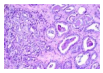
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

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

Evolution of Myeloid-Mediated Immunotherapy Resistance in Prostate Cancer

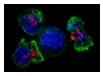


$SPP1^{hi}$ TAMs promote resistance to ICI treatment in prostate cancer (from Otis Brawley via NCI Visuals)

Immune checkpoint inhibitors (ICI) are largely ineffective against metastatic castration-resistant prostate cancer (mCRPC), in part because of immunosuppressive myeloid cells present in the tumors. Using single-cell RNA sequencing of patient biopsies, Lyu and colleagues find tumor-associated macrophages (TAM) expressing high levels of *SPP1* are enriched in mCRPC. *$Spp1^{hi}$*-TAMs are present in mouse models of prostate cancer where they drive resistance to ICI treatment and mediate immunosuppression through adenosine signaling. Inhibiting adenosine A2A receptors with ciforadenant in combination with ICI treatment reduces prostate tumor growth in mouse models and elicits clinical responses in patients with mCRPC, highlighting the clinical relevance of the study.

Lyu A, . . ., Fong L. ***Nature*** *2024 Dec 04;DOI:10.1038/s41586-024-08290-3.*

The Redox Sensor KEAP1 Facilitates Adaptation of T Cells to Chronic Antigen Stimulation by Preventing Hyperactivation

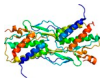


The KEAP1–NRF2 pathway helps regulate $CD8^+$ T-cell responses to chronic antigen stimulation (from NICHD/J. Lippincott-Schwartz via NIH Flickr)

The molecular pathways regulating $CD8^+$ T-cell adaptation to persistent antigen exposure during chronic infection and cancer are incompletely defined. In a model of chronic viral infection, Zhu and colleagues show that KEAP1 promotes the expansion and persistence of virus-specific $CD8^+$ T cells and the generation and responsiveness of stem-like $CD8^+$ T cells. KEAP1 suppresses expression of NRF2, which prevents NRF2 from epigenetically opposing a stem-like program driven by BACH2. The same KEAP1–NRF2 pathway promotes expansion, survival, and tumor-infiltration of GD2-targeted chimeric antigen receptor (CAR) T cells exposed *in vivo* to chronic CAR stimulation, suggesting new ways to improve CAR T-cell therapies.

Zhu Z, . . ., Yao C. ***Sci Immunol*** *2024 Nov 29;9:eadk2954.*

Interleukin-15-armoured GPC3 CAR T Cells for Patients with Solid Cancers



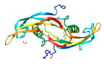
IL15 expression enhances CAR T-cell activity in patients with solid tumors (from Pleiotrope via Wikimedia Commons)

Engineering chimeric antigen receptor (CAR) T cells to express IL15 improves their efficacy in preclinical solid tumor models. Steffin and colleagues report that IL15 expression in glypican 3 (GPC3)-targeted CAR T cells increases their expansion, intratumoral survival, and antitumor activity in patients with $GPC3^+$ solid tumors. No objective responses were detected among the six patients receiving 3×10^7 GPC3 CAR T cells lacking IL15 expression, whereas 4 of 12 patients receiving 3×10^7 IL15-expressing GPC3 CAR T cells had partial response. Cytokine release syndrome was more common among patients receiving IL15-expressing GPC3 CAR T cells, but could be controlled, supporting ongoing clinical evaluation of the approach.

Steffin D, . . ., Heczey A. ***Nature*** *2024 Nov 27;DOI:10.1038/s41586-024-08261-8.*

doi: 10.1158/2326-6066.CIR-13-2-WWR

Neutralizing GDF-15 Can Overcome Anti–PD-1 and Anti–PD-L1 Resistance in Solid Tumours



GDF-15 targeting could be a new cancer intervention (from Goultard59 via Wikimedia Commons)

GDF-15, a divergent TGFβ superfamily member expressed in certain solid cancers, impairs responses to anti–PD-1 in preclinical models. Data from the first-in-human phase 1-2a clinical trial, reported by Melero and colleagues, shows that adding the GDF-15–blocking antibody visugromab to the anti–PD-1 nivolumab leads to durable and long-lasting tumor control in some patients with non-squamous non–small cell lung cancer and urothelial cancer refractory to anti–PD-1/L1. Increased T-cell infiltration into the tumor microenvironment, along with heightened T-cell proliferation, activation, and IFNγ signaling, contributed to overcoming resistance to anti–PD-1/L1. The data support further clinical evaluation of GDF-15 blockade as a novel cancer immunotherapy.

Melero I, ..., Leo O. ***Nature*** *2024 Dec 11;DOI: https://doi.org/10.1038/s41586-024-08305-z.*

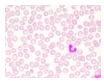
Single-cell Profiling of Acral Melanoma Infiltrating Lymphocytes Reveals a Suppressive Tumor Microenvironment

ALM and cutaneous melanoma have differing immune landscapes (from Mikael Häggström via Wikimedia Commons)

Immune checkpoint inhibitors (ICI) are not effective treatments for acral lentiginous melanoma (ALM). To understand why, Minowa and colleagues use paired single-cell RNA and T-cell receptor sequencing to comprehensively characterize ALM tumor-infiltrating T lymphocytes (TILs). In comparison with publicly available data from cutaneous melanoma, which responds to ICI therapy, TILs in AML are more immunosuppressive, with increased tumor-specific Tregs and reduced tumor-reactive $CD8^+$ T-cell infiltration. *KLRC1*, which encodes NKG2A, is upregulated on tumor-reactive $CD8^+$ TILs in ALM. Targeting NKG2A in combination with anti–PD-1 successfully reinvigorates the responses to AML *in vitro*, suggesting a potential approach to improving immunotherapy for this subtype of melanoma.

Minowa T, ..., Torigoe T. ***Sci Transl Med*** *2024 Dec 4;DOI:10.1126/scitranslmed.adk8832.*

Cancer Cells Impair Monocyte-Mediated T Cell Stimulation to Evade Immunity



Monocytes with inflammatory properties can help T cells fight cancer (from Echinaceapallida via Wikimedia Commons)

Effective control of tumor growth by tumor-infiltrating primed T cells requires restimulation of the cells in the tumor, but the events underlying this are incompletely understood. Using mouse models of BrafV600E-driven melanoma, Elewaut and colleagues show that tumor-infiltrating T cells are restimulated by inflammatory monocytes that obtain and present peptide–MHC I complexes from tumor cells by "cross-dressing". Increased MAPK signaling in tumor cells reduces production of type I IFN and increases prostaglandin E2 (PGE_2) secretion, which impairs myeloid polarization to an inflammatory state and consequently impairs intratumoral T-cell stimulation. Enhancing type I IFN signaling and blocking PGE_2 improves tumor control, suggesting new approaches to combination cancer immunotherapy.

Elewaut A, . . ., Obenauf AC. ***Nature*** *2024 Nov 27;637,716–725.*