EXPLORING THE POTENTIAL OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL) FOR GENERATING LEUKEMIA-SPECIFIC T CELL RESPONSES THAT CAN BE THERAPEUTICALLY HARNESSSED WITH IMMUNOTHERAPY

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Background T cell Acute Lymphoblastic Leukemia (T-ALL) is a devastating malignancy found primarily in pediatric populations. Unfortunately, standard of care for T-ALL has not progressed from highly toxic, intensive regimens of chemotherapy, which fails to cure all patients. Immunotherapies designed to activate patients' leukemia-specific T cells may provide a new therapeutic avenue to increase complete response rates, reduce toxicity without the need to engineer (e.g. CAR) cells. However, it is unknown whether T-ALL is capable of being recognized by T cells due given its relatively low mutation-rate. These studies therefore sought to investigate whether signs of leukemia-specific T cell responses are generated by T-ALL. Because T-ALL results in systemic disease and infiltrates multiple lymphoid and non-lymphoid tissues, these studies also determined how the divergent immune contexts of these TMEs impacts T cell responses to T-ALL. From this, we aim to identify immunotherapeutic targets capable of activating T cells across tissues to eradicate leukemia systemically.

Methods Primary leukemia cells isolated from a spontaneous murine model (LN3 mice) into immune-competent, congenic (CD45.1) recipient mice. Tissues were harvested at distinct stages of disease for analysis by flow cytometry or utilizing NanoString Technologies' GeoMX Digital Spatial Profiling (DSP) platform.

Results Flow cytometric analysis of T cells revealed extensive changes in response to T-ALL that included multiple features of exhaustion typically associated with anti-tumor responses as determined by upregulation of co-inhibitory receptors and TOX. This included a surprisingly high-frequency of PD1+ T cells, which was accompanied by PDL1- and PDL2-expressing myeloid cells that likely are restraining these subsets. Importantly, combination immunotherapy with OX40 agonists while inhibiting PD1 resulted in drastically reduced tumor burden and concomitant expansion of proliferating granzyme-expressing CD8 T cells. To gain better insight into T cell responses within distinct organs, we analyzed tissue sections using DSP. This technique enabled us to evaluate T cells in direct contact with leukemia infiltrates compared to T cells in regions without T-ALL, which further revealed an enrichment of activated subsets. Importantly, these studies have provided critical insight needed to better understand how T cells responding to T-ALL diverge between distinct types of tissues.

Conclusions The results from these studies collectively suggest that T cells are activated by T-ALL and that they can be therapeutically harnessed despite relatively low mutation-rates. Future studies will continue analysis of individual organs and use these results to rationally design combinations of immunotherapies by tailoring to activate T cells in all tissue types.

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