PROSPECTS OF THE POTENTIAL STRATEGIES TO IMPROVE THE EFFICACY OF ANTI-PD-1/PD-L1 THERAPY

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PD-1 is an immune-checkpoint regulator in T cells that transduces an inhibitory signal and inactivates T cells, while PD-L1 is the PD-1 ligand expressed in various cell types, including antigen-presenting cells (APCs) and cancer cells.1 The PD-L1/PD-1 axis plays a key role in the immune escape of cancer cells, and inhibitory monoclonal antibodies (mAbs) against PD-1 or PD-L1 are currently used for treatment of a wide variety of cancer types.2 These immune checkpoint inhibitors (ICIs) exhibit drastic therapeutic effects on a subset of patients and have revolutionized cancer therapy. However, the overall response rates are far from satisfactory due to intrinsic and acquired resistance.3 Therefore, in order to reduce unnecessary treatment and improve the response rates, it is an urgent need to identify the appropriate markers that can discriminate responders and non-responders to ICIs. So far, several markers associated with the positive response to PD-1/PD-L1 mAbs have been proposed, including, tumour infiltrated lymphocytes (TIL), tumour mutation burden (TMB), microsatellite instability, and PD-L1 expression in tumors.4

Among them, the PD-L1 expression is used in clinic for several cancer types, and some immunohistochemistry (IHC) assays to quantify PD-L1 expression in tumour tissues have been approved by the U.S. Food and Drug Administration (FDA).5 However, in multiple clinical studies, PD-L1 expression in tumours does not correlate with clinical responses to anti-PD-1/PD-L1 therapy,4 which is a puzzle in the field.

Recently, the puzzle seems to be resolved to some extent. PD-L1 is highly glycosylated, and this post-translational modification is critical for PD-L1 protein stability and function.6,7 PD-L1 glycosylation is regulated by various oncogenic signalling pathways such as the epidermal growth factor receptor (EGFR) pathway, which inhibits phosphorylation of extracellular domain of PD-L1 by GSK3β.8 The phosphorylation by GSK3β hinders PD-L1 from its glycosylation, leading to its ubiquitin-mediated proteasome degradation.6 In addition, another study also indicates that glycosylation of PD-L1 interferes PD-L1 protein detection by some traditional PD-L1 antibodies that are designed to recognize its polypeptide antigens.9

Human cancer cell lines or tissues section of several cancer types treated with a glycosidase have the higher signals of PD-L1 in IHC staining than that of the untreated one, indicating that removal of N-linked glycosylation of PD-L1 enhances binding of traditional anti-PD-L1 mAb to PD-L1.9 Thus, it was proposed that inconsistent observations between PD-L1 IHC staining and clinical responses...
FIGURE 1  A potential strategy to improve PD-L1 detection. TNBC tumour samples from patients are treated with glycosidase for deglycosylation, followed by immunohistochemistry (IHC) staining with anti-PD-L1 antibody. Compared to the conventional strategy without deglycosylation, it improves the detection of PD-L1, thereby reducing false negative results. Thus, this strategy is expected to improve the predictive value of PD-L1 expression as a marker to select patients for immune checkpoint inhibitors (ICI) treatment.

In conclusion, PD-L1 detection after deglycosylation by glycosidase pre-treatment may improve the predictive value of PD-L1 expression as a marker to select patients for ICI treatment (Figure 1).

In addition, through mechanism studies, many druggable targets that are involved in the resistance to ICIs were identified and the combination therapy was shown to be able to increase therapeutic efficacy and/or reverse the resistance. For instance, Tyro3 was shown to contribute to the resistance to ICI treatment through inhibition of ferroptosis that is required for T cell-mediated cancer cell killing, providing a combination therapy of a Tyro3 inhibitor and ICIs to treat these types of resistant patients. Several markers that were shown to increase therapeutic efficacy of ICIs by combination therapy from a subset of cancer cells through different kinds of mechanisms have also provided such type of marker-guided effective therapy (MGET). Thus, appropriate markers to stratify patients for different combination therapy may pave a way to increase therapeutic efficacy for ICIs.

In conclusion, PD-L1 detection after deglycosylation by glycosidase pre-treatment may improve the predictive value of PD-L1 expression as a marker to select patients for ICI treatment (Figure 1). In addition, to increase therapeutic efficacy to benefit majority of patients, MGET continues to be needed to select right patients to be treated with right combination therapy. All these are worthy of validation by further clinical trials to enhance the therapeutic efficacy of ICIs.

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CONFLICT OF INTEREST
Mien-Chie Hung holds a patent on the methodology for de-glycosylation staining.

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REFERENCES
1. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol. 2007;8:239–245.
2. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med. 2016;375:1767–1778.
3. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168:707–723.
4. Grossman JE, Vasudevan D, Joyce CE, Hildago M. Is PD-L1 a consistent biomarker for anti-PD-1 therapy? The model of bal-stilimabin avirally-driven tumor. Oncogene. 2021;40:1393–1395.
5. Prince EA, Sanzari JK, Pandya D, Huron D, Edwards R. Analytical concordance of PD-L1 assays utilizing antibodies from FDA-approved diagnostics in advanced cancers: A systematic literature review. JCO Precis Oncol. 2021;5:953–973.
6. Li C-W, Lim S-Oe, Xia W, et al. Glycosylation and stabilization of programmed death ligand-1 suppresses T-cell activity. Nat Commun. 2016;7:12632.
7. Li C-W, Lim S-Oe, Chung EM, et al. Eradication of triple-negative breast cancer cells by targeting glycosylated PD-L1. Cancer Cell. 2018;33:187–201. e110.
8. Yamaguchi H, Hsu J-M, Yang W-H, Hung M-C. Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. Nat Rev Clin Oncol. 2022. Online ahead of print. https://doi.org/10.1038/s41571-022-00601-9
9. Lee H-H, Wang Y-N, Xia W, et al. Removal of N-linked glycosylation enhances PD-L1 detection and predicts anti-PD-1/PD-L1 therapeutic efficacy. Cancer Cell. 2019;36:168–178. e164.
10. Mei J, Xu J, Yang X, et al. A comparability study of natural and deglycosylated PD-L1 levels in lung cancer: Evidence from immunohistochemical analysis. Mol Cancer. 2021;20:11.
11. Xu J, Yang X, Mao Y, et al. Removal of N-linked glycosylation enhances PD-L1 detection in colon cancer: Validation research based on immunohistochemistry analysis. Technol Cancer Res Treat. 2021;20:153303382110194.
12. Ou-Yang F, Li C-L, Chen C-C, et al. De-glycosylated membrane PD-L1 in tumor tissues as a biomarker for responsiveness to atezolizumab (Tecentriq) in advanced breast cancer patients. Am J Cancer Res. 2022;12:123–137.
13. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379:2108–2121.
14. Miles D, Gilgore J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol. 2021;32:994–1004.
15. Jiang Z, Lim S-O, Yan M, et al. TYRO3 induces anti-PD-1/PD-L1 therapy resistance by limiting innate immunity and tumoral ferroptosis. J Clin Invest. 2021;131:e139434.
16. Cha J-H, Chan L-C, Li C-W, Hsu JL, Hung M-C. Mechanisms controlling PD-L1 expression in cancer. Mol Cell. 2019;76:359–370.
17. Sun X, Li C-W, Wang W-J, et al. Inhibition of c-MET upregulates PD-L1 expression in lung adenocarcinoma. Am J Cancer Res. 2020;10:564–571.
18. Chan L-C, Li C-W, Xia W, et al. IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. J Clin Invest. 2019;129:3324–3338.
19. Hsu J-M, Xia W, Hsu Y-H, et al. STT3-dependent PD-L1 accumulation on cancer stem cells promotes immune evasion. Nat Commun. 2018;9:1908.
20. Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res. 2017;23:3711–3720.
21. Li H, Li C-W, Li X, et al. MET inhibitors promote liver tumor evasion of the immune response by stabilizing PD1L. Gastroenterology. 2019;156:1849–1861. e1813.
22. Morel KL, Sheahan AV, Burkhart DL, et al. EZH2 inhibition activates dsRNA-STING-interferon stress axis that potentiates response to PD-1 checkpoint blockade in prostate cancer. Nat Cancer. 2021;2:444–456.
23. Zhang J, Bu X, Wang H, et al. Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance. Nature. 2018;553:91–95.

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