Abstracts

A TRANSCRIPTIONAL SIGNATURE SHARED BY CIRCULATING CANCER-SPECIFIC CD8 T CELLS

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Background Predicting which patients will respond to PD-1 blockade and identifying the relevant underlying mechanisms are major challenges in immuno-oncology. Emerging data suggest that the frequency of cancer-specific T-cells in blood can predict anti-PD-1 response,1,2 but identifying these cells in most cancers is not routinely feasible. Prior studies have identified gene signatures shared by cancer-specific T cells within tumors, however, these cannot be applied to blood samples because gene expression patterns are strikingly different between cancer-specific T-cells in tumors versus blood. If gene signatures could be developed to identify cancer-specific T cells in blood, this could enable prediction of response. We leveraged the small antigenic space of Merkel cell polyomavirus (MCPyV) oncoproteins and our existing suite of reagents to identify and characterize cancer-specific T-cells in blood from patients with Merkel cell carcinoma (MCC).

Methods Single-cell RNA sequencing was performed on 17 pre-anti-PD-(L)1 blood from patients with advanced MCC. MCPyV-specific CD8 T cells were identified using a panel of 19 HLA multimer reagents. Differential gene expression was used to analyze transcripts enriched in MCPyV multimer-binding cells relative to other non-naive CD8 T-cells.

Results We identified a 27-gene signature that was enriched in MCPyV-specific CD8 T cells across 17 patients. An independent validation cohort of 8 virus-driven MCC patients revealed that this gene signature was able to identify peripheral MCC-associated CD8 T cells with a sensitivity of 69% and a specificity of 90% (figure 1A). We determined if this gene signature could also identify T cells from a cohort of 17 Epstein Barr Virus-driven nasopharyngeal carcinoma (NPC) patients. NPC-associated CD8 T cells were identified using a previously determined protein signature.3 Indeed, the gene signature was able to identify peripheral NPC-associated CD8 T-cells with a sensitivity of 72% and a specificity of 75% (figure 1B).

Conclusions The tumor-specific T-cell gene signature generated via one cohort of MCC patients robustly identified tumor-specific T cells in two other cohorts (one composed of MCC patients and one of NPC patients) with comparable accuracy. Taken together, our data indicate that, compared to other non-naive peripheral CD8 T-cells, tumor-specific CD8 T-cells have a distinct gene expression profile. It is plausible that this gene expression profile could also identify cancer-specific CD8 T-cells in mutationally driven cancers. This would allow us to gain important insights into the mechanisms of response and resistance to T-cell-based immunotherapies and enable clinically feasible identification of TCRs for transgenic T cell therapies for most cancers.

Trial Registration This abstract includes patient samples collected on NCT02267603.

REFERENCES

Ethics Approval All patients represented here participated with written informed consent. Training cohort samples were provided by Cancer Immunotherapy Trials Network (trial registration: ClinicalTrials.gov NCT02267603) and analyzed with approval by the Fred Hutchinson Cancer Center's Institutional Review Board (FH 6585). MCC validation cohort samples were collected and analyzed with approval by the Fred Hutchinson Cancer Center's Institutional Review Board (FH 6585). NPC validation cohort samples were obtained from the National Cancer Centre Singapore, and de-identified patient information from this cohort was obtained with approval by the institutional review board at the Fred Hutchinson Cancer Research Center (IR File#: 6007–1053).

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Abstract 1018 Figure 1 Receiver operating characteristic (ROC) curve demonstrating performance of the tumor-specific gene expression signature in independent validation cohorts from MCC (A) and NPC (B).