SciForschen
Open HUB for Scientific Research

ISSN 2471-5026

Journal of Blood Disorders and Medicine

Mini Review | Volume: 1.3 | Open Access

# Inhibitory Immune Checkpoints and T-Cell Exhaustion in Lymphoma

**Zhi-Zhang Yang***

*Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, MN, USA*

***Corresponding author:** Zhi-Zhang Yang, MD, Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, MN, USA, Tel: (507)-266-2161; Fax: (507)-266-9277; **E-mail:** yang.zhizhang@mayo.edu

**Received date:** 05 Jul 2016; **Accepted date:** 27 Sep 2016; **Published date:** 03 Oct 2016.

**Citation:** Yang Z-Z (2016) Inhibitory Immune Checkpoints and T-Cell Exhaustion in Lymphoma. J Blood Disord Med 1(3): doi http://dx.doi.org/10.16966/2471-5026.110



With a wave of FDA approvals for PD-1 blocking antibody to treat cancer patients with melanoma, lung cancer and Hodgkin's lymphoma, it puts immune checkpoints on the hot spot and draws tremendous interests from clinicians and research scientists.

Immune checkpoints consist of a number of members that include both stimulatory (CD27, CD28, CD40, OX40, CD137,etc) and inhibitory (PD-1, TIM-3, LAG-3, CTLA-4, 2B4, Tigit, etc) checkpoint molecules. While PD-1 is mostly investigated biologically and clinically and shows great promising in treating cancer patients, other checkpoint molecules may also have therapeutic potential among the inhibitory checkpoint members.

PD-1 was first cloned and characterized in murine cells by Ishida et al in 1992 [1]. The study found that the PD-1 gene was activated in both stimulated 2B4.11 and IL-3-deprived LyD9 cells that died by the classical type of programmed cell death, but not in other death-induced cell lines. Two years later, the same lab cloned and located human PD-1 gene to chromosomal 2q.37.3 [2]. Functional studies indicated that PD-1 is an immunoinhibitory receptor that leads to negative regulation of lymphocyte activation [3]. Meanwhile, the ligands for PD-1 have been identified and named differently as PD-L1/L2 or B7-H1/2 [3,4]. Since then, extensive investigation has been conducted on the biologic role and clinical relevance of PD-1 signaling in various cancers.

An important finding leading to the exploration of PD-1 therapy in cancers is that signaling through PD-1 pathway is critical for tumor cells to escape from host immune surveillance [5, 6]. In this regard, unleashing the immune system against tumors should allow the surveillance mechanism to eradicate cancer cells. Indeed, the outcomes from clinical trials have shown tremendous encouraging results in a number of types of cancers. The outcome is even more promising in patients with relapsed or refractory Hodgkin's lymphoma in which an overall response rate of 87% has been seen including 17% with a complete response and 70% with a partial response [7].

Correlative studies however found that the contribution of intratumoral PD-1+ T cells to patient outcome in follicular lymphoma (FL) is controversial. While some studies have found that increased numbers of PD-1+ T cells correlate with an inferior prognosis [8] or have no impact on patient outcome [9], other studies observed that the numbers of intratumoral PD-1$^{+}$ T cells are an indicator of a favorable outcome in FL [10]. This discrepancy may be explained by the finding that two PD-1$^{+}$ cell populations with distinct functions are present in the tumor microenvironment of FL [11]. We have observed that PD-1 is differentially expressed on two T-cell subpopulations, with bright expression (PD-1$^{high}$) on follicular T helper cells and dim expression (PD-1$^{low}$) on exhausted T cells. Supporting this finding, PD-1$^{high}$ T cells reside predominantly in the lymph node follicles, while PD-1$^{low}$ T cells are mainly located in an interfollicular pattern. Furthermore, these two PD-1+ subpopulations differentially impact patient outcome in FL.

The underlying mechanism behind the PD-1 blockade is unclear. It has been demonstrated that PD-1 is involved in the development of T-cell exhaustion, especially in the setting of chronic viral infection. In malignancies, infiltrating tumor antigen-specific CD8$^{+}$ T cells express high levels of PD-1 and are functionally impaired [12]. We have shown that highlyrepresented TIM-3+ T cells contribute to the development of T-cell exhaustion and are associated with inferior patient outcome in FL [13]. TIM-3 is expressed on PD-1$^{low}$ T cells and is absent on PD-1$^{high}$ T cells, which is consistent with the other study [11]. TIM-3+PD-1$^{low}$ T cells exhibit reduced proliferation, cytokine production and signaling transduction. The number of TIM-3$^{+}$ T cells correlates with a poor prognosis in FL patients. These findings indicate immune checkpoint TIM-3 plays an important role in mediating exhaustion of T cells thereby impacting patient outcome in FL.

Immune checkpoint research opens a new avenue for scientists and clinicians. PD-1 blockade is another successful regimen in cancer immunotherapy. With advanced research, we believe that blocking other immune checkpoint targets alone or in combination with each other or with other treatment options will bring more hope for cancer patients.

## References

1. Ishida Y, Agata Y, Shibahara K, Honjo T (1992) Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 11: 3887-3895.
2. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T (1994) Structure and chromosomal localization of the human PD-1 gene (PDCD1). Genomics 23: 704-706.
3. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, et al. (2000) Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192: 1027-1034.
4. Dong H, Zhu G, Tamada K, Chen L (1999) B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 5: 1365-1369.
5. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, et al. (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 99: 12293-12297.
6. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, et al. (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Na Med 8: 793-800.
7. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, et al. (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372: 311-319.

8. Muenst S, Hoeller S, Willi N, Dirnhofera S, Tzankov A (2010) Diagnostic and prognostic utility of PD-1 in B cell lymphomas. Dis Markers 29: 47-53.

9. Richendollar BG, Pohlman B, Elson P, Hsi ED (2011) Follicular programmed death 1-positive lymphocytes in the tumor microenvironment are an independent prognostic factor in follicular lymphoma. Hum Pathol 42: 552-557.

10. Carreras J, Lopez-Guillermo A, Roncador G, Villamor N, Colomo L, et al. (2009) High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol 27: 1470-1476.

11. Yang ZZ, Grote DM, Ziesmer SC, Xiu B, Novak AJ, et al. (2015) PD-1 expression defines two distinct T-cell sub-populations in follicular lymphoma that differentially impact patient survival. Blood Cancer J 5: e281.

12. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, et al. (2009) Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood 114: 1537-1544.

13. Yang ZZ, Grote DM, Ziesmer SC, Niki T, Hirashima M, et al. (2012) IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. J Clin Invest 122: 1271-1282.