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IMMUNE REGULATORY FUNCTION OF INTERFERON-GAMMA IN ACUTE LEUKEMIA

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ABSTRACT Programmed death ligand-1 (PDL-1) is an immune regulatory component that is expressed on normal cells, tumor cells, and non-tumor immune cells. The expression of these checkpoint components on the cell surface helps prevent the immune system's overactivity. PDL-1 is associated with immune evasion in many solid tumors and lymphomas, while its clinical significance is under exploration in leukemias. Structural and regulatory aspects are recently presented in reports that define the role of signaling components in regulating PDL-1. Immune interactions of soluble cytokines such as IFN-γ & TNF-α with PDL1 show relevance in liquid malignancies. Recent reports have shown that interaction occurs between IFN- γ and PDL 1, but the exact mechanism is not defined. PDL1 expression around 20-25% across the malignancies has put this immune checkpoint in clinical trials, and many solid malignancies have shown better clinical outcomes and survival rates. Still, resistance remains a significant hurdle. Immune resistance is the primary reason for the minimal impact of PDL-1 blockade therapy in various cancers. IFN-γ induced PDL1 immunotherapy could be effective in leukemias to overcome the resistance and provide effective immune responses and overall better clinical outcomes.

KEYWORDS : Acute Leukemia, Programmed death ligand-1, Interferon-gamma, Resistance, Immunotherapy

INTRODUCTION

AML is a bone marrow-derived heterogenous, clonal disorder that is characterized by blast cells in the bone marrow or blood (>20%) and the most common acute leukemia in adults with an 80% prevalence. (1) Blood factors such as cytokines interact with these growing blast cells and drive different clinical consequences. These fast-growing tumors interact with multiple factors in the budding tumor microenvironment that suppress the immune cells and mimic their central regulatory units – Immune checkpoint molecules. These cancer cells hijack cell regulatory machinery and use it for their growth. One of the machinery is the immune checkpoint system which is mainly expressed in immune cells to balance the destructive capacity of immune effector cells.

PDL-1 is one of the main components of the immune checkpoint system and is expressed by immune cells, epithelial cells, and tumors. While proliferating, Tumor cells express this protein on their cell surface and inhibit the PD-1 expressing effector T cells. This interaction of PDL-1-PD-1 sends the inhibitory signals into T cells. They get exhausted in the vicinity of the tumor micro-environment. That is one of the reasons for the high number of exhausted T cells found in many solid tumors. (2) Meanwhile, PDL-1 acts as an anti-apoptotic factor for tumor cells by inhibiting pro-apoptotic factors, including interferon-gamma. There is a link between PDL-1 and IFN-γ pathway in both positive and negative ways at different cellular levels. This link is presented throughout the literature in many cellular mechanisms and cancers. (3) (4) Interactions of PDL-1 with its receptors (PD-1, CD80) are a complex matter and depend on various factors. Regulation of PDL-1 at genetic, epigenetic, transcriptional, post-transcriptional, translational & post-translational levels is done by many factors whose interplay gives a final expression status of this protein.

In many tumor types, PDL-1 is considered as a prognostic factor, and PDL-1 blockade therapy for various cancers is approved while many clinical trials are under progress. In this review, we provide a combination of biology, clinical significance, and recent progress in the role of IFN-γ in PDL-1 expression in leukemia and why IFN-γ and PDL1 show significance in leukemias.

IFN-γ mediated PDL-1 expression

PDL-1 prevents apoptosis in tumor cells by inhibiting the proapoptotic signals. (5) It is well-known that IFN-γ is a potent transcriptional activator of PDL-1 (6)**,** and inhibition of this IFN-γ pathway would prevent the adaptive PDL-1 expression. IFN-γ is a cytokine with antiviral, antiproliferative, and immunomodulatory effects and helps fine-tune the immune responses by activating the immune system. (7) There are well-known cellular pathways and their mechanisms through which IFN-γ acts on the cells and affects their functions. Mainly the JAK/STAT1 pathway is used by cells for their action through this cytokine. (8) On proper signals from stressed cells, IFN-γ is secreted by immune cells and helps maintain the immune response in inflammation and cancer.

A recent report on multiple myeloma patients showed the potential activity of IFN-γ to induce or activate the expression of PDL-1 in CD138 purified plasma cells via STAT1 activation, via MEK/ERK, and MyD88/TRAF6 pathway, and the inhibition of T cells. (9) Subsequently, in AML, a similar report showed the increased expression of PDL-1 on blast cells by IFN-γ & TLRs via the same pathway and showed the inhibition of T cells. These effects were abrogated and restored the function of cytotoxic T cells by using small molecules against this pathway (MEK inhibitors). (10) In lung cancer cell lines, the IFN- γ showed the PDL-1 promoting function by JAK/STAT3 and PI3K/AKT signaling pathways and cancer progression. (11)

Furthermore, in melanoma cells, the IFN-γ upregulates the expression of PDL-1 & PDL-2 by JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis, which provides the insight that these pathways could be used for patient selection in PD-1/PDL-1 blockade therapy. (12)

Furthermore, in a recent report, non-responding patients of melanoma to anti-CTLA-4 therapy have mutations in the IFN-γ pathway. (13) Mutations in IFNGR and JAK1/2 are associated with a high tumor burden and lower response to immune checkpoint therapy. IGN-γ is an anti-tumor proliferation and apoptosis cytokine which, on the induction by certain factors, gets secreted by T cells and inhibits tumor progression by either killing or developing apoptosis in tumor cells. Its pathway mutations stop its function in cancer but are used by tumor cells to develop resistance to chemo or immunotherapy. Studies have shown that IRF1 increases the PDL1 expression in melanoma cell lines, and immune therapy resistance can be due to mutations in the IFN-γ pathway. One other reason could be the incapability of immune effector cells to restore their functions due to IFN-γ mutations as it is the activator for immune cells. (14)

Understanding the mechanistic expression of PDL-1 across tumor types has devised that IRF1 is the key transcriptional regulator of PDL-1 expression by IFN-γ. Furthermore, epigenetic regulators, BET proteins, mainly BRD4, co-regulate the IFN-γ induced PDL-1 expression with IRF-1 (15)**,** and BET inhibition significantly induced the anti-tumor immunity in different tumor types. This indicates that IFN-γ has a strong positive correlation with PDL-1 expression, and IRF1 & BRD4 are the central transcriptional and epigenetic regulators for this system.

The above data indicate that IFN-γ is a crucial factor for immunotherapy in cancer. Mutation in its pathway develops resistance to immunotherapy. Furthermore, IFN-γ activates PDL1 expression on tumor cells which can be used for immunotherapy and activate the T effector cells for immune response in cancer.

IFN-γ pathways: PDL-1 dependent & independent resistance to immunotherapy

IFN-γ mainly potentiates PDL-1 expression with the STAT1 pathway,

and STA3 plays a significant but small inductive factor. STA3 induced the PDL-1 expression on mature blast cells with IFN-γ in AML/MDS. This expression seemed less effective than STAT1 with JAK1/JAK2. (16)

Studies in malignant melanoma showed that resistance to anti-PD-1 therapy is associated with a mutation in IFN-γ receptor-associated JAK1/JAK2. (6)

IFN-γ signaling is associated with PDL-1 mediated resistance to immunotherapy, where IFN-γ receptors and downstream signals, mainly STAT1, are associated with this PDL-1 dependent resistance mechanism. There are other PDL-1 independent mechanisms to immunotherapy rendered by IFN-γ signaling. Recent reports on melanoma tumors demonstrated that prolonged signaling by IFN-γ is associated with multigenic resistance mechanisms independent of PDL-1 and STAT1& IFN-γ target genes are associated with this resistance. Targeting this IFN- γ pathway can help to improve treatment without the requirement of combinatorial therapy. (17)

PDL-1 protects the tumor cells from IFN-γ activity

PD-L1 can protect tumor cells from the cytotoxic effects of type I and type II interferons, and cytotoxic T lymphocyte (CTL) mediated cytolysis with no requirement of PD-1 signaling in T cells. (18). In physiological or infectious conditions, PDL-1 is expressed by antigen-presenting cells and PD-1 on T cells. The expression of PDL-1 is also found on other types of cells based on pathophysiological conditions such as tumor cells. PDL1 uses its conserved sequence motif to overcome the IFN-γ activity and prevents apoptosis of tumor cells. (5) **(8)** The exact tumor microenvironment is unclear when IGN-γ helps promote the PDL1 expression or when PDL1 inhibits the IFN-γ expression to avoid apoptosis.

PDL-1 interacts with other CD28 family members, mainly CD80 (T cells), and sends the signals to inhibit PD-1/CTLA-4 inhibitory signals that activate the pro-immunity CD28 signaling. (19)

This fundamental role of PDL-1 has been a part of the debate for a long time. Recent research found that it may inhibit or activate the immune system based on tumor type, microenvironment, signaling components, & expression of co-molecules. These conflicting reports on the interaction of IFN-γ and PDL1 have provided the basis that certain microenvironmental conditions, levels of IFN-γ, and involvement of different immune cells are necessary components to define its exact function and particular mechanism of immune modulation. Indeed, a robust model is required to determine the precise functional mechanism of IFN-γ in cancer.

Why this interaction makes relevance in leukemia?

As a liquid malignancy, leukemia blast cells are more effectively moving in the blood and interact more with blood cytokines (IFN-γ). As reports have established in leukemia, IFN- γ interacts with PDL1 and affects overall immune balance.

Their interaction increases the PDL1 expression, which could be understood as follows-

- IFN-γ treatment would create more scope for PDL1 blockade in leukemia by stimulating PDL1 expression on blast cells and acting as a activation signal for immune cells
- Blood cells are highly accessible to IFN-γ treatment, so with enough levels of blast population, PDL1 and IFN-γ could provide an excellent combinatorial therapy.
- There are studies where IFN-γ pathway blockade provides good outcomes in different malignancies, and intervention with IFN-γ in vitro and in vivo leukemia studies could give insights into the mechanical function of both PDL1 and IFN-γ.

IFN-γ versus small-molecule inhibition

As IFN-γ increases, the expression of PDL1 by specified pathways in leukemias and the use of small-molecule inhibitors in these pathways restore the function of immune cells. PDL1 expression only comprises 20-25% of leukemia patients and could only benefit this set of patients. On the other hand, the use of IFN-γ to increase PDL1 expression in leukemia could be used for potential treatment with PDL1 immunotherapy. Also, PDL1 protects tumor cells from IFN-γ mediated apoptosis without PD-1 interaction, indicating that a certain level of IFN-γ could be established to get proper PDL1 expression across leukemia cells and activate immune cells.

PDL-1 in Acute leukemia: clinical significance

PDL-1, as an immune checkpoint molecule, has been associated with worse clinical outcomes in various cancers. PDL-1 is a well-established immune inhibitory molecule expressed on tumors and associated cells (e.g. MDSCs, DCs). PDL-1 in acute leukemias has been highly expressed on blast cells and is associated with poor clinical outcomes. (20)

Combinatorial therapy of anti-PDL-1, anti-CXCR-4 with conventional chemotherapy Ara-C improved the survival rate of the AML mice model. Suppression of myeloid blast cells in spleen & bone marrow tissues was found overwhelming compared to wild type, Ara-C only or Ara-C & plerixafor. (21) Recent studies showed that PDL1 expression on non-malignant stromal cells in leukemia has poor overall survival than no PDL1 expression. (22)

Currently, there are 1000 clinical trials in progress for PD-1/PDL-1 targets. Anti-PD-1 mAbs (nivolumab & pembrolizumab) and two anti-PD-L1 monoclonal antibodies (atezolizumab and durvalumab) are used in these trials. (23) Role of IFN- γ in PDL1 expression is depicted in figure 1.

Scope for IFN- γ in leukemia

Recent reports on IFN- γ and its activity of PDL1 expression give an understanding that there is a scope to use a combinatorial therapy of PDL1 inhibition and IFN-γ in cancer. The present reports on IFN-γ in cancer are unclear, and more studies are required to define its role. Though the reports on IFN-γ pathway inhibition in cancers have shown promising outcomes, its function is not yet determined. To define its proper role, it can be studied as a treatment component with PDL1immunotherapy or its pathway inhibition in leukemia. Further evaluation of the IFN- γ pathway can help to define the resistance mechanisms and associated factors. Also, screening patients with IFN-γ pathway mutations could provide the different populations for selections of patients with or without mutations. They can help define the resistance mechanisms and choose combinatorial therapy.

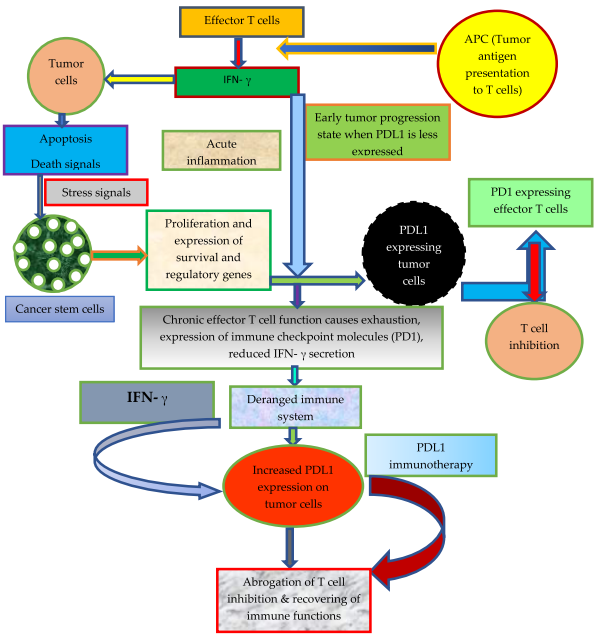

Figure1: Role of IFN- γ in PDL1 expression and PDL1 immun otherapy

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