

PD-1/PD-L Pathway: Its Preclinical Rationale and Clinical Application in Lymphoid Neoplasms

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Received: June 26, 2017; Published: June 29, 2017

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Abstract

The PD-1/PD-L1 pathway plays an important role in mediating immune tolerance in physiological state and is an important mechanism by which malignancies can evade the host immune response. PD-1 inhibitors may be particularly attractive for hematologic malignancies because the activation of adoptive immunity has been proven effective in the form of allogeneic stem cell transplantation. Clinical trials of anti-PD-1 monoclonal antibodies have demonstrated promising results in lymphoma patients with advanced disease.

Abbreviations: PD-1: Programmed Death-1; FL: Follicular Lymphoma; cHL: Classical Hodgkin Lymphoma; BL: Burkitt Lymphoma; DLBCL: Diffuse Large B-Cell Lymphoma; PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; PTEN: Phosphatase And Tensin Homologue; PCNSL: Primary Central Nervous System Lymphoma; PTL: Primary Testicular Lymphoma; HRS: Hodgkin And Reed-Sternberg; TCL: T-Cell Lymphomas

Introduction

PD-1

Is a 55-kDa type I transmembrane protein that belongs to the immunoglobulin superfamily. PD-1 exists as a monomer on the cell surface of activated T cells, B cells, natural killer T cells, monocytes, and some dendritic cell subsets. PD-1 delivers a co-inhibitory signal upon binding to either of its two ligands, PD-L1 or PD-L2 [1]. PD-L genes have been shown to be key targets of structural amplification of chromosome 9p24.1 [2].

PD-L1 and PD-L2 expression

PD-L2 expression is mostly restricted to hematopoietic cells while PD-L1 is expressed on hematopoietic cells and peripheral tissues as well as many malignant cells, and [2] immune regulatory cells of the tumor microenvironment, such as myeloid-derived suppressor cells that may work in concert with malignant cells [3].

In the physiologic setting

The PD-1/PD-L1 pathway plays a critical role in maintaining immunologic equilibrium after initial T-cell response, which prevents over activation, collateral tissue damage, and the inappropriate expansion of auto reactive T-cell populations [3]. PD-1 is also a negative regulator of B cells [1].

PD and PD-L and lymphoid malignancies:

Genetic alterations, transcriptional activation by certain oncogenic signaling pathways, viral infection, and inflammatory cytokines contribute to the constitutive expression of PD-Ls by tumor cells [1].

In cHL

PD-1 is expressed on tumor-infiltrating and peripheral T cells, whereas PD-ligands are frequently expressed by HRS cells and tumor infiltrating macrophages. PD-L1 over expression is not commonly seen on **B NHL** cells. PD-L1 over expression has been described in the non-germinal center B cell-like type of DLBCL [2]. PD-L1 is also expressed by MCL cell lines and in FL tumor microenvironment. Preclinical data confirms PD-1 and PD-L1 expression in peripheral **TCL** [2]. Also, in NK/T cell lymphoma and lymphomatoid granulomatosis [4] PD-1 is expressed on both T and **CLL** cells, while PD-L1 is highly expressed in the different compartments of the tumor microenvironment, including CLL cells [2].

PD-1 is expressed on circulating T cells of advanced **myeloma** patients and its expression is reduced in patients achieving a minimal disease state following high-dose chemotherapy. PD-L1 is highly expressed on plasma cells of MM patients while it is not expressed on normal plasma cells, plasma cells in monoclonal gammopathy of undetermined significance. PD-L1 expression is up regulated on plasma cells in relapsed and refractory disease which suggests its role in clonal resistance development [3].

In malignancy

Up regulation of PD-1/PD-L1 pathway prevent the activation and function of tumor-reactive T-cell populations, which contributes to immune escape and tumor growth [3] and produces a tumor-permissive microenvironment [1].

The cellular composition of the Tumor Microenvironment

Generally mirrors that of the normal tissue at the site of development [5] with significant heterogeneity between the lymphoma subtypes. Tumor cells retain a degree of dependence on interactions with non-malignant cells and stromal elements of the tumor microenvironment that promote tumor escape from immune surveillance and disease progression [5].

Three major models for tumor microenvironments have been proposed in B-cell lymphomas.

- i. The first, re-education: is typified by FL, in which malignant cells retain dependence on the microenvironment for survival and proliferation signals;
- ii. The second, recruitment: is observed in cHL in which the infrequent Reed-Sternberg cells are surrounded by an extensive support milieu of nonmalignant cells that is distinct from the composition of normal lymphoid tissue;
- iii. The Third, effacement: is seen in BL and to some extent in DLBCL, whereby genetic aberrations, within the malignant cell lead to autonomous, microenvironment-independent growth and survival [5].

Prognostic value of alteration in PD-1/PD-L1 pathway:

- a. The prognostic impact of PD-1 expression on survival in FL tumor microenvironment has shown controversial findings.
- b. PD-L1 over expression in the non-germinal center B cell-like type of DLBCL was found to be a predictor of poor OS.
- c. sPD-L1 might be a biomarker for response to treatment in CLL.

PD-L1 expression on tumor-cells has been shown to be inconclusive predictive marker in solid tumors. This might be due to complex dynamics of expression depending on the tumor microenvironment and the lack of standardized immunohistochemistry [2].

Anti-PD-1 Therapy

PD-1 inhibitors may be particularly attractive for hematologic malignancies because activation of adoptive immunity has been effective in the form of allogeneic stem cell transplantation [1]. It enhances T-cell activity; restores NK cell activity, and induces PD-L1+ B-cell antibody production thus blunt the inhibition of tumor-specific immune response [1]. To date, PD-1 inhibitors have been evaluated only in relapsed or refractory disease, with encouraging response rates particularly in cHL, and also in FL and DLBCL [2]. Nivolumab, a fully humanized IgG4 blocking monoclonal antibody against PD-1 [1], was approved in May 2016 by the US Food and Drug Administration for treatment of cHL [6]. HSCT after PD-1 blockade appears feasible with a low rate of relapse. However, there may be an increased risk of early immune toxicity, which could reflect persistent depletion of PD1+ T cells and alterations in T-cell differentiation triggered by prior PD-1 blockade which impact subsequent treatment [6].

Toxicity of anti PD-1:

- a. ORR around 20-50% could be achieved with anti PD-1. Adverse events occurred in up to 60% of patients but grade 3/4 toxicity occurred in <10% of cases. Immune related adverse events including thyroid dysfunction, hepatitis and pneumonitis are more serious and may lead to cessation of treatment [7].
- b. Immune related pneumonitis occurs in <5% of patients with anti-PD-1 monotherapy, but severe clinical presentations and cases of treatment-related death make this complication of an utmost concern of many clinicians [2].
- c. Another immune-related adverse event of particular interest is the development or worsening of GvHD after allogeneic SCT in a subset of patients. Severe GvHD was documented in patients undergoing allogeneic SCT after treatment with nivolumab in the phase I trial [2].

Future direction

- a. Clinical trials of anti-PD-1 monoclonal antibodies have demonstrated promising results in lymphoma patients with advanced disease [6].
- b. The combination of ibrutinib and an anti-PD-L1 antibody showed synergistic effects in a mouse model resistant to either agent given alone [2].
- c. PD-1 blockade might be efficient in controlling human immunodeficiency virus infection. This renders anti-PD-1 antibodies interesting agents in human immunodeficiency virus-associated lymphomas. Epstein-Barr virus -related lymphomas might be susceptible to a similar approach [2]. This is consistent with the ability of the virus to usurp the PD-1 pathway [2].
- d. Based on the shared genetic characteristics of PCNSL and PTL which are [8] unique high frequency of 9p24 copy gain and increased PD-1 ligand expression, as well as chromosomal translocations resulting in PD-L1/PD-L2 deregulation [9], it was hypothesized that PD-1 blockade was a rational therapeutic approach in relapsed and refractory [10] PCNSL and PTL [9].

Conclusion

The immunological milieu of both host and tumor should be considered in deciding patient treatment. Highly immunogenic tumors (such as cHL) may have different approach from immunologically inert lymphomas.

References

1. Xia Y, Medeiros LJ, Young KH (2016) Signaling pathway and dysregulation of PD1 and its Ligands in lymphoid malignancies. *Biochim Biophys Acta* 1865(1): 58-71.
2. Hude I, Sasse S, Engert A, Bröckelmann PJ (2017) The emerging role of immune checkpoint inhibition in malignant lymphoma. *Haematologica* 102(1): 30-42.
3. Rosenblatt J, Avigan D (2017) Targeting the PD-1/PD-L1 axis in multiple myeloma: a dream or a reality? *Blood* 129(3): 275-279.

4. Gatalica Z, Bilalovic N, Vranic S, Arguello D, Reddt S, et al. (2015) PD-L1 and PD1 expression in lymphomas. *Blood* 126: 3899.
5. Fowler NH, Cheah CY, Gascoyne RD, Gribben J, Neelapu SS, et al. (2016) Role of the tumor microenvironment in mature B-cell lymphoid malignancies. *Haematologica* 101(5): 531-540.
6. Merryman RW, Kim HT, Zinzani PL, Carlo-Stella C, Ansell SM, Perales M-A, et al. (2017) Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood* 129(10): 1380-1388.
7. Menter T, Bodmer-Haechi A, Dimhofer S, Tzankov A (2016) Evaluation of the diagnostic and prognostic value of PD-L1 expression of Hodgkin and B-cell lymphomas. *Hum Pathol* 54: 17-24.
8. Nayak L, Iwamoto FM, LaCasce A, Mukundan S, Roemer MGM, et al. (2017) PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood* 129(23): 3071-3073.
9. Christian B (2017) Checkpoint inhibition in CNS lymphoma. *Blood* 129(23): 3045-3046.
10. Nayak L, Iwamoto FM, LaCasce A, Mukundan S, Roemer MG, et al. (2017) PD-1 blockade with nivolumab in relapsed / refractory primary central nervous system and testicular lymphoma. *Blood* 129(23): 3071-3073.



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