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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

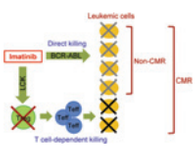
Mitochondrial fragmentation limits NK cell–based tumor immunosurveillance

Fragmentation limits surveillance (from LunarSeaArt via Pixabay)

Tumor-infiltrating natural killer (TINK) cells isolated from patients with liver cancer have fragmented mitochondria, less mitochondrial mass, higher ROS concentrations, and less electron transport chain activity. Hypoxia enhances activity of mTOR-Drp signaling, which is key to mitochondrial fragmentation and apoptosis. The aberrant respiration from fragmentation could be abrogated with use of an inhibitor of fragmentation. Restoring mitochondrial morphology correlates with improved NK cell cytolytic activity. Thus, fragmentation and *Drp1* expression may be potential targets for strengthening TINK cell activity.

Zheng X, . . ., Wei H. ***Nat Immunol*** *2019 Oct 21;20:1656–67.*

Tyrosine kinase inhibitor imatinib augments tumor immunity by depleting effector regulatory T cells



Dual-duty imitinab depletes Tregs (from Tanaka et al. J Exp Med 2019)

Antibody depletion of regulatory T cells (Tregs) increases antitumor activity in tumor models and human cancers. Imatinib, a small-molecule inhibitor of BCR-ABL kinase, can also inhibit LCK. Tanaka et al. find that imatinib not only directly kills leukemic cells but can deplete effector Tregs, which already have low LCK activity compared to effector/memory CD8 T cells, making them selectively susceptible to signal-deprived apoptosis. This resulted in increased antitumor responses, suggesting that development of similar small-molecule "depletors" may be an approach to augment anticancer immunity.

Tanaka A, . . ., Sakaguchi S. ***J Exp Med*** *2019 Nov 8. DOI: 10.1084/jem.20191009.*

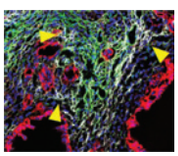
Small-molecule MYC inhibitors suppress tumor growth and enhance immunotherapy

Small blocker prevents tumor deluge (by Pieter1 via Wikimedia Commons)

MYC is key to tumor progression, and development of a nontoxic small-molecule inhibitor is needed. Systematic, iterative chemical optimization and *in vivo* screening identify a well-tolerated drug. This MYC inhibitor uncouples MYC from its partner MAX, allowing phosphorylation, degradation, and immunogenic cell death of the tumor. Increases in T- and NK-cell infiltration, and PD-L1 expression, follow. Potentially, a short course may sensitize refractory tumors to anti–PD-1, increasing the fraction of patients who respond to immunotherapies.

Han H, . . ., Abdulkadir SA. ***Cancer Cell*** *2019 Nov 11;36:483–97.E15.*

Single-cell RNA sequencing reveals stromal evolution into LRRC15$^+$ myofibroblasts as a determinant of patient response to cancer immunotherapy



LRRC15 and PDPN in the pancreas (from Dominguez et al. Cancer Discov 2019)

The effect of the microenvironment in pancreatic ductal adenocarcinoma (PDAC) tumors on cancer-associated fibroblasts (CAFs) is poorly understood. Single-cell RNA sequencing of PDAC tumors reveals various populations of PDPN$^+$ CAFs that coevolve as tumors progress, driven by TGFβ or IL1. Late-stage mouse and human PDAC tumors have high fractions of LRRC15$^+$ PDPN$^+$ CAFs, which enhance tumor cell growth. LRRC15$^+$ CAF signatures are also present in other human cancers, with high expression associating with poor responses to immune checkpoint blockade, suggesting that targeting this population could be beneficial.

Dominguez CX, . . ., Turley SJ. ***Cancer Discov*** *2019 Nov 7. DOI: 10.1158/2159-8290.CD-19-0644.*

VISTA is an acidic pH-selective ligand for PSGL-1

Taking advantage of acidity (by Border colliez via Wikimedia Commons)

V-domain immunoglobulin suppressor of T-cell activation (VISTA) is an immune checkpoint molecule that limits T-cell function and antitumor immunity, yet how VISTA engages its ligand remains unknown. VISTA preferentially engages PSGL-1 on T cells in an acidic environment, such as the tumor microenvironment (TME) via PSGL-1 sulfated tyrosines interacting with protonated histidine residues on VISTA. An antibody selective for the residues that become available only in acidic environments preferentially binds to VISTA in the TME, inducing tumor rejection when combined with PD-1 blockade.

Johnston RJ, . . ., Korman AJ. ***Nature*** *2019 Oct 23;574:565–70.*

Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy

Diversity provides strength (by Wonder woman0731 via Flickr)

HLA-I genotypes with divergent alleles present more diverse immunopeptidomes, but does this affect antitumor immunotherapies? In metastatic melanoma and non–small cell lung carcinoma patients treated with immune checkpoint blockade, high mean HLA-I evolutionary divergence (HED) correlates with better overall survival and clinical responses. High HED correlates with an increased number of neopeptides, viral peptides, and self-peptides presented by HLA-I and with increased TCR clonality. Combining HED with tumor mutational burden gives stronger survival associations than either alone.

Chowell D, . . ., Chan TA. ***Nat Med*** *2019 Nov 7;25:1715–20.*

Cancer Immunology Research

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Cancer Immunol Res 2020;8:1.