The Predictive Role of Intra-Tumoral CD8^{+}T Cells with Stem Cell-Like Properties in Response to and Efficacy of Anti-PD-1/L1 Treatment

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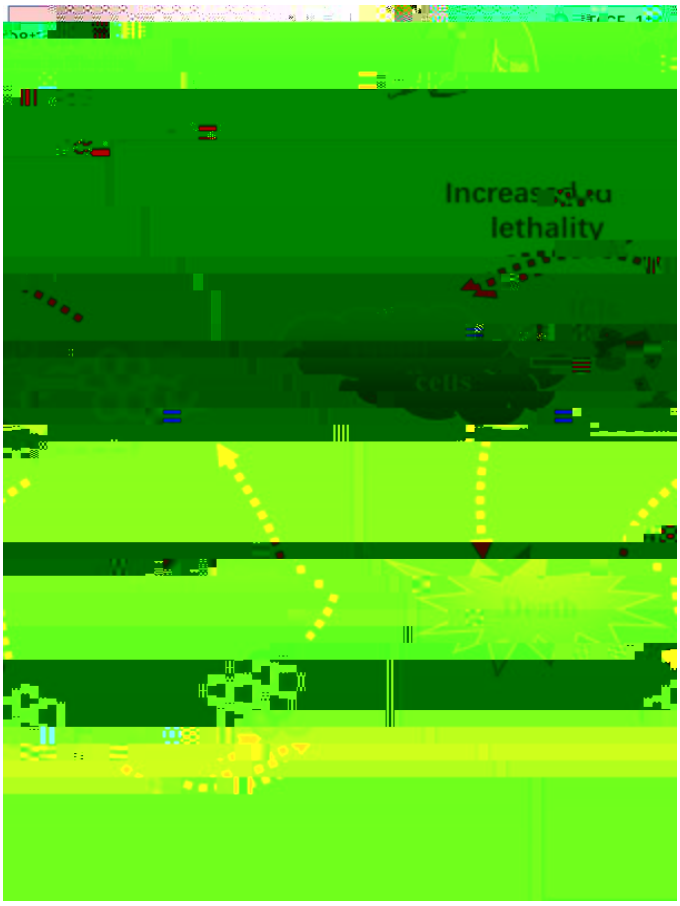
Abstract

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



The working model of TCF-1$^+$PD-1$^+$CD8$^+$T cells respond to PD-1/L1 blockade: Anti-PD-1/L1 treatment can increase the number of TCF-1$^+$PD-1$^+$CD8$^+$T cells, which can further differentiate into terminal effector T cells to respond to and enhance the efficacy of PD-1/L1 blockade.

As the progenitor exhaust T cells are potential biomarker for PD-1 blockade in patients with melanoma, the predictive role of TCF-1$^+$PD-1$^+$CD8$^+$T cells in response to and prognosis of anti-PD-1/L1 treatment in NSCLC has been evaluated in our previous study [13]. Our results demonstrated that patients with high frequency of TCF-1$^+$PD-1$^+$CD8$^+$T cells have a longer PFS and OS after PD-1/L1 immunotherapy with or without chemotherapy. Importantly, a significant association was established between increased frequency of this subset and response to anti-PD-1/L1 therapies in patients with NSCLC, which was not observed in patients with melanoma as aforementioned study. Furthermore, this subpopulation was almost undetected in hyper progressive patients after anti-PD-1/L1 treatment, indicating it may also sensitive biomarker for predicting the hyper progression of PD-1/L1 blockade in NSCLC. Collectively, our research is not only confirming the positive correlation between the expression of TCF-1$^+$PD-1$^+$CD8$^+$T cells and efficacy of anti-PD1/L1 treatment with or without chemotherapy, but also uncover that this cell subset may be a favorable biomarker for selecting the patients with clinical benefit or hyper progressive disease after immunotherapy.

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$^+$ 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 be 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$^+$PD-1$^+$CD8$^+$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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