

LANDSCAPE ANALYSIS OF THE NEOEPITOPE-SPECIFIC T CELL RESPONSES IN PATIENTS WITH AND WITHOUT CLINICAL BENEFIT FROM IMMUNE CHECKPOINT BLOCKADE THERAPY

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Background The primary target of T-cell responses to cancer cells are peptides derived from non-synonymous mutations presented by HLA. However, the large diversity of HLA alleles and restricted availability of clinical samples has limited the study of the antigenic determinants recognized by T cells (termed neoepitopes) at the scale needed for a landscape analysis of antitumor immune responses in patients.

Methods We applied a newly developed technology to perform a longitudinal landscape analysis of the neoepitope-specific T cells in peripheral blood and tumor from 11 patients with metastatic melanoma, 7 with response (R) or 4 with no response (NR) to immune checkpoint blockade (ICB) immunotherapy. Briefly, based on the computational prediction of patient-specific putative neoepitopes, hundreds of capture reagents were made consisting of the patient HLA class I subtypes loaded with the corresponding predicted neoepitope; neoepitope-specific T cells were then isolated, and the TCR alpha and beta sequenced. The tumor reactivity of the isolated neoepitope-specific TCRs (neoTCR) was assessed upon co-culture of autologous melanoma cell lines from each patient with primary human T cells expressing the neoTCRs generated using a CRISPR-based non-viral precision genome engineering to replace the endogenous TCRs.

Results The tumor mutation burden ranged between 2562 and 54 and 297 to 31 for patients with R and NR, respectively. We screened an average of 157 (range 243 to 17) predicted neoepitope-HLA per patient across their 6 HLA molecules, and isolated neoTCRs in all 11 patients. The number of mutations targeted ranged between 13 and 1. We assessed tumor reactivity in samples from 3 R and 3 NR; 39 of the 64 neoTCRs demonstrated specific recognition and cytotoxicity to patient-matched melanoma cell lines. Multiple T cells with different neoTCRs (T cell clonotypes) recognized a limited number of mutations in 7 patients with R (average of 31 different neoTCR clonotypes per patient). These T cell specificities were recurrently detected at different time points in blood and tumors. Samples from 4 patients with NR also demonstrated neoepitope-specific T cell responses in blood and tumor to a similarly restricted number of mutations but lacked TCR polyclonality (average 3 neoTCR clonotypes per patient) and were not recurrently detected in sequential samples.

Conclusions Effective ICB therapy is associated with polyclonal neoepitope-specific T cell responses in the tumor and blood that recognize a limited number of immunodominant mutations and are recurrently recognized over time.

Ethics Approval Patients with metastatic melanoma were selected as they signed an informed consent to collect PBMC and tumour biopsies while receiving therapy with anti-PD-1 therapy alone or in combination with other drugs. Biopsies and blood samples were collected under the University of California, Los Angeles (UCLA) Institutional Review Board approvals 11-003254.

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