

## The Predictive Role of Intra-Tumoral CD8<sup>+</sup>T Cells with Stem Cell-Like Properties in Response to and Efficacy of Anti-PD-1/L1 Treatment

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### Abstract

A Checkpoint Inhibitor-Based Immunotherapy (ICIs) has demonstrated outstanding efficacy in many solid tumors. However, some treated patients with positive expression of PD-L1 do not respond, and even develop hyper progression, and some patients with negative expression of PD-L1 can also benefit from immunotherapy combined with chemotherapy. There is growing need to identify biomarkers that will improve the selection of patients who will best respond to therapy. Intra-tumoral effective T cells are critical for anti-tumor effect, and some subpopulation of it have been verified as potential biomarkers for ICIs. In our previous study, a subset of intra-tumoral CD8<sup>+</sup> T cells with stem-like properties has been identified as sensitive biomarker for predicting the response to and efficacy of PD-1/L1 blockade treatment with or without chemotherapy. In the current comment, the role and challenges of this cell subpopulation in anti-PD-1/L1 immunotherapy will be discussed.

**Keywords:** Non-small cell lung cancer; PD-1/L1 immunotherapy; CD8<sup>+</sup> T cells; Biomarker

### About the Study

Nowadays, PD-1/L1 blockades, a Checkpoint Inhibitor-Based Treatment (ICIs), have been widely used in various solid tumors and demonstrated favorable therapeutic effect [1-3]. Some ICIs, such as pembrolizumab and nivolumab, have been adopted to treat advanced Non-Small Cell Lung Cancer (NSCLC) as first-line treatment depends on the expression of PD-L1 [4].

However, a large body of clinical evidence showed that many ICIs combined with chemotherapy significantly improve survival time of patients with NSCLC regardless of PD-L1 expression [5,6]. These results indicate that PD-L1 may not absolutely reflect the patients' response to immunotherapy. There is a growing need to identify biomarkers that will improve the selection of patients who will best respond to therapy.

### Tumor infiltrating lymphocytes as potentially sensitive markers

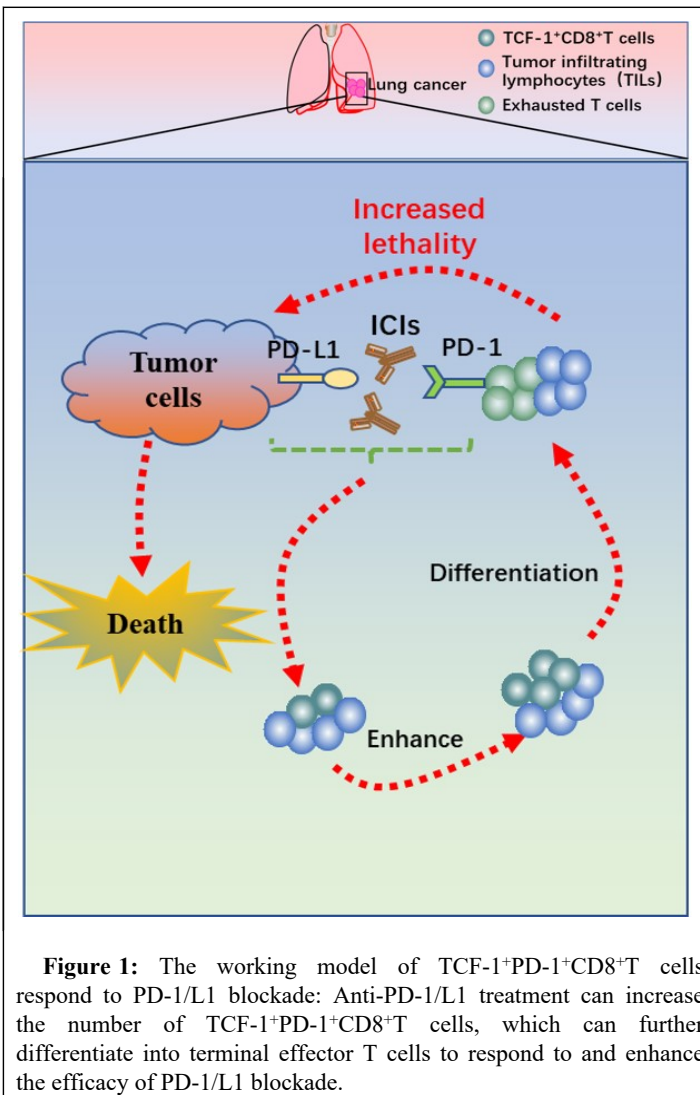
It is well known that PD-1/L1 immunotherapy perform the anti-tumor effect due to its preventive influence against CD8<sup>+</sup> T cell exhaustion. Therefore, the function of T lymphocytes may critical for PD-1/L1 blockade. Lately, some researches demonstrated that a few subsets of Tumor-Infiltrating Lymphocytes (TILs) served as potential biomarkers for response to PD-1/L1 immunotherapy in patients with NSCLC. CD103<sup>+</sup>CD8<sup>+</sup> TILs have been identified to be associated with the efficacy of PD-1/L1 blockade [7]. PD-L1<sup>+</sup>CD4<sup>+</sup>CD25<sup>+</sup>Tregs served as a diagnostic biomarker for response to ICIs [8].

Furthermore, the higher density of intra-tumoral CD3<sup>+</sup>CD45RO<sup>+</sup>CD8<sup>+</sup>T cells in melanoma was associated with durable beneficial in anti-PD-1 therapy [9]. Therefore, tumor with an active immune microenvironment, which exemplified by infiltration of activated, effector T cells, will be better primed to respond to PD-1/L1 immunotherapy.

### Intra-tumoral CD8<sup>+</sup> T cells with stem cell-like properties mediate tumor control and response to ICIs

As TILs are critical for anti-tumor and response to immunotherapy, the evolution of TILs, especially for CD8<sup>+</sup> T cells are studied extensively. Recently, a subpopulation of CD8<sup>+</sup> T cells were identified to possess stem cell-like properties that express the T cell Transcription Factor 1 (TCF-1) and differentiate into 'terminally exhausted' TILs, namely "progenitor exhausted cells" (TCF-1<sup>+</sup>PD-1<sup>+</sup>CD8<sup>+</sup> T cells) [10].

This subset was first identified during inflammatory infection; it was needed for PD-1<sup>+</sup>CD8<sup>+</sup> T cells expansion in response to PD-1 blockade [11]. Subsequently, few researches confirmed the presence of TCF-1<sup>+</sup>PD-1<sup>+</sup>CD8<sup>+</sup>T cells in human melanoma using multiplex staining, and this subpopulation expanded and/or persisted preferentially in response to PD-1 blockade [12]. The importance of TCF-1<sup>+</sup>PD-1<sup>+</sup>CD8<sup>+</sup>T cells in immunotherapy-driven tumor control was further confirmed in preclinical mouse models using adoptive cell transfers [12]. Collectively, these results indicated that TCF-1<sup>+</sup>PD-1<sup>+</sup>CD8<sup>+</sup>T cells are potential target cells of PD-1 blockade; it may represent a biomarker for therapy outcome prediction (Figure 1).



## Conclusion

Although PD-L1 expression in tumor cells enriches the responders to ICIs in many solid tumors, it is not an absolute predictor of therapeutic response since the mechanism of ICIs is to inhibit the exhaustion of effective T cells. Therefore, it is necessary to consider the status of T cells in addition to the expression of PD-L1 in tumor cells. Currently, some subpopulations of intra-tumoral T cells have been identified as potentially sensitive biomarkers for ICIs. In our previous study, we found that subsets of intra-tumoral CD8<sup>+</sup> T cells, which possess the stem cell-like properties, are tightly correlated with the response to and efficacy of anti-PD-1/L1 immunotherapy with or without chemotherapy in NSCLC. Thus, we need to comprehensively consider the function of intra-tumoral T cells and the expression of PD-L1 when selecting patients who will benefit from PD-1/L1 blockade treatment. However, there are also some challenges for exploring the intra-tumoral T cells as potential biomarkers. Firstly, the specific mechanism of the response of TCF-1<sup>+</sup>PD-1<sup>+</sup>CD8<sup>+</sup>T cells to anti-PD-1/L1 treatment remains largely unknown. Secondly, the predictive role of this cell subset needs to be verified by larger samples and in multiple types of solid tumors. Finally, it is necessary to establish a standard process for detecting this subpopulation in order to be transformed easily into clinical application in the further.

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