

BASELINE MTOR TRANSCRIPTIONAL SIGNATURES IN CD8 T CELLS ARE ASSOCIATED WITH IMMUNE-RELATED ADVERSE EVENTS BUT NOT ANTI-TUMOR RESPONSES IN PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS

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Background Immune checkpoint inhibitors (ICIs) have changed the cancer treatment landscape, but immune-related adverse events (irAEs) can affect a wide range of tissues in patients receiving ICIs. Severe irAEs can be life-threatening or fatal and prohibit patients from receiving further ICI treatment. While the clinical features of irAEs are well documented, the pathological mechanisms and predictive biomarkers are largely unknown. In addition, there is a critical need to preserve ICI-induced anti-tumor immunity while controlling for irAEs, which requires deciphering molecular and cellular signatures associated specifically with irAEs beyond those more generally linked to anti-tumor immunity.

Methods To unbiasedly identify immune cells and states associated with irAEs, we applied CITE-seq to measure transcripts and surface proteins (83 protein markers) from PBMCs collected from patients with thymic epithelial tumors before and after treatment with an anti-PD-L1 antibody (avelumab, NCT01772004, NCT03076554).

Results Samples from 9 patients were analyzed. No patient had a history of pre-existing paraneoplastic autoimmune disease. Anti-tumor activity was observed in all cases, and 5 patients had clinical and/or biochemical evidence of immune-related muscle inflammation (myositis with or without myocarditis). Multilevel models applied within highly resolved cell clusters revealed transcriptional states associated with ICI response and more uniquely with irAEs. A total of 190,000 cells were included in the analysis after quality control. Most notably, CD45RA+ effector memory CD8 T cells with an mTOR transcriptional signature were highly enriched at baseline and post treatment in patients with irAEs.

Conclusions Our findings suggest the potential therapeutic avenues by using mTOR inhibitors to dampen autoimmune responses while potentially sparing anti-tumor activity, to prevent treatment discontinuation and improve clinical outcomes for cancer patients treated with ICIs.

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Ethics Approval This study is approved by NCI institutional review board.

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