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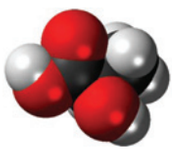
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Metabolic reprogramming of donor T cells enhances graft-versus-leukemia effects in mice and humans



Space-filling model of the D-isomer of lactic acid [by Jynto (talk) via Wikimedia Commons]

Patients with acute myeloid leukemia (AML) who relapse after an allogeneic hematopoietic cell transplant (allo-HCT) have a poor prognosis. Uhl et al. show that $CD8^+$ T cells from such patients have reduced glycolytic activity, oxidative phosphorylation, and IFNγ production. In mouse models, AML cells are found to produce lactic acid, reducing intracellular pH in $CD8^+$ T cells and leading to impaired glycolytic and antitumor activity. Sodium bicarbonate improves metabolic fitness and antitumor activity of $CD8^+$ T cells in mouse models and patients, suggesting a new approach to improving outcomes for patients who have relapsed after allo-HCT.

Uhl FM, . . ., Zeiser R. ***Sci Transl Med*** *2020 Oct 28;12:eabb8969.*

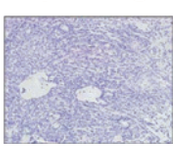
Innate immune training of granulopoiesis promotes anti-tumor activity

Innate immune training can have antitumor effects (by Arafat Uddin, BD, via Noun Project)

Trained innate immunity is the enhanced responsiveness of innate immune cells when they re-encounter pathogens. Some microbial components that cause innate immune training have antitumor effects, including fungal-derived β-glucan; whether the antitumor effects of these agents involve innate immune training is not known. Kalafati et al. find that β-glucan–induced innate immune training reduces tumor growth in mouse models of melanoma and lung cancer. This is mediated by type I IFN–mediated rewiring of granulopoiesis, which drives neutrophils toward an antitumor phenotype. The data suggest that it might be possible to harness trained innate immunity for cancer immunotherapy.

Kalafati L, . . ., Chavakis T. ***Cell*** *2020 Oct 29;183:771–85.E12.*

Improving CAR T-cell therapy for solid tumors



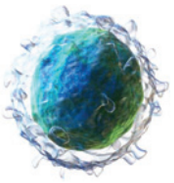
Immunostaining of tumor-bearing mouse brain tissues (from Fig. 6B, top left panel, of Jiang et al. Cancer Immunol Res 2018)

CAR T-cell therapy has limited activity against solid tumors. Addressing this issue is a high priority. Hao et al. use cell–surface anchor-engineering technology to insert an anchor into the plasma membrane of T cells and then click liposomal avasimibe to the anchor. Avasimibe increases plasma-membrane cholesterol concentrations, enhancing TCR clustering and, thereby, T-cell function. Anchoring liposomal avasimibe to GD2-targeted CAR T cells improves antitumor activity in a glioblastoma (GBM) model. Using kinome-wide genetic screening, Ma et al. identify PAK4 as a driver of functional abnormalities in human GBM endothelial cells, including aberrant vascularization. Adding a PAK4 inhibitor to EGFRvIII-targeted CAR T cells improves antitumor activity in two GBM models. These studies open new avenues for enhancing CAR T-cell therapy for solid tumors.

Hao M, . . ., Zhang C. ***Sci Transl Med*** *2020 Nov 25;12:eaaz6667.*

Ma W, . . ., Fan Y. ***Nat Cancer*** *2020 Nov 30. DOI: 10.1038/s43018-020-00147-8.*

Defining HPV-specific B cell responses in patients with head and neck cancer

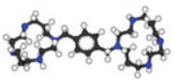


HPV-specific B cells can be detected in HPV^+ head and neck cancers (by Blausen Medical via Wikimedia Commons)

Antigen specificity of tumor-infiltrating B cells is not yet fully characterized. Using a variety of methods, Wieland et al. show that B cells and antibody-secreting cells (ASC) infiltrate human papillomavirus (HPV)–positive head and neck cancers and have specificity against multiple HPV proteins. Both activated B cells and ASCs are localized to stromal regions within germinal centers in the tumor microenvironment and possess characteristics of chronic antigen stimulation. The data highlight a role for B cells in antitumor responses and could provide an avenue for development of new therapeutics targeted to humoral responses against cancer-associated viral antigens.

Wieland A, . . ., Ahmed R. ***Nature*** *2020 Nov 18. DOI: 10.1038/s41586-020-2931-3.*

CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response



Plerixafor can boost antitumor responses (ball-and-stick model of plerixafor by Fvasconcellos via Wikimedia Commons)

CXCR4 inhibition has antitumor efficacy, but the mechanisms behind this are not well-known. Biasci et al. find that pancreatic and colorectal tumor cells have a CXCL12 "coat" and that interaction with CXCR4 on immune cells leads to impaired immune-cell chemotaxis, as well as immune suppression in the tumor microenvironment. Patients with microsatellite-stable pancreatic and colorectal cancers continuously treated short-term with a CXCR4 inhibitor (plerixafor/AMD3100) have increased $CD8^+$ T-cell and NK-cell infiltration into metastatic lesions and induction of intratumoral B-cell responses. Using this data, a gene signature indicative of an "integrated immune response" is identified, named INTIRE.

Biasci D, . . ., Jodrell DI. ***Proc Natl Acad Sci U S A*** *2020 Nov 17;117:28960–70.*

Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade

PGE2 interaction can prevent NK-cell activity (U.S. Navy football game by Dominic Montez via Wikimedia Commons)

Inflammation is a double-edged sword when it comes to promoting or suppressing antitumor responses. Bonavita et al. identify NK cells as modulators of direct and indirect antitumor responses in the tumor microenvironment (TME) of multiple cancer types. Through production of IFNγ, NK cells shape $CD8^+$ T-cell responses, and interaction of tumor-derived PGE2 with receptors on NK cells in the TME can prevent this cytotoxic unleashing. A Cox-2/PGE2–associated inflammatory TME signature is identified, called COX-IS, which can accurately predict survival and response to immunotherapy.

Bonavita E, . . ., Zelenay S. ***Immunity*** *2020 Dec 15;53:1215–29.E8.*

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