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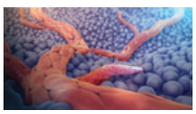
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Senescence-induced vascular remodeling creates therapeutic vulnerabilities in pancreas cancer



Senescence-induced vascularization (by Manu5 via Wikimedia Commons)

Mutated, activated KRAS is a common feature of pancreatic ductal adenocarcinoma (PDAC). Inhibitors of the downstream MEK and CDK4/6 pathways suppress PDAC growth by inducing cellular senescence and production of chemokines, cytokines, and matrix metalloproteinases. This triggers vasculature remodeling of the PDAC tumors and subsequent NF-κB– and VEGFR-driven tumor infiltration by $CD8^+$ T cells. MEK and CDK4/6 inhibitors lead to exhaustion of the recruited T cells, which are rescued by PD-1 blockade. Inducing senescence with immune checkpoint blockade may improve outcomes.

Ruscetti M, . . ., Lowe SW. ***Cell*** *2020 Apr 16;181:424–41.e21.*

Tumor cells suppress radiation-induced immunity by hijacking caspase 9 signaling

Radiation therapy (by Jakembradford via Wikimedia Commons)

Radiation induces genomic DNA (gDNA) fragmentation but little cytosolic DNA sensing with IFN-I production. Radiation also induces mitochondrial permeabilization, and the mitochondrial DNA (mtDNA) activates caspase-9, leading to intrinsic apoptosis. By disrupting caspase-9, apoptosis is inhibited and the cytosolic mtDNA activates the STING pathway and increases IFN-I, promoting cross-priming by DCs and activating T cells. However, the T cells become exhausted, and combining PD-L1 blockade with radiation therapy and caspase inhibition increases antitumor activity and abscopal effects.

Han C, . . ., Fu Y-X. ***Nat Immunol*** *2020 May 1;21:546–54.*

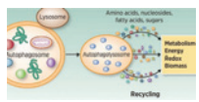
Pooled knockin targeting for genome engineering of cellular immunotherapies

Centuries-old Egyptian knock-in technique (in Wirth Gallery, Royal Ontario Museum)

Adoptive cell therapies (ACT) have had limited success in solid tumors. The authors develop pooled knock-in sequencing (PoKI-seq), a high-throughput barcoding method in which pooled, targeted, knock-in constructs in T cells are assessed via combined single-cell transcriptome analysis and pooled knock-in screening, as a strategy to identify constructs that can improve T-cell abundance and function for treating solid tumors. Among a large panel of natural and synthetic genes, knock-in of a synthetic TGFβR2-41BB chimeric receptor was found to best improve *in vitro* activity and efficacy of ACT in melanoma.

Roth TL, . . ., Marson A. ***Cell*** *2020 Apr 30;181:728-44.e21.*

Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I

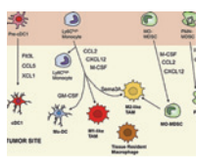


Autophagy recycles class I MHC (from Fig. 1 of White et al., Clin Cancer Res 2015)

Pancreatic ductal adenocarcinoma (PDAC) rarely responds to immune checkpoint blockade (ICB). Although MHC-I is downregulated in PDAC, it is not due to mutations in, or loss of heterozygosity of, antigen presentation or structural genes. Instead, surface MHC-I is selectively targeted by lysosomes via NBR1-mediated autophagy. Autophagy inhibition restores MHC-I expression and improves antitumor immunity, effects dependent on $CD8^+$ T cells and enhanced by concurrent dual ICB. This autophagy-mediated immune evasion mechanism in PDAC cells suggests that its targeting could boost antitumor responses.

Yamamoto K, . . ., Kimmelman AC. ***Nature*** *2020 May 1;581:100–5.*

The governing of myeloid cells



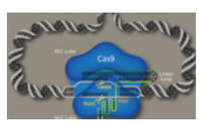
Myeloid subsets sensitive to external cues (from Fig. 1 of Clappaert et al., Front Immunol 2018)

Factors that regulate function of the heterogeneous myeloid cells in cancer are not fully known. Zhang et al. find that in patients and mice with colorectal tumors, myeloid cell–targeting immunotherapies have distinct macrophage and DC subset–specific effects, revealing myeloid cells as central players in cell interaction networks in the tumor. Mohamed et al. demonstrate that myeloid-derived suppressor cell (MDSC) function relies on PERK, the unfolded protein response–related kinase, via activation of transcription factor NRF2. PERK deletion disrupts mitochondrial homeostasis and induces IFN by activating the STING pathway, reprogramming the MDSC to promote $CD8^+$ T-cell responses. Thus, intelligent targeting of defined myeloid cells can manipulate regulation and improve antitumor responses.

Zhang L, . . ., Yu X. ***Cell*** *2020 Apr 16;181:442–59.e29.*

Mohamed E, . . ., Rodriguez PC. ***Immunity*** *2020 Apr 14;52:668–82.e7.*

Safety and feasibility of CRISPR-edited T cells in patients with refractory non-small-cell lung cancer



CRISPR/Cas9–edited T cells for therapy (by Guido4 via Wikimedia Commons)

CRISPR-Cas9 is being investigated to improve immunotherapy responses. A phase I clinical trial shows that T cells with a disrupted PD-1 gene infused into patients with treatment-refractory non–small cell lung cancer had only grade 1/2 treatment-related adverse events. The edited T cells persist post-infusion and are trackable. Off-target mutation frequency was 0.05%. These data support the safety and feasibility of clinical use in T cell–based immunotherapies.

Lu Y, . . ., Mok T. ***Nat Med*** *2020 Apr 27. DOI: 10.1038/s41591-020-0840-5.*