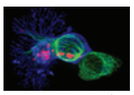
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

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

Oncometabolite D-2HG alters T cell metabolism to impair CD8$^+$ T cell function

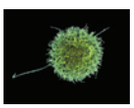


D-2HG inhibits CD8$^+$ T-cell function (from Alex Ritter, Jennifer Lippincott Schwartz and Gillian Griffiths via NIH Flickr)

D-2-hydroxyglutarate (D-2HG), which accumulates in cancers with mutations in isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*, can act as an oncometabolite by promoting cancer-cell intrinsic epigenetic alterations. Notarangelo et al. show in preclinical models that D-2HG also inhibits CD8$^+$ T-cell proliferation, cytotoxicity, and IFNγ production, which are all critical for antitumor immunity. These effects, which are acute and reversible, occur because D-2HG alters CD8$^+$ T-cell metabolism by inhibiting lactate dehydrogenase activity, thereby altering glycolytic flux and NAD(H) balance. Samples from patients with IDH-mutant glioma similarly show reduced lactate levels and IFNγ signatures, highlighting the clinical relevance of the data.

Notarangelo G, . . ., Haigis MC. ***Science*** *2022 October 5;377:1519–29.*

KIR-based inhibitory CARs overcome CAR-NK cell trogocytosis-mediated fratricide and tumor escape



NK cells with two CARs show enhanced antitumor activity (from NIAID via Wikimedia Commons)

Natural killer (NK) cells engineered to express a chimeric-antigen receptor (CAR) are being evaluated in cancer clinical trials. Li et al. find that activation of CARs on CAR-NK cells can drive trogocytosis, whereby the antigen target of the CAR is transferred from the tumor cells to the CAR-NK cells. This leads to loss of tumor control because the density of the target antigen is reduced on the tumor cells and CAR-NK cells that acquire target antigen by trogocytosis are killed by other CAR-NK cells. Adding an additional inhibitory CAR to the engineered CAR-NK cells prevents trogocytosis-induced fratricide and enhances *in vivo* antitumor efficacy, suggesting new avenues of investigation to further develop CAR-NK cell therapies.

Li Y, . . ., Rezvani K. ***Nat Med*** *2022 September 29;28:2133–44.*

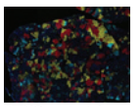
Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy

Induction of ferroptosis can be harnessed as a therapy (from Albedo-ukr via Wikibooks)

Understanding the metabolic pathways activated in cancer can reveal new opportunities for treatment. Using a multiomic approach, Yang et al. defined the ferroptosis-related metabolic phenotypes of triple-negative breast cancer (TNBC), finding that the luminal androgen receptor (LAR) subtype of TNBC shows upregulation of glutathione metabolism. Inhibition of glutathione peroxidase 4 (GPX4) in preclinical models not only induces tumor cell ferroptosis, but also boosts antitumor responses and enhances the efficacy of anti–PD-1. The data suggest that ferroptosis can be harnessed to improve treatment of TNBC and identify a novel combination that has potential for treating the LAR subtype.

Yang F, . . ., Shao ZM. ***Cell Metab*** *2022 October 17. DOI:10.1016/j.cmet.2022.09.021.*

STING-induced regulatory B cells compromise NK function in cancer immunity



STING agonists induce Breg cells in pancreatic cancer (from Ravikanth Maddipati via NIH Flickr)

Agonists of stimulator of interferon genes (STING) have shown little efficacy as monotherapies in clinical trials despite preclinical promise. Li et al. provide new insight into the effects of STING agonists, finding that they induce a population of IL35$^+$IL10$^+$ regulatory B (Breg) cells that impair NK cell–mediated antitumor responses in mouse models of pancreatic cancer. Combining STING agonist treatment with either genetic ablation of IL35 or anti-IL135 therapy reduces tumor growth and increases infiltration, activation, and antitumor cytotoxicity of NK cells, highlighting a potential strategy to reverse STING agonist–induced immunosuppression in the pancreatic cancer tumor microenvironment.

Li S, . . ., Ting JPY. ***Nature*** *2022 October 5;610:373–80.*

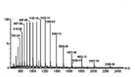
PD-1-cis IL-2R agonism yields better effectors from stem-like CD8$^+$ T cells

A new immunocytokine has therapeutic potential (from Simplelcon via Wikimedia Commons)

IL2 therapies have proven challenging to use in the clinic because of toxicity, in part due to binding to the IL2 receptor α-chain (CD25) on CD4$^+$CD25$^+$ regulatory T cells. Codarri Deak et al. have developed a new immunocytokine, PD1–IL2v, which bypasses the requirement of binding to CD25 by binding in *cis* to the IL2 receptor β- and γ-chain and to PD-1. The immunocytokine acts on PD-1$^+$TCF-1$^+$ stemlike CD8$^+$ T cells, enhancing their proliferation and effector differentiation, and was more effective than PD-1/PD-L1 antibodies alone and PD-1/PD-L1 antibodies in combination with IL2Rv (non–PD-1–targeted) in both infection and cancer models. The data highlight the potential of *cis*-targeted IL2 therapies.

Codarri Deak L, . . ., Umaña P. ***Nature*** *2022 September 28;610:161–72.*

Post-translational modifications reshape the antigenic landscape of the MHC I immunopeptidome in tumors



Identifying post-translationally modified MHC-bound peptides (from Alshaver via Wikimedia Commons)

The total collection of possible tumor-associated HLA I–bound peptides is expanded by post-translational modifications (PTM), which have so far been incompletely accounted for. Kacen et al. have developed Protein Modification Integrated Search Engine (PROMISE) to detect PTMs on MHC-associated peptides assayed by mass spectrometry. Analysis of previously published immunopeptidomic data sets using PROMISE identified biases in the sequential position of various PTMs, possibly reflecting positional preference for PTMs in HLA binding kinetics, biases in HLA alleles binding to specific PTMs, and a number of tumor-associated modified antigens in human patient samples. This work expands our ability to detect and target cancer-specific PTMs with immunotherapy.

Kacen A, . . ., Merbl Y. ***Nat Biotechnol*** *2022 October 6. DOI:10.1038/s41587-022-01464-2.*

doi: 10.1158/2326-6066.CIR-10-12-WWR