January 1, 2022 | Volume 10 | Number 1

CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

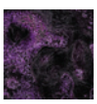
Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells

Nanotubes mediate mitochondrial transfer to tumor cells (by Michael Ströck via Wikimedia Commons)

Tumors use various mechanisms to escape immune detection in the tumor microenvironment (TME). Saha et al. show that tumor cells form nanotubes that physically interact with immune cells in the breast cancer TME. Mitochondria are then transferred from immune cells to tumor cells, leading to tumor metabolic enhancement and loss of specific immune-cell subsets needed for antitumor responses. Targeting nanotube formation reversed these effects and when combined with immune checkpoint blockade, resulted in improved outcomes in a murine breast cancer model. The data highlight a new immune "hijacking" mechanism that tumors cells could use to promote cancer progression.

Saha T, . . ., Sengupta S. ***Nat Nanotechnol*** *2021 Nov 18. DOI: 10.1038/s41565-021-01000-4.*

Lack of CD8$^+$ T cell effector differentiation during priming mediates checkpoint blockade resistance in non–small cell lung cancer



Lung cancers can become infiltrated by dysfunctional CD8 T cells (by Eric Synder via NCI Visuals Online)

Many non–small cell lung cancers (NSCLC) infiltrated with CD8$^+$ T cells are resistant to immune checkpoint blockade. In an orthotopic NSCLC model, Horton et al. find lung tumors are infiltrated with CD8$^+$ T cells but do not respond to combination anti–CTLA-4 and anti–PD-1. The CD8$^+$ T cells have a dysfunctional phenotype molecularly distinct from T-cell exhaustion. The dysfunctional phenotype is induced during T-cell priming in lymph nodes and characterized by failure to acquire an effector program. Treatment with IL2 and IL12 restores effector T-cell differentiation. As CD8$^+$ T cells from NSCLC patients have an analogous gene expression program of dysfunction, the data have translational potential.

Horton BL, . . ., Spranger S. ***Sci Immunol*** *2021 Oct 29;6:eabi8800.*

Development of ICT01, a first-in-class, anti-BTN3A antibody for activating Vγ9Vδ2 T cell–mediated antitumor immune response

γδ T cells infiltrate many tumor types and are highly cytotoxic (from Fig. 5C of Gherardin et al., Cancer Immunol Res 2021)

Antibodies specific for butyrophilin 3A (BTN3A) can induce Vγ9Vδ2 T–cell cytolytic activity. De Gassart et al. have engineered a humanized BTN3A-specific antibody (ICT01) that induces Vγ9Vδ2 T–cell killing of several human tumor cell lines and primary tumor cells *in vitro* and xenografted tumors in mice following Vγ9Vδ2 T–cell transfer. Preliminary data from six patients with solid tumors administered ICT01 in the phase I/IIa EVICTION clinical trial (NCT04243499) show the antibody can be well tolerated, has caused no major safety events, and appears to induce broad immune-cell infiltration of tumors. Further studies should reveal the full potential of this strategy.

De Gassart A, . . ., Frohna P. ***Sci Transl Med*** *2021 Oct 20;13:eabj0835.*

The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1

Histamine can suppress antitumor responses (by NEUROtiker via Wikimedia Commons)

Identification of obstacles to effective antitumor immunity sometimes reveals surprising participants. Li et al. find that histamine, a mediator of allergic responses, plays an inhibitory role in antitumor responses. Histamine is frequently found in the tumor microenvironment and can activate macrophages via histamine receptor H1 (HRH1), promoting polarization to a suppressive M2-like phenotype and upregulation of the inhibitory checkpoint VISTA. Such macrophages suppress T-cell responses and promote tumor growth and therapy resistance. Knockout of HRH1 or use of antihistamines rescues experimental antitumor responses. The study highlights a role for histamine in modulating antitumor responses and suggests antihistamines as potential adjuvants for cancer immunotherapies.

Li H, . . ., Yu D. ***Cancer Cell*** *2021 Nov 24. DOI: 10.1016/j.ccell.2021.11.002.*

Cross-HLA targeting of intracellular oncoproteins with peptide-centric CARs

PC-CAR T cells could unlock the immunotherapeutic potential of intracellular antigens (by Paris on Ponce & Le Maison Rouge via Flickr)

Developing chimeric receptor (CAR) T cells specific for intracellular tumor-specific antigens is challenging because these antigens are only available to the immune system as peptides presented on the cell surface by MHC class I. Yarmarkovich et al. overcome this challenge by generating peptide-centric CARs (PC-CAR), which can recognize peptides derived from intracellular oncoproteins presented by multiple HLA types. PC-CAR T cells targeting a peptide from the neuroblastoma oncoprotein PHOX2B selectively kill neuroblastoma cells *in vitro* and clear tumors transplanted into mice. This study indicates PC-CARs have the potential to unlock the vast number of intracellular oncoproteins as potential targets for CAR T-cell immunotherapy.

Yarmarkovich M, . . ., Maris JM. ***Nature*** *2021 Nov 3;599:477–84.*

Myeloid antigen-presenting cell niches sustain antitumor T cells and license PD-1 blockade via CD28 costimulation

TILs accumulate in ovarian cancer islets (from Fig. 1C of Heath et al., Cancer Immunol Res 2021)

The tumor microenvironment (TME) factors that regulate exhaustion of CD8$^+$ tumor-infiltrating lymphocytes (TIL) are not fully understood. Duraiswamy et al. found activated, tumor-specific CD8$^+$ TILs concentrated in ovarian cancer islets, where they are closely associated with myeloid antigen-presenting cells (APC) but restrained by PD-1 signaling. Activated islet-resident APCs can provide CD28 costimulation, which is required for exhausted TILs to effectively respond to anti–PD-1 treatment *in vitro*. These findings suggest that a TME with insufficient CD28 signaling from myeloid APCs could explain poor responses to anti–PD-1 in tumors with substantial TIL populations and that activating the APCs with reagents such as anti-CD40 may rescue therapeutic responses.

Duraiswamy J, . . ., Coukos G. ***Cancer Cell*** *2021 Dec 13;39:1623–42.e20.*

doi: 10.1158/2326-6066.CIR-10-1-WWR

Downloaded from http://aacrjournals.org/cancerimmunolres/article-pdf/10/1/1/3013189/1.pdf by guest on 24 May 2024