

New insights into the anti-PD-L1 and anti-PD-1 reagents in cancer therapy

European Journal of Inflammation
2016, Vol. 14(1) 61–65
© The Author(s) 2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1721727X15626423
eji.sagepub.com



Cheng Chen^{1,2} and Jian-An Huang^{1,2}

Abstract

Immunotherapy that inhibits the interaction between programmed death ligand 1 (PD-L1), present on the surface of tumor or antigen-presenting cells, and programmed death 1 (PD-1), present on the surface of activated lymphocytes, is generating much excitement and enthusiasm. Although considerable knowledge has been accumulated on anti-PD-L1 and anti-PD-1 reagents, discovering immunotherapy-associated issues still remains a pressing task for the researchers and clinicians.

Keywords

cancer, immune evasion, immunotherapy, PD-L1, PD-1

Date received: 9 October 2015; accepted: 17 December 2015

Introduction

Since anti-programmed death ligand 1 (PD-L1) and anti-programmed death 1 (PD-1) mAbs revolutionized the cancer immunotherapy in 2012, an impressive variety of clinical trials on checkpoint blockade, ranging from head-to-head to combinations, were either proposed or already underway.^{1–4} We believe these intriguing reports contribute to our understanding of the immune checkpoint targeting in cancer therapy. Despite progress in these fronts, securing long-term strategies of immunotherapy to cancer requires addressing more urgent issues. Here, this review attempts to propose several new insights on the anti-PD-L1 and anti-PD-1 mAb immunotherapy against cancer, and to discuss how to improve the immunotherapy leading to more effective eradication of cancer.

PD-L1/PD-1 axis blockade enhances immune response by multiple mechanisms

Like the CTLA-4, the PD-1/PD-L1 pathway downmodulates T-cell response by regulating overlapping signaling proteins in the immune checkpoint pathway. However, their functions are slightly different.

The CTLA-4 focuses on regulating the activation of T cells, while the PD-1/PD-L1 pathway regulates the effector T cell activity in peripheral tissues.^{5–7} Current cancer immunotherapy strategies mostly aim at restoring T cell-mediated antitumor immunity. T cell-mediated immunity includes multiple sequential steps: clonal selection of antigen-specific T cells and T cell activation; proliferation; trafficking; and cytolytic effect (execution of direct effector function). In addition, PD-L1 is not only expressed on cancer cells, but also in cells of antigen-presenting cells (APCs) and myeloid-derived suppressor cells (MDSCs).^{8–14} Thus, the PD-L1 expression of dendritic cell (DCs) and macrophages might also be responsible for the fine-tuning of APCs-mediated T cell activation.^{15–18} Taken together, the PD-1/PD-L1

¹Respiratory Department, The First Affiliated Hospital of Soochow University, Suzhou, PR China

²Institute of Respiratory Diseases, Soochow University, Suzhou, PR China

Corresponding author:

Cheng Chen, Respiratory Department, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, 215006, PR China.
Email: 210332029@suda.edu.cn

axis is an inhibitory pathway physiologically counterbalancing the co-stimulatory pathway leading to fine-tuning the immune responses. Blockade of this interaction either by cancer cells or APCs could enhance the anti-tumor immunity, and decrease proliferation of the tumor infiltrating T-regulatory (Treg) cells, thus leading to a new era in cancer treatment through the multilevel immune interference.^{19,20}

Predictive biomarkers of anti-PD-1/ PD-L1 therapies

PD-L1-positive cancers correlated with poor prognosis may indicate tumors sensitive to anti-PD-1 and/or PD-L1 therapies. As supported, recent evidence has shown that tumor PD-L1 expression is intimately correlated with tumor regression by the anti-PD-1 blockade, and to a greater extent than tumor PD-1 and PD-L2 expressions.^{1,21} It was also found that PD-L1 expressed on tumor infiltrated immune cells is also a biomarker of therapy, suggesting that the functional restoration of tumor infiltrated immune cells can be derived from the PD-L1/PD-1 blockade.^{22,23}

However, there are still some controversies for this viewpoint. Recently, Julie Brahmer reported, among patients with advanced, but previously treated squamous-cell non-small cell lung cancer (NSCLC), overall survival, response rate, and progression-free survival were significantly better with PD-1 antibody treatment than with Docetaxel, regardless of tumor PD-L1 expression level.²⁴ Further complicating matters is that while PD-L1 expression analysis was required before administration of anti-PD-L1 and anti-PD-1 reagents: (1) It was once believed that the lack of standardization of the PD-L1 testing makes it difficult to compare results derived from different trials; (2) the two leading hypotheses on PD-L1 expression were described as an innate versus adaptive immune response. In some settings, expression of PD-L1 in tumors was constitutive, and was (neither) not associated with the degree of T cell infiltration.^{25,26} Conversely, in the adaptive model, tumors started to express PD-L1 only after exposure of tumors to tumor infiltrating T lymphocytes in an attempt to resist immune surveillance;^{27,28} and (iii) In addition to tumor cells, this interaction has also shown to involve in proliferation of Treg cells, and antigen presentation of APCs. So, at this stage, it does not seem a necessity to say

that PD-L1 expression analysis will be the key step to immune checkpoint therapies.

Clinical evaluation criteria of immunotherapy

Clinical experience using immunotherapy approaches indicates that the Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria may not adequately or accurately characterize the therapeutic responses to checkpoint inhibitors. The current data suggest that disease stabilization can be durable for months or even years, and may even lead to regression of the disease long after cessation of therapy. Furthermore, complete or partial responses or disease stabilization can occur in patients who have had some brief disease progression by RECIST or WHO criteria.^{29,30} It has also been noted in other malignancies that the anti-PD-1/ PD-L1 therapy may induce transiently worsening and disease progression, and that responses of tumors to the treatment may be delayed. Then, it is required to develop a set of criteria more suited for measuring clinical responses to immunotherapeutics, which is called an immune-related response criteria.

Side-effect of anti-PD-L1 and anti-PD-1 mAbs

Immunologically, the activation of PD-1/PD-L1 pathway weakens immune responses, limits inflammations and avoids development of immune injuries. The relationship between an overactive immune response and a clinical outcome of the checkpoint inhibitors has not been delineated. Overall, the immune therapy was relatively well tolerated. However, drug-related adverse events were frequently found. The mechanism of toxicity related to the PD-1/PD-L1 inhibition is autoimmune in nature and is distinct from that of other cancer therapies. These side effects consist of immune-related adverse events that are defined by inflammatory conditions, including dermatitis, colitis, hepatitis, pancreatitis, pneumonitis, and hypophysitis.^{31–33} If a sustainable therapy with PD-1/PD-L1 antagonists is available, the immune associated damage will (was) not be evitable. Then, an optimal dose and a course of immunotherapy are yet to be definitively established.

Resistance to anti-PD-L1 and anti-PD-1 mAb immunotherapy

Acquired resistance to reagent is the most important limiting factor for treatment efficiency in cancer. But there are limited evidences for the existence of resistance induced by the continuation of anti-PD-L1 and anti-PD-1 mAb treatments. This new pharmacological reagent would have been developed for acquired resistance via bystander immune pathways, called cell-intrinsic pathways that regulate T cell activation.³⁴ Other contributing factors for the failure of cancer vaccines are perhaps the antibody internalization and anti-idiotypic antibodies.

Beyond PD-L1/PD-1 axis

It is well established that tumors use several mechanisms to avoid elimination by the immune system, one of which involves hijacking these checkpoint pathways. It is unlikely that a single immunologic target mediating immune escape can be identified. In addition to the PD-L1/PD-1, multiple other immune checkpoints play roles in immune regulation. For example, B7 homology 4 (B7-H4) and T cell immunoglobulin and mucin-domain containing protein 3 (Tim3) can also inhibit T-cell activation, proliferation, and cytokine production.^{35–38} Therefore, inhibition of the PD-L1/PD-1 interaction alone could result in an incomplete rescue of immune cells fighting cancers. Given the complexity of regulation of T cell responses by multiple signaling pathways, both negative and positive, it will be necessary to determine other components within the tumor microenvironment for development of combinational strategies with greater clinical benefits.

Conclusion

An in-depth understanding of how tumors evade immune surveillance will help to develop more effective therapeutic strategies that can be used for the benefit of cancer patients. PD-L1 and PD-1 are crucial molecules fine-tuning the immune responses. It is well established that tumors use this pathway to avoid elimination by the immune system. Blockade therapy utilizes monoclonal antibodies to release brakes from suppressing T cells might allow them to be activated and recover their antitumor activity.

However, several key issues regarding the anti-PD-L1 and anti-PD-1 immunotherapy need to be highlighted. For example, the development of pharmacodynamic, side effect, predictive, or prognostic biomarkers faces unique challenges. Especially, those reagents that block immune checkpoints unleash the dynamic and complexed immune responses.

Acknowledgements

The authors thank Prof. Jim Xiang (Cancer Research Unit, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, Canada) for providing constructive criticism and helpful suggestions for this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work was supported by the Project of National Natural Science Foundation of China (no. 30972718 and no. 81000919), Project of Department of Public Health of Jiangsu Province (no. H201208), and Natural Science Foundation of Jiangsu Province University (no. 13KJB320021).

References

1. Topalian SL, Hodi FS, Brahmer JR et al. (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *New England Journal of Medicine* 366: 2443–2454.
2. Brahmer JR, Tykodi SS, Chow LQ et al. (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New England Journal of Medicine* 366: 2455–2465.
3. Hodi FS, Lee S, McDermott DF et al. (2014) Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: A randomized clinical trial. *Journal of the American Medical Association* 312: 1744–1753.
4. Hamid O, Robert C, Daud A et al. (2013) Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *New England Journal of Medicine* 369: 134–144.
5. Keir ME, Liang SC, Guleria I et al. (2006) Tissue expression of PD-L1 mediates peripheral T cell tolerance. *Journal of Experimental Medicine* 203: 883–895.
6. Freeman GJ, Long AJ, Iwai Y et al. (2000) Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *Journal of Experimental Medicine* 192: 1027–1034.

7. Francisco LM, Sage PT and Sharpe AH (2010) The PD-1 pathway in tolerance and autoimmunity. *Immunology Reviews* 236: 219–242.
8. Dong H, Strome SE, Salomao DR et al. (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. *Nature Medicine* 8: 793–800.
9. Velcheti V, Rimm DL and Schalper KA (2013) Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1). *Journal of Thoracic Oncology* 8: 803–805.
10. Gao Q, Wang XY, Qiu SJ et al. (2009) Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clinical Cancer Research* 15: 971–979.
11. Thompson RH, Kuntz SM, Leibovich BC et al. (2006) Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with longterm follow-up. *Cancer Research* 66: 3381–3385.
12. Iwai Y, Ishida M, Tanaka Y et al. (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proceedings of the National Academy of Sciences of the United States of America* 99: 12293–12297.
13. Hino R, Kabashima K, Kato Y et al. (2010) Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. *Cancer* 116: 1757–1766.
14. Krönig H, Julia Falchner K, Odendahl M et al. (2012) PD-1 expression on Melan-A-reactive T cells increases during progression to metastatic disease. *International Journal of Cancer* 130: 2327–2336.
15. Curiel TJ, Wei S, Dong H et al. (2003) Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. *Nature Medicine* 9: 562–567.
16. Krempski J, Karyampudi L, Behrens MD et al. (2011) Tumor-infiltrating programmed death receptor-1+ dendritic cells mediate immune suppression in ovarian cancer. *Journal of Immunology* 186: 6905–6913.
17. Fujimura T, Ring S, Umansky V et al. (2012) Regulatory T cells stimulate B7-H1 expression in myeloid-derived suppressor cells in rat melanomas. *Journal of Investigative Dermatology* 132: 1239–1246.
18. Kuang DM, Zhao Q, Peng C et al. (2009) Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. *Journal of Experimental Medicine* 206: 1327–1337.
19. Francisco LM, Salinas VH, Brown KE et al. (2009) PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *Journal of Experimental Medicine* 206: 3015–3029.
20. Topalian SL, Drake CG and Pardoll DM (2012) Targeting PD-1/B7-H1 (PD-L1) pathway to activate antitumor immunity. *Current Opinion in Immunology* 24: 207–212.
21. Topalian SL, Sznol M, McDermott DF et al. (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology* 32: 1020–1030.
22. Robert C, Long GV, Brady B et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation. *New England Journal of Medicine* 372: 320–330.
23. Weber JS, Kudchadkar RR, Yu B et al. (2013) Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naïve melanoma. *Journal of Clinical Oncology* 31: 4311–4318.
24. Brahmer J, Reckamp KL, Baas P et al. (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *New England Journal of Medicine* 373: 123–135.
25. Parsa AT, Waldron JS, Panner A et al. (2007) Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nature Medicine* 13: 84–88.
26. Xu C, Fillmore CM, Koyama S et al. (2014) Loss of Lkb1 and Pten leads to lung squamous cell carcinoma with elevated PD-L1 expression. *Cancer Cell* 25: 590–604.
27. Abiko K, Mandai M, Hamanishi J et al. (2013) PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. *Clinical Cancer Research* 19: 1363–1374.
28. Liu J, Hamrouni A, Wolowiec D et al. (2007) Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN- γ and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood* 110: 296–304.
29. Weber JS, O'Day S, Urba W et al. (2008) Phase I/II study of ipilimumab for patients with metastatic melanoma. *Journal of Clinical Oncology* 26: 5950–5956.
30. Di Giacomo AM, Danielli R, Guidoboni M et al. (2009) Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: Clinical and immunological evidence from three patient cases. *Cancer Immunology Immunotherapy* 58: 1297–1306.
31. Weber JS, Kähler KC and Hauschild A (2012) Management of immune-related adverse events and kinetics of response with ipilimumab. *Journal of Clinical Oncology* 30: 2691–2697.
32. Weber J (2009) Ipilimumab: Controversies in its development, utility and autoimmune adverse events. *Cancer Immunology Immunotherapy* 58: 823–830.

33. Gangadhar TC and Vonderheide RH (2014) Mitigating the toxic effects of anticancer immunotherapy. *Nature Reviews Clinical Oncology* 11: 91–99.
34. Sakuishi K, Apetoh L, Sullivan JM et al. (2010) Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *Journal of Experimental Medicine* 207: 2187–2194.
35. Sica GL, Choi IH, Zhu G et al. (2003) B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. *Immunity* 18: 849–861.
36. Kryczek I, Zou L, Rodriguez P et al. (2006) B7-H4 expression identifies a novel suppressive macrophage population in human ovarian carcinoma. *Journal of Experimental Medicine* 203: 871–881.
37. Dangaj D, Lanitis E, Zhao A et al. (2013) Novel recombinant human b7-h4 antibodies overcome tumoral immune escape to potentiate T-cell antitumor responses. *Cancer Research* 73: 4820–4829.
38. Ngiow SF, Teng MW and Smyth MJ (2011) Prospects for TIM3-targeted antitumor immunotherapy. *Cancer Research* 71: 6567–6571.

