Heterogeneous PD-L1 expression in metastases impacts immunotherapy response

Xiaoqian Hu,[a] Xinpei Deng,[b] Jindong Xie,[b] Hailin Tang,[b,**] and Yutian Zou[b,*]

[a]Faculty of Medicine, School of Biomedical Sciences, The University of Hong Kong, 21 Sassoon Road, Hong Kong 999077, China
[b]State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, 651 East Dongfeng Road, Guangzhou 510060, China

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As a groundbreaking approach in cancer treatment, immunotherapy has achieved sustained responses and notable survival benefits across diverse metastatic tumors. However, a substantial portion of cancer patients still fail to derive desired therapeutic benefit from it.[1] Therefore, it is crucial to identify reliable biomarkers to accurately guide patient selection and predict immunotherapeutic response. PD-L1 which induces immune escape, is the most adopted immune checkpoint target in immunotherapy, yet several challenges have impeded its value as a prognostic biomarker.[2] Our previous study identified the presence of intra-patient heterogeneity in PD-L1 expression among primary tumors and metastases, raising the question of how to personalize immunotherapy regarding the discrepant PD-L1 expressions.[3] Furthermore, disparate assays with different diagnostic agents, cut-off points, as well as sites and timing for biopsy sampling,[3,4] diminishes the reproducibility of PD-L1 assessment and thereby complicates the interpretation of PD-L1 expression as a predictive metric for immune checkpoint therapy.

In this issue of eBioMedicine, Placke and colleagues provide insights into how the expression of PD-L1 from different tissue types in non-resectable stage III/IV metastatic melanoma affects clinical outcomes of immune checkpoint therapy.[5] A total of 448 patients were included, and PD-L1 expression was assessed in 95 primary tumors, 153 skin/subcutaneous metastases, 115 lymph node (LN) metastases, and 85 organ metastases. Their results indicated that PD-L1 positivity was predictive for best overall response when assessed in LN metastases, but not in skin/subcutaneous metastases. Primary tumors or metastatic organs with PD-L1 positivity demonstrated a lower predictive value. Consequently, the authors concluded that PD-L1 expression of LN rather than that of skin/subcutaneous metastases is more reliable for predicting the outcome of immunotherapy in melanoma. These results conduce to personalizing therapeutic strategies for melanoma patients based on PD-L1 expression profiles.

The heterogeneity of PD-L1 expression in different tumor sites from a single patient is a well-established phenomenon,[3] yet the underlying mechanisms of metastatic melanoma are still being investigated. Spatial heterogeneity may arise from subclonal drivers originating from the primary site, resulting in the generation of varied neoantigens, diverse T-cell receptor repertoires, and ultimately leading to distinct microenvironments among metastatic sites.[6] These unique microenvironments are further shaped by posttranslational modifications, including *N*-linked glycosylation, serine/threonine phosphorylation and polyubiquitination, and thereby modulate immunosuppression in melanoma patients. Moreover, the dynamic nature of host immunity and the prompt induction of PD-L1 expression caused by chemotherapy, radiotherapy, and targeted therapy contribute to the temporal heterogeneity of PD-L1 expression.[7] Therefore, PD-L1 positive patients with PD-L1 expression that was not present during the initial tissue sampling may have been opted out from ideal immunotherapy. As such, these spatial and temporal heterogeneity of PD-L1 obfuscate its utility as a dependable biomarker for prognostic prediction of immunotherapy. Placke and colleagues proposed that skin metastases may arise from specific cell clones with distinctive characteristics that make them prone to reside *in situ* rather than spread to other organs.[5] Conversely, tumor cells from LN metastases, via the lymphatic system, have higher potential to metastasize to internal organs. As a result, the predictive value of PD-L1 expression in lymph node metastases was higher than that in tumor cell clones of skin/subcutaneous metastases. These hypotheses could be tested with next-generation sequencing at single-cell level to provide spatial and pharmacodynamic information for PD-L1 expression-guided immunotherapy.

Furthermore, in conjunction with the inherent biological heterogeneity, the absence of universally established criteria pertaining to sample processing, turnaround times, and quality assurance measures for immunohistochemistry (IHC) assays of PD-L1 expression also impedes its predictive value.[3] Luckily, novel technologies offer potential alternatives to optimize the detection of PD-L1 expression. A finding proposed to use IFN-stimulated exosomal PD-L1 as a blood-based biomarker to stratify responsive patients with melanoma for immunotherapeutic intervention.[8] Additionally, advances in

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*Corresponding author.
**Corresponding author.
E-mail addresses: zouyt@sysucc.org.cn (Y. Zou), tanghl@sysucc.org.cn (H. Tang).

proteomics may help to precisely quantify PD-L1 protein levels in circulation or secreted forms, providing a more cost-effective and serially performable approach. To identify biomarkers with translational potential and establish standardized detection procedures to optimize immunotherapy strategies for cancer patients, the Cancer Immune Monitoring and Analysis Centers and Cancer Immunologic Data Commons (CIMAC-CIDC) Network was established through the support of National Institutes of Health.[9] The CIMAC-CIDC Network is currently evaluating this hypothesis by incorporating PD-L1 standard IHC into a panel of biomarkers for comparison with other methods, including immunofluorescence, transcriptomic profiling, mass cytometry, and multiplex assessments of soluble factors. Also, the incorporation of digital pathology and image analysis in laboratories holds promise for automating the quantification of PD-L1 following IHC assays.[10] However, this implementation requires rigorous validation of image analysis algorithms and continuous quality control overseen by pathologists.

Despite the hurdles encountered, we firmly believe that there is significant potential for enhancing the utility and reliability of PD-L1 as a predictive biomarker for immunotherapy. This requires innovative evaluation approaches, integrating PD-L1 into comprehensive models, and unifying assessment. By streamlining procedures, clinicians can bolster it as a guiding tool for precise and personalized medicine.

Contributors

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Declaration of interests

The authors declare no conflicts of interest.

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