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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

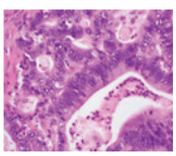
Single-cell mapping of human brain cancer reveals tumor-specific instruction of tissue-invading leukocytes

Tumors as teachers have more influence than does the school district (tissue) in which they reside (from bluefield.edu via Flickr)

Brain tumors are highly immunosuppressive. Use of 74-parameter CyToF for single-cell analysis of 36 patients reveals differences dependent on tumor origin in tumor microenvironment (TME) composition. Tumors arising from gliomas are immunosuppressed by brain-resident microglia, but brain metastases from other sites recruit monocyte-derived TAMs, Tregs from the blood, and $CD8^+$ TILs (whose exhaustion increases with more severe disease). Thus, the tumor source, rather than tissue localization, most influences the character of the immunosuppressive TME.

Friebel E, . . ., Becher B. ***Cell*** *2020 May 28. DOI: 10.1016/j.cell.2020.04.055.*

Accumulation of long-chain fatty acids in the tumor microenvironment drives dysfunction in intrapancreatic $CD8^+$ T cells



Pancreatic ductal adenocarcinoma (from Tayao et al., PLoS One 2016;11:e0150338)

Pancreatic ductal adenocarcinomas stifle antitumor activity. Analysis of the composition of the TME's lipid milieu reveals that T-cell regions contain an overabundance of very long-chain fatty acids (VLCFAs), correlating with T-cell dysfunction that increases as the tumor develops. The accumulation of VLCFAs is due to low expression of the dehydrogenase that catabolizes them. These non-metabolizable VLCFAs are thus not an energy source and disrupt mitochondrial function. Boosting the dehydrogenase enhances T-cell persistence. The mouse findings were recapitulated in human samples and suggest a mode of immunosuppression that may be susceptible to modulation.

Manzo T, . . ., Nezi L. ***J Exp Med*** *2020 Jun 3;217:e20191920.*

Pooled knockin targeting for genome engineering of cellular immunotherapies

Knock-in using older technology (by J. Janowiec, Marine Corp Recruiting Command)

Engineered T cells need help ovecoming immunosuppression and subpar T-cell persistence. A CRISPR-targeted knock-in technology creates pools of barcoded constructs that can be targeted to the same or different genomic loci for comparing T-cell fitness *in vitro* and *in vivo*. A novel TGFβR2-41BB chimera in primary T cells is identified as an effective construct to enhance solid tumor clearance. This technique allows rapid comparison of new or known constructs to assess antitumor activity.

Roth TL, . . ., Marson A. ***Cell*** *2020 Apr 30;181:728–44.E21.*

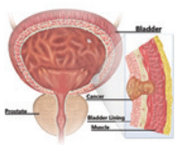
Regulatory myeloid cells paralyze T cells through cell–cell transfer of the metabolite methylglyoxal

Transfer to a killer (by Tech. Sgt. S.A. Cuomo, U.S. Air Force, via Wikimedia Commons)

T cells within tumors can be incapacitated by checkpoint receptors, Tregs, or inhibitory myeloid-derived suppressor cells (MDSCs). Tumor MDSCs have reduced glycolytic activity and accumulate the dicarbonyl radical methylglyoxal. MDSCs can transfer this in their cytosol to nearby T cells, thereby inhibiting activation-induced signaling. Cell–cell transfer of methylglyoxal suppresses $CD8^+$ T-cell functions by removing free L-arginine in T cells. Neutralizing dicarbonyl activity overcomes MDSC-mediated suppression and synergizes with immune checkpoint blockade.

Baumann T, . . ., Höchst B. ***Nat Immunol*** *2020 May 1;21:555–66.*

Intratumoral $CD4^+$ T cells mediate anti-tumor cytotoxicity in human bladder cancer

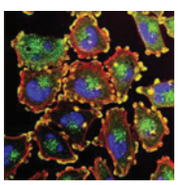


Muscle-invasive bladder cancer (from NHGRI, U.S. National Institutes of Health via Wikimedia Commons)

A minority of patients with bladder cancer respond to anti–PD-1. Single-cell RNA and TCR sequencing of localized muscle-invasive bladder tumor and nontumor tissue from patients is used to characterize intratumoral T cells. Clonally expanded cytotoxic $CD4^+$ T cells and Tregs, but not $CD8^+$ T cells, are enriched in these specimens. The cytotoxic $CD4^+$ T cells, which can kill autologous tumor, are susceptible to Treg suppression. The cytotoxic $CD4^+$ T-cell signature can be used to predict clinical response to anti–PD-L1 in metastatic bladder cancer.

Oh DY, . . ., Fong L. ***Cell*** *2020 Jun 3. DOI: 10.1016/j.cell.2020.05.017.*

Multimodel preclinical platform predicts clinical response of melanoma to immunotherapy



Melanoma cells [by J.C. Valencia (NCI) via Wikimedia Commons]

Immune checkpoint blockade (ICB) is efficacious in treating some melanomas, but not all patients respond. A panel of four molecularly and phenotypically distinct syngeneic melanoma models reveals varying responses to anti–CTLA-4, similar to patients' diverse responses. Analysis of transcriptomes, immune infiltration, and mutations identifies a melanocytic plasticity signature that contributes to T-cell dysfunction and ICB resistance. This signature is validated using patient datasets and is predictive of patient outcomes in response to ICB. This panel of models provides a platform recapitulating melanoma's clinical behavior that can be employed to identify mechanisms and treatment strategies to improve patient care.

Pérez-Guijarro E, . . ., Merlino G. ***Nat Med*** *2020 May 1;26:781–91.*