CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature
Article Recommendations from Our Deputy and Senior Editors

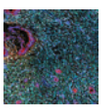
Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments

Lactic acid is a metabolic checkpoint for Treg cells (from Jynto via Wikimedia Commons)

The intratumoral ratio of $CD8^+$ T cells to regulatory T (Treg) cells impacts responsiveness to PD-1 blockade. Kumagai et al. find the ratio of $CD8^+$ T cells to Treg cells is low in highly glycolytic tumors, including MYC-amplified tumors and liver metastases, and that expression of PD-1 is lower in $CD8^+$ T cells than Treg cells. This effect is mediated by tumor-derived lactic acid and leads to resistance to PD-1 blockade in mouse models of Myc-overexpressing colon cancer and intrahepatic tumors. Blocking lactic-acid production or its uptake by Treg cells overcomes this resistance, suggesting potential new targets for cancer immunotherapy.

Kumagai S, . . ., Nishikawa H. ***Cancer Cell*** *2022 Feb 14;40:201–18.e9.*

Disrupting N-glycan expression on tumor cells boosts chimeric antigen receptor T cell efficacy against solid malignancies



Pancreatic cancer can be protected from CAR T cells by N-glycans (from Neelima Shah and Edna Cukierman via NCI Visuals Online)

Chimeric antigen receptor (CAR) T-cell therapy has limited efficacy against solid tumors. Greco et al. identify expression of N-linked glycans as a targetable barrier to killing of solid tumors by CAR T cells. Knockout of mannoside acetylglucosaminyltransferase 5 and exposure to 2-deoxy-D-glucose (2DG), both of which disrupt N-glycan expression, render T3M-4 human pancreatic cancer cells sensitive to killing by CD44v6-targeted CAR T cells *in vitro*. Treatment with 2DG enhances tumor-cell killing by CAR T cells in xenograft models of pancreatic, ovarian, bladder, and lung cancer, suggesting a new approach to improve CAR T-cell therapy for solid tumors.

Greco B, . . ., Casucci M. ***Sci Transl Med*** *2022 Jan 19;14:eabg3072.*

SLAMF3 and SLAMF4 are immune checkpoints that constrain macrophage phagocytosis of hematopoietic tumors

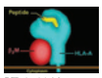
Blocking "don't eat me" signals increases macrophage phagocytosis (from QuidsUp)

Modulation of macrophage phagocytosis is a tumor escape mechanism. Li et al. find a role for signaling lymphocytic activation molecule (SLAM) family receptors (SFR) in limiting macrophage phagocytosis by hematopoietic tumors. Specifically, SLAMF3 and SLAMF4 are identified as "don't eat me" receptors on macrophages. Deficiency in SFRs, with and without CD47 deficiency, increases phagocytosis of hematopoietic cells (i.e., "self") and malignant cells, highlighting a novel signaling pathway that can modulate the function of macrophages in the tumor microenvironment.

Li D, . . ., Dong Z. ***Sci Immunol*** *2022 Jan 21;7:eabj5501.*

doi: 10.1158/2326-6066.CIR-10-3-WWR

*HLA-A*03* and response to immune checkpoint blockade in cancer: an epidemiological biomarker study

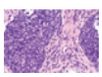


*HLA-A*03 is associated with poor response to immune checkpoint blockade (from Pdeitiker via Wikimedia Commons)*

Human leukocyte antigens (HLA) play a vital role in immunity, and thus, could impact immunotherapy efficacy. Using multiple large-scale datasets, Naranbhai et al. identify HLA-A*03 as a biomarker of response to immunotherapy but not response to other types of cancer treatment. Expression of this HLA associates with worse progression-free survival and lower responses to immune checkpoint inhibitors, which was validated in several independent cohorts of patients with various tumor types.

Naranbhai V, . . ., Carrington M. ***Lancet Oncol*** *2022 Jan 1;23:172–84.*

Single-cell analysis of human non-small cell lung cancer lesions refines tumor classification and patient stratification



Understanding of the NSCLC immune landscape continues to deepen (from Libnepath via Wikimedia Commons)

Deepening understanding of the immune landscape of non–small cell lung cancer (NSCLC) can help identify biomarkers of response to immunotherapy. Using single-cell RNA sequencing and cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), Leader et al. find a strong correlation between $PDCD1^+CXCL13^+$ activated T cells, IgG^+ plasma cells, and $SPP1^+$ macrophages; they refer to these cells collectively as the lung cancer activation module (LCAM). The $LCAM^{hi}$ phenotype correlates with tumor mutational burden, *TP53* mutations, and response to anti–PD-L1 therapy but not chemotherapy, suggesting that it could be a new biomarker of NSCLC response to immunotherapy.

Leader AM, . . ., Merad M. ***Cancer Cell*** *2021 Dec 13;39:1594–609.e12.*

TRIB3 reduces $CD8^+$ T cell infiltration and induces immune evasion by repressing the STAT1-CXCL10 axis in colorectal cancer

TRIB3 regulates $CD8^+$ T-cell exclusion in the tumor microenvironment (from Max Pixel)

Colorectal cancer resistance to immune checkpoint therapy is partly attributable to a lack of tumor-infiltrating T cells. Shang et al. report that TRIB3 expression in tumor cells correlates with $CD8^+$ T-cell exclusion in mouse models of colorectal cancer and human samples. TRIB3 expression inhibits expression of the T cell–recruiting chemokine CXCL10 by activating STAT3, which inhibits transcription of STAT1 and subsequently CXCL10. Inhibition of the P300 acetylase, which acetylates TRIB3 and prevents E3 ligase–mediated degradation, improves $CD8^+$ T-cell infiltration and sensitizes colorectal tumors to checkpoint blockade *in vivo*, suggesting a therapeutic strategy to improve immunotherapy efficacy in immunologically "cold" colorectal tumors.

Shang S, . . ., Hua F. ***Sci Transl Med*** *2022 Jan 5;14:eabf0992.*