

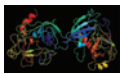
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE
READING

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Granzyme B nanoreporter for early monitoring of tumor response to immunotherapy

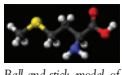


Structure of the granzyme B protein (based on PyMOL rendering of PDB 1jg3) by Emsw via Wikimedia Commons

Immune checkpoint inhibitors (ICI) are effective against many cancer types, but an approach to accurately and rapidly identify which patients have tumors responding to ICIs is lacking. Nguyen et al. combine an imaging probe activated by granzyme B (GrB) with a low-molecular-weight polymer and a PDL1-targeted ICI to create a GrB nanoreporter (GNR). GrB is detected in MC38 tumors, which are highly responsive to ICIs, within 24 hours of low-dose GNR administration. In tumors less responsive to ICIs, B16/F10 tumors, higher doses of the GNR achieved responses. The data suggest that GNRs may prove useful as a tool for sensitive and noninvasive early assessment of ICI efficacy.

Nguyen A, . . . Kulkarni AA. *Sci Adv* 2020 Oct 2;6:eabc2777.

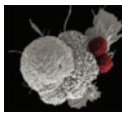
Cancer SLC43A2 alters T cell methionine metabolism and histone methylation



Ball-and-stick model of the L-isomer of methionine in electrically neutral form by Jyuto (talk) via Wikimedia Commons

The exhausted T cells found in many tumors acquire distinct epigenetic profiles associated with dysfunction, but all the factors contributing to the epigenetic changes have not been elucidated. Bian et al. show that tumor cells outcompete T cells for methionine because they express high levels of the methionine transporter SLC43A2. Low methionine levels decrease dimethylation of lysine 79 of histone H3 (H3K79me2) in the T cells, which reduces STAT5 expression and impairs T-cell immunity. Methionine supplementation, and genetic and biochemical inhibition of SLC43A2 enhance spontaneous antitumor T-cell immunity in mice and synergize with anti-PDL1 treatment. Thus, targeting cancer methionine signaling may provide a new avenue for immunotherapy.

Bian Y, . . . Zou W. *Nature* 2020 Sep 2;585:277–82.

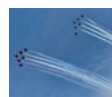
Losing CD226 impairs CD8⁺ antitumor immunity

Cancer immunotherapy (via National Cancer Institute/Duncan Comprehensive Cancer Center at Baylor College of Medicine)

CD226 is an activating receptor on NK cells and CD8⁺ T cells, but its role in antitumor immunity remains elusive. Braun et al. show that some mouse and human CD8⁺ tumor-infiltrating lymphocytes (TIL) lose CD226 expression and these cells have impaired effector function compared with CD226⁺CD8⁺ TILs. Loss of CD226 is a result of proteasomal degradation of the protein driven by CD155 on tumor cells. Weulersse et al. find that the transcription factor Eomes also has a role in loss of CD226 on CD8⁺ TILs and show that the absence of CD226 can abrogate the effects of anti-PD1 immune checkpoint blockade (ICB) in mice. These data are consistent with the observation made by Braun et al. that response to ICB in melanoma patients correlates with the presence of CD226⁺CD8⁺ TILs and suggest that targeting CD226 loss may help overcome ICB resistance.

Braun M, . . . Bald T. *Immunity* 2020 Oct 13;53:805–23.e15.

Weulersse M, . . . Martinet L. *Immunity* 2020 Oct 13;53:824–39.e10.

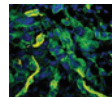
Two subsets of stem-like CD8⁺ memory T cell progenitors with distinct fate commitments in humans

Two distinct subsets were identified (the U.S. Navy Blue Angels and the U.S. Air Force Thunderbirds) by Ron Cogswell via Wikimedia Commons

Inducing robust, long-lasting antitumor CD8⁺ T-cell responses is key for many immunotherapies. However, different CD8⁺ T-cell subsets can function differently, and better elucidating the characteristics of cells committed to specific differentiation states would enhance understanding of immune responsiveness. Galletti et al., through single-cell RNA-sequencing and flow cytometry, find that memory CD8⁺ T cells in healthy humans have two distinct, previously unknown stem-like subsets—one with functionally committed CCR7⁺ progenitors lacking inhibitory receptors and the other comprised of CCR7⁺ progenitors expressing PD-1 and TIGIT committed to an exhausted-like lineage. Such cell-fate commitments should be considered when developing immunotherapeutics, including vaccine strategies and cell engineering.

Galletti G, . . . Lugli E. *Nat Immunol* 2020 Oct 12. DOI: 10.1038/s41590-020-0791-5.

TGF-β suppresses type 2 immunity to cancer

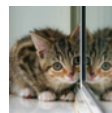


Remodeling of the vasculature can aid in the killing of tumor cells (from Fig. 2D, middle/far right (triple therapy) of Di Taccio et al. *Cancer Immunol Res* 2019)

TGFβ can modulate antitumor responses, but the mechanisms behind its pleiotropic effects are not fully known. Liu et al. show that TGFβ has differential effects on CD8⁺ versus CD4⁺ T cells. Depletion of *TGFBR2* in CD4⁺ T cells, but not CD8⁺ T cells, facilitates IL4-dependent healing responses and remodeling of the vasculature. This, in turn, “cuts off” the tumor, leading to tumor-cell hypoxia and death in avascular areas, independent of CD8⁺ T cells. The data highlight a beneficial role for T_H2 antitumor responses in cancer.

Liu M, . . . Li MO. *Nature* 2020 Nov 1;587:115–20.

Onco-fetal reprogramming of endothelial cells drives immunosuppressive macrophages in hepatocellular carcinoma



The fetal and HCC liver environment resemble each other (by Paul Reynolds via Wikimedia Commons)

Changes that occur in tissues and organs from development, through maturation, to a disease state, including cancer, are not fully known. By comparing human and mouse fetal, adult, and hepatocellular carcinoma (HCC) livers, Sharma et al. find in both humans and mice a shared immune-suppressive environment, whereby the composition of the tumor microenvironment (TME) of HCC includes PLVAP⁺VEGFR2⁺ fetal-associated endothelial cells and immune-suppressive FOL2R⁺ fetal-like macrophages. Mechanistically, VEGF and NOTCH signaling maintain the fetal-like TME through interactions with ligands on the fetal-like macrophages. This remodeling of the TME in HCC reveals onco-fetal reprogramming of the tumor ecosystem to be immunologically tolerant and suggests novel targets for therapeutic interventions in HCC and other cancers.

Sharma A, . . . DasGupta R. *Cell* 2020 Oct 15;183:377–94.e21.