acid and MTOR metabolic pathways as a potential novel therapeutic targets for complementary therapy to restore immune function in melanoma and SCC patients.

Ethics Approval This study was performed under an IRB approved protocol.

P853 SINGLE CELL TRANSCRIPTOME ANALYSIS IDENTIFIES UNIQUE FEATURES IN CIRCULATING CD8+ T CELLS THAT CAN PREDICT IMMUNOTHERAPY RESPONSE IN MELANOMA PATIENTS

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10.1136/LBA2019.7

Background Immune checkpoint blockade (ICB) has greatly advanced the treatment of melanoma. A key component of ICB is the stimulation of CD8+ T cells in the tumor. However, ICB therapy only benefits a subset of patients and a reliable prediction method that does not require invasive biopsies is still a major challenge in the field.

Methods We conducted a set of comprehensive single-cell transcriptomic analyses of CD8+ T cells in the peripheral blood (mPBL) and tumors (mTIL) from 8 patients with metastatic melanoma.

Results Compared to circulating CD8+ T cells from healthy donors (hPBL), mPBLs contained subsets resembling certain features of mTIL. More importantly, three clusters (2, 6 and 15) were represented in both mPBL and mTIL. Cluster 2 was the major subset of the majority of hPBL, which phenocopied hallmark parameters of resting T cells. Cluster 6 and 15 were uniquely presented in melanoma patients. Cluster 15 had the highest PD-1 levels, with elevated markers of both activation and dysfunction/exhaustion; while Cluster 6 was enriched for 'dormant' cells with overall toned-down transcriptional activity except PPAR signaling, a known suppressor for T cell activation. Interestingly, unlike other mTIL clusters that would classically be defined as exhausted, Cluster 15 exhibited the highest metabolic activity (oxidative-phosphorylation and glycolysis). We further analyzed total sc-transcriptomics using cell trajectory algorithms and identified that these three clusters were the most distinct subtypes of CD8 T cells from each other, representing: resting (cluster 2), metabolically active-dysfunctional (cluster 15), and dormant phenotypes (cluster 6). Further, three unique intracellular programs in melanoma drive the transition of resting CD8+ T cells (cluster 2) to both metabolic/dysfunctional (cluster 15) and dormant states (cluster 6) that are unique to tumor bearing conditions. Based on these high-resolution analyses, we developed original algorithms to build a novel ICB response predictive model using immune-blockade co-expression gene patterns. The model was trained and tested using previously published GEO datasets containing CD8 T cells from anti-PD-1 treated patients and presented an AUC of 0.82, with 92% and 89% accuracy of ICB response in the two datasets.

Conclusions We identified and analyzed unique populations of CD8+ T cells in circulation and tumor using high-resolution single-cell transcriptomics to define the landscape of CD8+ T cell states, revealing critical subsets with shared features in PBLs and TILs. Most importantly, we established an innovative model for ICB response prediction by using peripheral blood lymphocytes.

Ethics Approval This study was performed under an IRB approved protocol.

Checkpoint blockade therapy

P854 CONSTRUCTION OF THE IMMUNE LANDSCAPE OF DURABLE RESPONSE TO CHECKPOINT BLOCKADE THERAPY BY INTEGRATING PUBLICLY AVAILABLE DATASETS

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10.1136/LBA2019.8

Background Immune checkpoint blockade (ICB) has revolutionized cancer treatment. However, long-term benefits are only achieved in a small fraction of patients. Understanding the mechanisms underlying ICB activity is key to improving the efficacy of immunotherapy. A major limitation to uncovering these mechanisms is the limited number of responders within each ICB trial. Integrating data from multiple studies of ICB would help overcome this issue and more reliably define the immune landscape of durable responses. Towards this goal, we formed the TimIOs consortium, comprising researchers from the Society for Immunotherapy of Cancer Sparkathon TimIOs Initiative, the Parker Institute of Cancer Immunotherapy, the University of North Carolina-Chapel Hill, and the Institute for Systems Biology. Together, we aim to improve the understanding of the molecular mechanisms associated with defined outcomes to ICB, by building on our joint and multifaceted expertise in the field of immuno-oncology. To determine the feasibility and relevance of our approach, we have assembled a compendium of publicly available gene expression datasets from clinical trials of ICB. We plan to analyze this data using a previously reported pipeline that