IMPACT OF TET2-MUTANT CLONAL HEMATOPOIESIS ON SOLID TUMOR IMMUNOLOGY AND RESPONSE TO CHECKPOINT BLOCKADE

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Background Clonal hematopoiesis (CH) is an age-related phenomenon characterized by the overrepresentation of blood cells arising from a single, mutant clone and is detectable in 10-20% of individuals over 70. CH has now been implicated in a variety of non-hematological disorders, such as cardiovascular diseases and Covid-19 infections, by exacerbating the innate inflammatory response. However, the impact of CH in solid tumors and response to immune checkpoint blockade (ICB) is unknown.

Methods To assess the prevalence and role of CH in patients with solid tumors, we analyzed publicly available data from the MSKCC-IMPACT study. To mechanistically study CH in solid tumors, we established an orthotopic model of pancreatic adenocarcinoma (PDAC) in mice with Tet2+/- CH. CH and WT mice were treated with either ICB (αCTLA-4 + αPD-1) or vehicle control. Single-cell (sc-) RNAseq was performed on tumor infiltrating lymphocytes (n=3/group) while remaining mice were observed for disease progression and overall survival (n=10/group).

Results Analyzing CH frequencies in a cohort of patients with solid tumors, we observed that the prevalence of CH was approximately 5 times higher in patients with cancer when compared to healthy age-matched controls. Further, patients with detectable CH clones had significantly worse overall survival (figure 1A). In vivo, sc-RNAseq data revealed that myeloid cells present within the pancreatic tumors of mice with Tet2+/- CH were significantly enriched for both type I and type II interferon (IFN) signaling (figure 1B). Further, these IFN+ myeloid cells were ablated after ICB therapy in Tet2+/- WT mice but persisted in mice with Tet2+/- CH (figure 1C). PDAC tumors from mice with Tet2+/- CH had approximately half the total number of infiltrating CD8 T cells at baseline when compared to those from Tet2+/- WT mice. Upon ICB treatment, CD8 effector cells only expanded in the tumors from Tet2+/- WT mice. Functionally, this translated to more rapidly progressing tumors, resistance to ICB, and reduced overall survival in mice with Tet2+/- CH (figure 1D).

Conclusions CH is present in upwards of 30% of patients with solid tumors and is associated with significantly worsened prognosis. Modeling PDAC in the presence of Tet2+/- CH in vivo revealed distinct alterations in the tumor microenvironment that ultimately influenced tumor progression and response to ICB. This proposed research bridges the fields of solid tumor immunology and clonal hematopoiesis to address novel mechanisms of immunotherapy resistance that will span cancer type and, ultimately, improve patient care.

REFERENCES

Ethics Approval All mice were housed in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care and NIH standards. Experiments were conducted according to protocol 00000893-RN02 and approved by the University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee.