN-γ expression [181].

Given the importance of IL-12 in augmenting IFN-γ expression, and the cytolytic activity of T cells, its incorporation into immunotherapy regimens is still being pursued with emphasis on targeted delivery. Systemic administration of IL-12 has shown limited success, with numerous adverse events being observed in clinical trials, likely a consequence of off-target effects, as well as poor pharmacokinetics [182–184]. To target IL-12 expression to the tumor microenvironment, plasmids encoding IL-12 have been introduced via electroporation [185,186], intratumoral injection of viral vectors encoding IL-12 [187], engineered tumor-specific T cells expressing IL-12 [188–195] and intratumoral injection of microspheres containing slow-release IL-12 [196,197]. Recent attention has been given to an IL-12-fused anti-his-tone antibody (NHS-IL12) which targets sites of cell necrosis where free cellular DNA is abundant. When combined with radiation therapy in a mouse model, a significant anti-tumor immune response was observed alongside increased survival [198,199]. More recently, in a phase I clinical trial, NHS-IL12 was well tolerated, and was accompanied by an indication of anti-tumor immunity [200].

6. Conclusions

Coupled with an increasingly sophisticated understanding of anti-tumor immunity, the powerful tools of molecular immunology are allowing us to develop innovative new therapies to treat cancer. We have already seen encouraging improvements in potency of immunotherapy, and it is clear that many targets still exist for intervention. Given the complexity of tumor-mediated immunosuppression, it is very likely that integrating multiple facets of tumor immunity will be necessary to overcome the existing barriers. The pleiotropic nature of IFN-γ underscores this, and certainly maintains it as an attractive candidate for development, despite previous challenges. To better reflect a natural mechanism of localized activity, it is critical that the delivery of the right treatment is to the right place. Indeed, the continued honing of immunotherapy will undoubtedly yield more effective and better tolerated therapies in the clinic.

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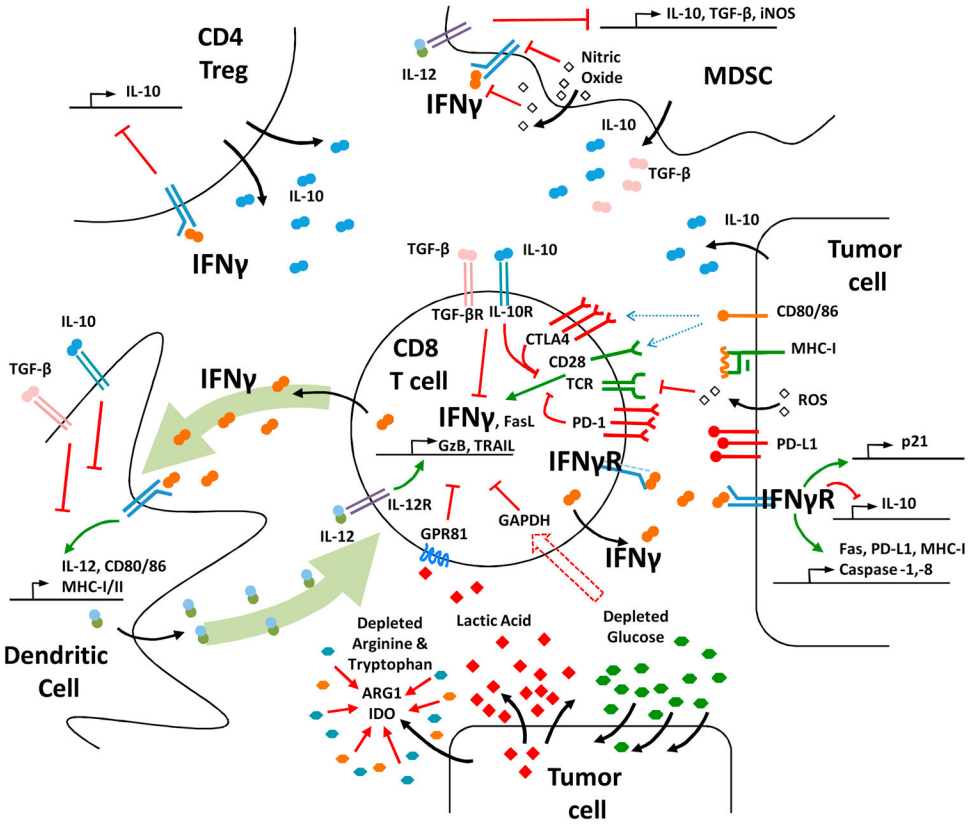

Fig. 1.

IFN-γ exerts pleiotropic effects to overcome tumor immunosuppression.

The tumor microenvironment exerts strong antagonism toward infiltrating lymphocytes through various cytokine, receptor and metabolic processes. To overcome these pathogenic barriers, IFN-γ and IL-12 operate in concert to amplify an anti-tumoral response through dampening immunosuppressive signals and increasing cytolytic effector function and direct antiproliferative signals.