

Uncovering the Immunoregulatory Function and Therapeutic Potential of the PD-1/PD-L1 Axis in Cancer

Michael R. Pitter^{1,2,3} and Weiping Zou^{1,2,3}

Immune checkpoint blockade involves the targeted antagonism of immunosuppressive interactions between antigen-presenting cells and/or tumor cells and effector T cells. Blockade of B7-H1, also known as programmed death-ligand 1 (PD-L1), prevents the ligation of inhibitory PD-L1 molecules to programmed cell death receptor 1 (PD-1) on T cells, engendering a potentiated response of tumor-specific T cells against tumor cells. In a *Cancer Research* article, Hirano and colleagues showed that T-cell-mediated tumor immunity becomes impaired when tumor cells interact with T cells

via PD-L1 in the mouse tumor microenvironment. They showed that targeting PD-L1 or PD-1 with mAbs increased tumor cell lysis by T cells and suggested that tumor PD-L1 forms a “shield” preventing tumor cell lysis. Alongside other original mouse and human studies, this work generated scientific rationales for a new generation of cancer treatment focused on targeting the inhibitory PD-1/PD-L1 signaling pathway in the tumor microenvironment.

See related article by Hirano and colleagues, *Cancer Res* 2005;65:1089–96

Discovery of PD-L1

Programmed death-ligand 1 (PD-L1) was discovered through the bioinformatic identification of its homology to the B7-1 costimulatory protein; thus, PD-L1, or homolog 1, closely resembles B7-1 yet differs in function. B7-1 and B7-2 (CD80 and CD86, respectively) are costimulatory surface proteins that promote T-cell survival and proliferation when binding to T-cell CD28. Conducting a BLAST search in the NCBI database using the published human B7-1 and B7-2 amino acid sequences as references revealed that there exists a sequence homologous with both B7-1 and B7-2 in both mouse and human. A B7 homology-based search of the cDNA expressed sequence tag (EST) libraries revealed ESTs overlapping with *B7-1* and *B7-2*, which would be identified as *B7-H1*. Using these sequences, the full-length human cDNA was derived from a human placental cDNA library, and, in parallel, the full-length mouse cDNA was isolated from a murine-activated T-cell cDNA library. PD-L1 protein is orthologous between human and mouse. Across species, PD-L1 shares common structures with other B7-family members, including the immunoglobulin V and C domains in the extracellular region, a hydrophobic transmembrane domain, and a charged intracellular region. The extracellular region of PD-L1 was observed to share 20% amino acid identity with B7-1 versus 15% with B7-2. Although PD-L1 was identified as a close homolog to B7-1, PD-L1 demonstrates distinct patterns of expression and function (1, 2).

Expression of PD-L1

IHC has revealed relatively high PD-L1 protein expression on several human tumor tissues, yet low expression on normal

tissues (3). Furthermore, both mouse and human tumor cell lines express negligible levels of PD-L1 protein without stimulation with IFN γ . The tumor masses excised from mice inoculated with tumor cell lines express PD-L1, indicating that tumor PD-L1 protein is stimulated *in vivo* in the tumor microenvironment. PD-L1 protein expression is also detected among myeloid cell subsets, including myeloid dendritic cells and macrophages, in the human tumor microenvironment and human tumor-draining lymph nodes (4). The discovery of PD-L1 expression on tumor cells and myeloid cells preceded the important work of elucidating the mechanisms through which tumor cell and/or host PD-L1 contributes to the impairment of tumor immunity in the tumor microenvironment.

Mode of Action of PD-L1

Initial studies of PD-L1 on tumor cells revealed that tumor surface protein promotes T-cell apoptosis (3). Hirano and colleagues in Lieping Chen's group reported in *Cancer Research* that cancer cell PD-L1 reduced T-cell cytolytic activity (Fig. 1), suggesting it can shield cancer cells and promote immune evasion (5). Subsequent studies have also shown that engagement of PD-L1⁺ cells with T cells may induce T-cell anergy, functional exhaustion, and IL10 production (6). Taken together, the ligation of PD-L1 to T-cell programmed cell death receptor 1 (PD-1) impairs mouse and human T cell-mediated anti-tumor immunity.

When tumor and myeloid PD-L1 binds to T-cell PD-1, this inhibits antitumor T-cell immunity through a variety of means. PD-L1-expressing cells utilize several mechanisms to evade T-cell immunity (6). For example, PD-L1 mediated induction of apoptosis in T cells. PD-L1-deficient mice have an accumulation of CD8⁺ T cells in the liver due to reduced apoptosis (7). T cells may also become functionally anergic/tolerant or unresponsive to tumor antigens following PD-1 ligation to antigen-presenting cell PD-L1. Similarly, T cells may become exhausted or dysfunctional, a phenomenon that occurs primarily in the context of chronic infection or inflammation whereby the T cells become unresponsive due to overstimulation. Indeed, the tumor microenvironment conditions resemble those often found in inflammatory diseases in which chronic irritation imposed on T cells disrupts their function. Furthermore, PD-L1 expression can promote the development

¹Department of Surgery, University of Michigan, Ann Arbor, Michigan. ²Center of Excellence for Cancer Immunology and Immunotherapy, University of Michigan Rogel Cancer Center, Ann Arbor, Michigan. ³Department of Pathology, University of Michigan, Ann Arbor, Michigan.

Corresponding Author: Weiping Zou, Department of Surgery, University of Michigan Medical School, 109 Zina Pitcher Place, Ann Arbor, MI 48109. E-mail: wzou@med.umich.edu

Cancer Res 2021;81:5141–3

doi: 10.1158/0008-5472.CAN-21-2926

©2021 American Association for Cancer Research

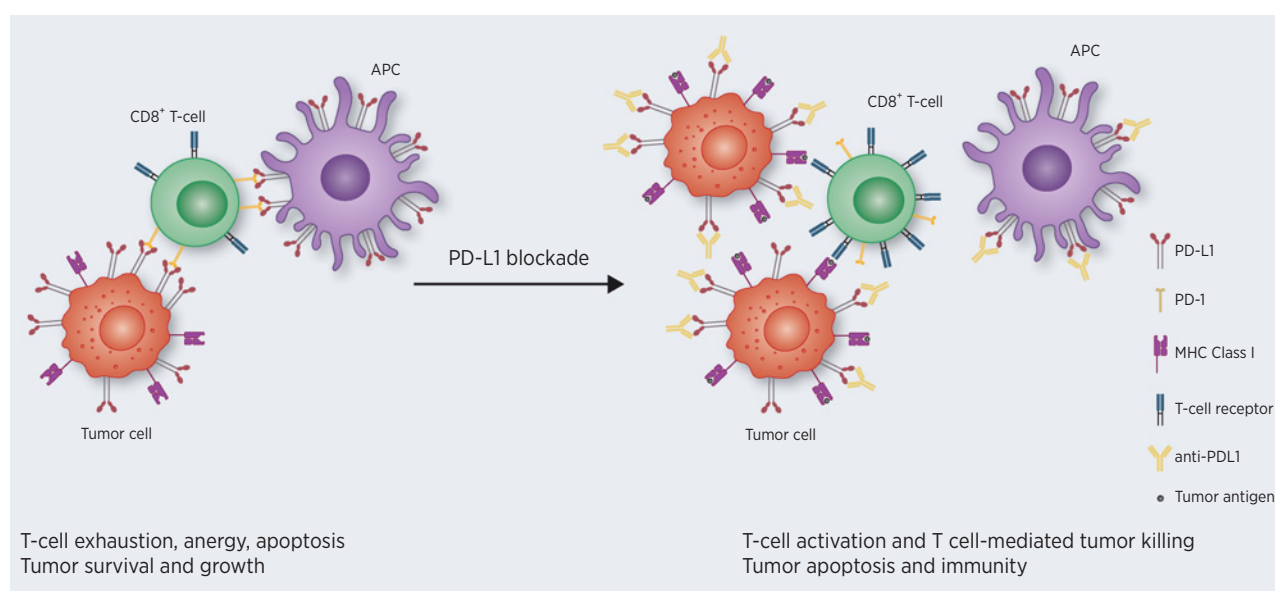


Figure 1.

Targeting PD-L1 in cancer. Treatment with PD-L1-blockade therapy reduces PD-L1 expressing cell-mediated T-cell inhibition. Interactions between T-cell PD-1 and PD-L1 on tumor cells or dendritic cells promotes immunosuppression and inhibits antitumor immunity. Antibody-mediated targeting of PD-L1 blocks its ligation to PD-1 to increase activity of tumor-specific T cells against tumor cells.

and function of regulatory T cells, which are known to promote tumor growth by means of maintaining immunosuppression and tolerance.

Therapeutically Targeting PD-L1 and PD-1

mAbs targeting PD-L1 and PD-1 have been approved by the FDA to treat several cancer types. In their original studies, Lieping Chen and colleagues showed that mAbs targeting the interaction between PD-L1 and PD-1 potentiate antitumor immunity in a human ovarian cancer xenograft model (4) and tumor-bearing mice (5). Notably, in addition to tumor PD-L1, early (4) and recent (8–10) studies have demonstrated the critical importance of PD-L1 in myeloid dendritic cells and macrophages in preclinical models and patients with cancer receiving immune checkpoint blockade (Fig. 1).

PD-1 in tumor-infiltrating T cells plays a complicit role in the immunosuppressive networks sufficient to disrupt antitumor immunity (5). In line with this, PD-1-deficient mice develop systemic and organ-specific autoimmune disorders. Interestingly, activated normal T cells can express PD-1, and PD-1 binding to PD-L1 serves to physiologically limit T-cell overactivation. However, this interaction constitutes a hurdle in the process of tumor immunity (2, 5, 6). Several mAbs against PD-1 have shown efficacy in rescuing antitumor T-cell function and generate clinical efficacy in several types of human cancers (6). In addition to PD-L1, PD-1 can also bind to PD-L2 and possibly other ligands (6). Thus, mechanistically, blockade of PD-L1 and PD-1 may not identically affect the T-cell responses. As the head-to-head randomized clinical trial, comparing mAbs against PD-L1 and PD-1, is not available, it

remains unknown whether targeting PD-L1 and PD-1 yields similar therapeutic efficacy in patients with cancer.

Combination Therapy

Lieping Chen's group observed that while contemporary immunotherapies such as CD137 mAb (also known as 4-1BB) or adoptive T-cell transfer were sufficient to elicit strong T-cell responses against tumor cells, expression of PD-L1 allowed cancer cells to circumvent these therapies and continue to grow (5). Tumor-associated PD-L1 was found to confer resistance to anti-CD137 antibody therapy for established tumors, and PD-L1 blockade sensitized the antitumor effects mediated by anti-CD137 antibody. Thus, combining PD-L1 and PD-1 pathway blockade with other therapeutic measures—including adoptive T-cell therapy, epigenetic reprogramming, antibodies targeting T-cell costimulation, metabolic reprogramming, and conventional cancer therapies, such as chemotherapy, radiotherapy, and targeted therapy—has become a common strategy to enhance tumor immunity, overcome resistance, and elevate therapeutic efficacy (6).

Conclusion

The original studies from Lieping Chen's team and others have paved the way for new insights and philosophies in tumor immunology and anticancer therapy.

Authors' Disclosures

No disclosures were reported.

Received August 30, 2021; accepted September 1, 2021; published first October 15, 2021.

References

1. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med* 1999;5:1365–9.
2. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000;192:1027–34.
3. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8:793–800.
4. Curiel TJ, Wei S, Dong H, Alvarez X, Cheng P, Mottram P, et al. Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. *Nat Med* 2003;9:562–7.
5. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005;65:1089–96.
6. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. *Sci Transl Med* 2016;8:328rv4.
7. Dong H, Zhu G, Tamada K, Flies DB, van Deursen JM, Chen L. B7-H1 determines accumulation and deletion of intrahepatic CD8⁺ T lymphocytes. *Immunity* 2004;20:327–36.
8. Lin H, Wei S, Hurt EM, Green MD, Zhao L, Vatan L, et al. Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression. *J Clin Invest* 2018;128:805–15.
9. Tang H, Liang Y, Anders RA, Taube JM, Qiu X, Mulgaonkar A, et al. PD-L1 on host cells is essential for PD-L1 blockade-mediated tumor regression. *J Clin Invest* 2018;128:580–8.
10. Oh SA, Wu DC, Cheung J, Navarro A, Xiong H, Cubas R, et al. PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer. *Nat Cancer* 2020;1:681–91.