CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

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

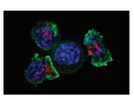
T cells specific for α-myosin drive immunotherapy-related myocarditis

Myocarditis is the most lethal ICI-associated adverse event (from OpenStax Anatomy and Physiology via Wikimedia Commons)

Myocarditis is a rare, often fatal, and poorly mechanistically understood adverse event associated with immune checkpoint inhibitor (ICI) therapy. Axelrod et al. find that in a mouse model of ICI-associated myocarditis—*Pdcd1*$^{-/-}$*Ctla4*$^{+/-}$mice—CD8$^+$ T cells are necessary for fatal myocarditis to develop. The cardiac-infiltrating CD8$^+$ T cells are highly clonal, with the T-cell receptors (TCR) from three clones recognizing MHC class I–presented α-myosin peptides. The clinical relevance of the data is supported by the detection of α-myosin–specific MHC class I–restricted TCRs in cardiac and skeletal muscle of patients with ICI-associated myocarditis.

Axelrod ML, . . ., Balko JM. ***Nature*** *2022 November 16;611:818–26.*

Expanding the therapeutic utility of CAR T cells



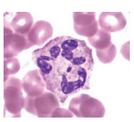
Research is identifying new ways to enhance the antitumor activity of CAR T cells (from Alex Ritter, Jennifer Lippincott Schwartz, and Gillian Griffiths via NIH Flickr)

Many research groups are working to expand the therapeutic utility of chimeric antigen receptor (CAR) T-cell therapies, which yield responses for a minority of patients with hematological malignancies, through innovative CAR design and T-cell engineering, as highlighted in two recent studies. Goodman et al. use a clinically relevant B-cell maturation antigen (BCMA)–specific CAR to show proof-of-principle that a multiplexed approach they call "CAR Pooling" can identify new CAR designs with enhanced activity in a xenotransplant model of disease. In the solid tumor setting, Jung et al. find that activity can be enhanced by knocking out the genes encoding B lymphocyte–induced maturation protein 1 (BLIMP1) and nuclear receptor subfamily 4 group A member 3 (NR4A3) in prostate-specific membrane antigen (PSMA)–specific CAR T cells, countering exhaustion and improving antitumor immunity in a model of prostate cancer.

Goodman DB, . . ., Roybal KT. ***Sci Trans Med*** *2022 November 9;14. DOI:10.1126/scitranslmed.abm1463.*

Jung IY, . . ., Fraietta JA. ***Sci Trans Med*** *2022 November 9;14. DOI: 10.1126/scitranslmed.abn7336.*

Liver tumour immune microenvironment subtypes and neutrophil heterogeneity

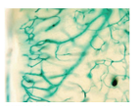


Neutrophils are phenotypically and functionally heterogenous (from Ed Uthman via Wikimedia Commons)

Understanding of how the heterogeneity of neutrophils underpins their pro- and antitumorigenic functions is emerging. Through comprehensive analysis of samples from 124 patients with liver cancer and mouse models of the disease, Xue et al. report a detailed landscape of neutrophil phenotypic heterogeneity in liver cancer. Neutrophils are particularly enriched and associated with worse prognosis in liver cancers characterized as having an immune-suppressive myeloid tumor microenvironment. Among the functional analyses performed, CCL4$^+$ and PD-L1$^+$ neutrophil subsets are shown to be protumorigenic, recruiting macrophages and suppressing T-cell cytotoxicity, respectively, suggesting these neutrophil subsets as potential targets for immunotherapy.

Xue R, . . ., Zhang N. ***Nature*** *2022 November 9;612:141–47.*

Cancer immunotherapies transition endothelial cells into HEVs that generate TCF1$^+$ T lymphocyte niches through a feed-forward loop

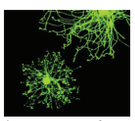


HEV differentiation can be induced by immunotherapy (from Art Anderson via Wikimedia Commons)

The mechanisms underlying changes in blood vessel architecture that are associated with improved T-cell infiltration into solid tumors following immunotherapy treatment are poorly understood. Hua et al. show that immunotherapy in tumor-bearing mice causes tumor endothelial cells to take on phenotypes similar to inflamed high-endothelial venules (HEV), structures characteristic of lymph nodes and tertiary lymphoid structures that facilitate T-cell migration and infiltration. Differentiation into HEVs and increased T-cell infiltration depends on continuous immunotherapy treatment and tumor-infiltrating CD8$^+$ T-cell and NK-cell signaling in a positive-feedback cycle, with HEV niches promoting cytotoxicity of PD1$^+$TCF1$^+$ T cells in the tumor. These findings reveal novel regulatory mechanisms of tumor microenvironment components to support an immunotherapy response.

Hua Y, . . ., Bergers G. ***Cancer Cell*** *2022 December 12;40:1600-18.E10.*

Nociceptor neurons affect cancer immunosurveillance



Sensory neurons induce exhaustion in tumor-infiltrating T cells (from Isabella Gavazzi via Wellcome Collection)

The interactions between neurons and immune cells in a tumor are not fully understood. Balood et al. show in mouse models of melanoma that tumor cells potentiate nociceptor (pain sensory) neurons via secretory leukocyte protease inhibitor (SLPI) secretion, subsequently driving secretion of neuron-derived calcitonin gene-related peptide (CGRP). CGRP in the tumor microenvironment promotes exhaustion of tumor-reactive infiltrating CD8$^+$ T cells, which can be reduced by depletion of nociceptor neurons, genetic knockout of the CGRP receptor Ramp1, or administration of a selective RAMP1 antagonist. These findings highlight a potentially targetable mechanism of immune evasion in solid tumors at the intersection of the peripheral nervous and immune systems.

Balood M, . . ., Talbot S. ***Nature*** *2022 November 2;611:405–12.*

Systemic vaccination induces CD8$^+$ T cells and remodels the tumor microenvironment

Intravenous delivery of cancer vaccine improves antitumor responses (from Nic McPhee via Flickr)

Vaccines that prime a patient's immune system against cancer neoantigens have so far not demonstrated wide success. By leveraging a neoantigen-delivering nanoparticle vaccine to treat tumor-bearing mice, Baharom et al. find that intravenous (IV) delivery of a booster dose improves T cell–dependent antitumor responses compared to a subcutaneous dose. IV administration enhances delivery to the tumor and increases immune cells in the tumor microenvironment and draining lymph nodes. Response to IV vaccine, which is shown to be independent of the neoantigen delivery, is mediated by IFNα and associated with a reduction in intratumoral regulatory-like CHIL3$^+$ monocytes, suggesting biomarkers and mechanistic pathways for this promising cancer vaccine strategy.

Baharom F, . . ., Seder RA. ***Cell*** *2022 November 10;185:4317-32.E15.*

doi: 10.1158/2326-6066.CIR-11-1-WWR