

399

CLASS I HLA-INDEPENDENT LYSIS OF CANCER CELLS BY TUMOR-INFILTRATING CD8 T CELLS

^{1,2}Hongyan Xie*, ^{2,3}Aiping Jiang, ²Jonathan Perera, ^{2,3}Moshe Sade-Feldman, ^{2,3}Nir Hacohen, ^{2,4}Robert T Manguso, ^{2,3}Russell W Jenkins. ¹Massachusetts General Hospital, Boston, MA, USA; ²Broad Institute of MIT and Harvard, Cambridge, MA, USA; ³Massachusetts General Hospital Cancer Center, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ⁴Center for Cancer Research, Massachusetts General Hospital, Boston, MA, USA

Background Cancer immunotherapy with immune checkpoint blockade (ICB) has transformed the treatment of melanoma, although treatment resistance is common and fatal. Tumor-infiltrating CD8+ T lymphocytes (TILs) are key determinants of ICB response, and strategies to enhance tumor cell sensitivity to TILs is an emerging approach to overcome ICB resistance.

Methods We developed a patient-derived CD8+ TILs and cancer cells co-culture system. To identify cancer cell-intrinsic genes/pathways critical for CD8+ TIL-mediated killing CD8+ TILs, we performed a CRISPR screen using co-cultures of CD8+ TILs and cancer cells derived from patients with ICB-resistant melanoma.

Results To our surprise, TILs from ICB-resistant patients effectively killed matched melanoma cells, and traditional antigen presentation by human leukocyte antigen (HLA) class I was not required, suggesting the existence of other pathways for recognition and elimination of ICB-resistant melanoma cells by TILs. We further confirmed that established mediators of HLA-independent T cell killing (e.g., CD1d and MR1) and natural killer (NK) cell-related pathways (e.g., NKG2D) were not required for TIL-mediated killing. To nominate cancer cell-intrinsic genes/pathways critical for TIL-mediated killing, we performed a CRISPR screen which nominated death receptor signaling pathways and type I/II interferon (IFN) sensing pathways as crucial determinants of tumor control. Validation studies confirmed that both death receptor signaling and IFN pathways are necessary and sufficient for tumor cell lysis.

Conclusions Taken together, these findings indicate that ICB-resistant melanoma cells can be effectively targeted by CD8+ TILs via a novel mechanism involving cell extrinsic death receptor signaling and IFN sensing pathways.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.0399>