TUMOR CONTEXT DICTATES RELIANCE ON TCF1 FOR RESPONSE TO IMMUNOTHERAPY

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Background Stem-like CD8 T cells that are regulated by the transcription factor TCF1 are key players in the response to immune checkpoint blockers (ICB). Recent findings indicate that the dependence on TCF1+ stem-like T cells for ICB efficacy may not be equal across patients and in different tumor contexts.

Methods Here we leveraged TCF1 conditional knock-out (TCF1-cKO) mice to investigate how TCF1 instructs the early fate and functions of CD8 cells upon ICB therapy in tumors that differ for immunogenicity and levels of tumor antigens expression.

Results Strikingly, we discovered that TCF1 expression in CD8 T cells is required for ICB efficacy in poorly immunogenic B16OVA melanomas but is dispensable in highly immunogenic MC38OVA colorectal tumors. Single-cell-RNA sequencing and immunophenotyping revealed defective priming and expansion of tumor-specific TCF1-cKO T cells in the tumor draining lymph-node (TDLN) of B16OVA- but not MC38OVA-bearing mice treated with ICB. In vitro, we found defective proliferation, reduced PD-1 and CD28 up-regulation and reduced phosphorylation of key molecules downstream the T cell receptor pathway when TCF1 cKO T cells were stimulated with low doses of antigens but not when stimulated with strong TCR signals. These data indicate that TCF1 poises T cells for optimal activation. Furthermore, transcriptional profiling of T cells in the TDLN further revealed the accumulation of a subset of tumor-specific naïve T cells poised to give rise to short-lived effectors in TCF1 cKO mice and thus is less suited to sustain anti-tumor responses in poorly immunogenic tumors where expansion of T cells retaining stem-like potential is required for durable anti-tumor responses. In tumors, single-cell-RNA sequencing and immunophenotyping showed that in MC38OVA tumors both WT and TCF1-cKO mice expanded a CD8 subset sharing a signature with transitory effector cells that mediate ICB efficacy in chronic viral infection models. Conversely, B16-OVA tumors retained a higher frequency of stem-like cells, failed to expand transitory effectors and accumulated Tox+ CD8 T cells, sharing a signature with CD8 cells expanded in non-responders to ICB. Importantly, loss of TCF1 was associated with reduced maintenance and proliferation of stem-like precursors and reduced expression of the Tox gene which was required for the survival of late effectors, altogether contributing to the failure of TCF1-cKO mice to sustain effective ICB responses.

Conclusions Our study highlights a role for TCF1 in the early stages of the CD8 T cell response with important implications for guiding the choice of optimal therapeutic interventions in tumors expressing low neoantigen levels.