SINGLE-CELL TRANSCRIPTOMIC ANALYSIS OF IMMUNE COMPARTMENTS FOLLOWING COMBINATION IMMUNOTHERAPY TREATMENT IN POORLY IMMUNOGENIC TUMORS

¹Ang Cui*, ²Kelly Moynihan, ¹Shuqiang Li, ²Chensu Wang, ³Jackson Southard, ¹Nir Hacohen, ²Darrell Irvine. ¹Broad Institute of MIT and Harvard, Cambridge, MA, USA; ²MIT, Cambridge, MA, USA; ³Dana-Farber Cancer Institute, Boston, MA, USA

Background A major goal in cancer immunology is to rationally design combination therapies that lead to a higher response rate, especially for poorly immunogenic tumors that do not respond to immune checkpoint blockade therapy alone. We previously developed a combination therapeutic strategy, termed AIPV, consisting of a tumor-targeting antibody, a recombinant interleukin-2 with an extended half-life, an anti-PD-1 antibody, and a T cell vaccine [1]. The full AIPV therapy can eradicate large, aggressive, poorly immunogenic tumors in multiple mouse tumor models. However, the exact cellular and molecular pathways involved in such an effective response remain poorly understood.

Methods In this study, we used single-cell RNA-sequencing to define the detailed cellular and molecular changes in tumors and tumor-draining lymph nodes following the full AIPV therapy or a less effective sub-combination therapy in mice with poorly immunogenic B16F10 tumors.

Results Using our approach, we were able to uncover T cells, NK cells, neutrophils, macrophages/monocytes, classical dendritic cells, and plasmacytoid dendritic cells in tumors. We observed profound remodeling of every immune cell type following the effective therapeutic treatment. In particular, we found that classical dendritic cells take up tumor antigens, become activated, and migrate to draining lymph nodes following the AIPV therapy, but not following the less effective IPV therapy. We characterized the transcriptomic changes of these dendritic cells and found that they over-express molecules involved in antigen uptake.

Conclusions Our study comprehensively characterized a system that can overcome resistance to immune checkpoint blockade therapy, paving a cellular and molecular roadmap for immune-based therapeutic strategies that offer clinical benefits for poorly immunogenic tumors.

REFERENCES

1. Moynihan KD, Opel CF, Szeto GL, Tzeng A, Zhu EF, Engreitz JM, et al. Eradication of large established tumors in mice by combination immunotherapy that engages innate and adaptive immune responses. *Nat Med.* 2016;22: 1402–1410.

Ethics Approval All mouse experiments were reviewed and approved by the Koch Institute and Broad Institute Animal Care and Use Committee (IACUC) (ID 0222-08-18).

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.564>