Phenotypic analysis of peripheral tumor-reactive CD8+ T Cells expanded by PD-1 blockade in murine melanoma

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Abstract

Identifying tumor-reactive $CD8^+$ T cells in the periphery is crucial for developing predictive biomarkers for PD-1 blockade cancer immunotherapy. Recent evidence indicates that PD-1 blockade does not rejuvenate terminally exhausted T cells but rather expands less differentiated, self-renewable $CD8^+$ T cells. However, pinpointing markers of these precursor-like $CD8^+$ T cells specific to tumor rejection antigens (TRA) in the periphery is challenging in human samples due to limitations in treatment protocols and difficulties in identifying antigen specificity.

To address this, we established a mouse model to analyze peripheral blood and tumors both before and after PD-1 blockade therapy using murine melanoma expressing a foreign antigen (SIY) that responds to the therapy. By single-cell RNA sequencing coupled with T cell receptor profiling, we found significant changes in the dominant clones of intratumoral TRA-specific (SIY tetramer-positive) $CD8^+$ T cells following PD-1 blockade therapy. SIY tetramer-positive clonotypes that expanded after treatment were detected in the periphery before treatment, even in small numbers. This expanded population originated from a specific cluster with unique gene expression patterns, including those associated with precursor-like $CD8^+$ T cells. This study provides specific marker candidates for the precursor-like TRA-specific $CD8^+$ T cells in the periphery before PD-1 blockade therapy.