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Characterization of Circulating T Cell Receptor Repertoire Provides Information about Clinical Outcome after PD-1 Blockade in Advanced Non-Small Cell Lung Cancer Patients

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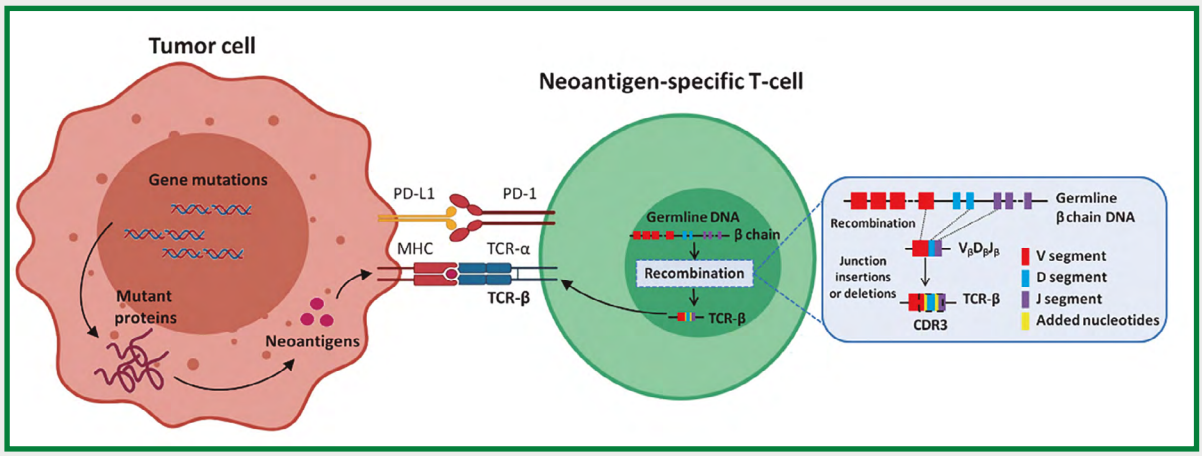
Immune checkpoint blockers (ICBs) have demonstrated durable anti-tumor responses in advanced non-small cell lung cancer (NSCLC). Despite progress in development of predictive biomarkers, such as PD-L1 expression, tumor mutational burden (TMB), or microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR), there is still an urge for a better selection of patients that will benefit from the blockade of PD-1/PD-L1 axis. Among others, T cell profiling may have great relevance since it is closely related to the presence of tumor neoantigens.



Neoantigens are mutant proteins generated by a variety of non-synonymous genetic alterations of tumor cell genomes. After being processed within the tumor cell and presented by the major histocompatibility complex (MHC) molecules, neoantigens can be captured and recognized by specific T cell receptors (TCR) via TCR/peptide/MHC interactions. In this scenario, TCR repertoire study may allow a more accurate approach and opens a new possibility for a more selective and effective biomarker assessment.

This study aimed to explore minimally invasive approaches to characterize circulating TCR beta chain (TCR-β) repertoire in a cohort of advanced NSCLC patients treated with first-line pembrolizumab. Peripheral blood samples were obtained at two time points: i) pretreatment (PRE) and ii) first response assessment (FR). Next-generation sequencing (NGS) was used to analyze the hypervariable complementary determining region 3 (CDR3) of TCR-β chain. Richness, evenness, convergence, and Jaccard similarity indexes plus variable (V) and joining (J)-gene usage were studied.

Sequencing data across the CDR3 region of TCR-β of the 52 libraries resulted in a mean of 1,431,317 (552,776 –2,427,120) total productive reads per sample. When performing correlation analysis between TCR characteristics and the clinical variables, we observed that TCR-β richness was significantly lower (p = 0.040) in smokers compared with non-smokers. Further study of the correlation with clinical outcomes to anti-PD-1 treatment revealed that increased richness during treatment was associated with durable clinical benefit (DCB; p = 0.046), longer progression-free survival (PFS; p = 0.007) and overall survival (OS; p = 0.05). On the other hand, patients with Jaccard similarity index ≥0.0605 between PRE and FR samples showed improved PFS (p = 0.021). According to the distribution of the V and J segments of peripheral TCR-β repertoire, we found that TRBV20-1 was the most abundant segment V in our cohort. Furthermore, higher TRBV20-1 PRE usage was associated with DCB (p = 0.027). TRBV20-1 frequencies ≥9.14% in PRE and ≥9.02% in FR significantly increased PFS (p = 0.025 and p = 0.016) and OS (p = 0.035 and p = 0.018).

Overall, our results suggest that characterization of blood TCR repertoire provides valuable clinical information using a minimally invasive approach; furthermore, the analysis of TRBV20-1 segment frequencies highly predicts host response and survival in anti-PD-1 treated NSCLC patients.

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