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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

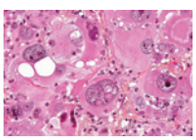
Transient rest restores functionality in exhausted CAR-T cells through epigenetic remodeling

Intermittent resting of CAR T cells by preventing tonic signaling prevents and reverses exhaustion (from PxHere)

Persistent, antigen-independent signaling through chimeric antigen receptors (CAR)—tonic signaling—can lead to CAR T-cell exhaustion. Weber et al. show that the functional, transcriptional, and epigenetic hallmarks of exhaustion that occur in CAR T cells because of tonic signaling can be prevented and reversed by intermittent cessation of tonic signaling by either switching a drug-regulated CAR on and off or using the small molecule dasatinib to inhibit proximal CAR signaling. Intermittently rested CAR T cells improve tumor control and survival in xenograft models, highlighting the potential clinical applicability of the data.

Weber EW, . . ., Mackall CL. ***Science*** *2021 Apr 2;372:eaba1786.*

Glioblastomas acquire myeloid-affiliated transcriptional programs via epigenetic immunoediting to elicit immune evasion

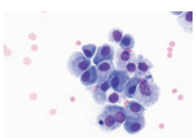


Epigenetic immunoediting creates an immunosuppressive TME in GBM (from Nephron via Wikimedia Commons)

Glioblastoma multiforme (GBM) is refractory to immunotherapy, but knowledge of the immunosuppressive mechanisms at play in the tumor microenvironment (TME) is limited. Using a new model of GBM in which GBM stem cells (GSC) are serially transplanted into immunocompetent mice, Gangoso et al. find that sustained immune attack causes transcriptional and epigenetic changes in the GSCs. This immunoediting creates a myeloid-rich, immunosuppressive TME. Human GSCs from mesenchymal GBMs have similar transcriptional and DNA methylation changes, suggesting that epigenetic immunoediting may contribute to immune evasion in this GBM subtype.

Gangoso E, . . ., Pollard SM. ***Cell*** *2021 Apr 29;184:2454–70.e26.*

The IRENA lncRNA converts chemotherapy-polarized tumor-suppressing macrophages to tumor-promoting phenotypes in breast cancer



Macrophages can promote antitumor immunity and chemoresistance (from Librepath via Wikimedia Commons)

The role of macrophages in the effects of chemotherapy is unclear. Liu et al. show that chemotherapy has dual effects: It enhances macrophage promotion of antitumor immunity and chemoresistance. Chemotherapy-induced type I IFN production in tumors initiates NF-κB and Jak–STAT1 signaling in macrophages, leading to chemoresistance and antitumor immunity, respectively. STAT1 signaling also induces expression of cytoplasmic long noncoding RNA IFN-responsive NF-κB activator (IRENA) in macrophages, and this triggers the NF-κB–mediated chemoresistance. Knocking out IRENA in macrophages improves responses to chemotherapy in a mouse breast cancer model. As IRENA expression in postchemotherapy macrophages is associated with poor patient survival, these data have translational relevance.

Liu J, . . ., Song E. ***Nat Cancer*** *2021 Apr 12;2:457–73.*

A pan-cancer transcriptome analysis of exitron splicing identifies novel cancer driver genes and neoepitopes

EIS can lead to generation of different neoantigens (from Horia Varlan via Wikimedia Commons)

Exitron splicing (EIS) is a process that generates cryptic introns in protein-coding regions, and its role in cancer development and progression is not well-known. Wang et al. find that this process takes place in multiple cancer types and can alter expression of cancer driver genes and tumor neoantigens. This has the potential to impact antitumor responses, including those associated with immunotherapy responses. The study provides another perspective in the discovery of targetable neoantigens and emphasizes that EIS events should be considered when analyzing cancer-associated mutations.

Wang T-Y, . . ., Yang R. ***Mol Cell*** *2021 Apr 15. DOI: 10.1016/j.molcel.2021.03.028.*

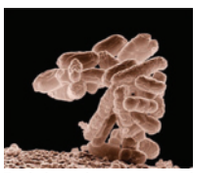
BFAR coordinates TGFβ signaling to modulate Th9-mediated cancer immunotherapy

TGFβ is a double-edged sword for immunity (from Søren Niedziella via Flickr)

TGFβ can both promote and suppress antitumor responses. Pei et al. investigated TGFβ in the context of Th9-mediated antitumor responses. TGFβ induces downregulation of BFAR (bifunctional apoptosis regulator), which then results in dampened TGFβ signaling and impaired Th9-mediated antitumor responses due to BFAR's role in modulating ubiquitination of TGFβR1 and Th9 differentiation. The study identifies BFAR as a regulator of TGFβ signaling and Th9 antitumor responses and offers a potential marker that should be considered in Th9-based immunotherapy.

Pei S, . . ., Xiao Y. ***J Exp Med*** *2021 Apr 29;218:e20202144.*

Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver



E. coli plays a role in metastatic spread of CRC (from Eric Erbe and Christopher Pooley via Wikimedia Commons)

Mechanisms behind the formation of the premetastatic niche are not fully understood. Bertocchi et al. find that PV-1 (plasmalemma vesicle–associated protein), a marker of gut vascular barrier (GVB) damage, is a biomarker for recurrent colorectal cancer (CRC) and that patients with PV-1^{high} primary CRC have more bacterial colonization in metastatic liver lesions, especially by *Escherichia coli*. *E. coli* upregulates virulence-related genes and induces upregulation of PV-1, leading to GVB disruption that then allows migration of bacteria, immune cells, and tumor cells out of the colon and into the liver (i.e., a premetastatic niche is created). The data highlight a role of the gut microbiome in CRC metastatic spread and offer insights into possible targets to prevent metastases.

Bertocchi A, . . ., Rescigno M. ***Cancer Cell*** *2021 May 10;39:708–24.e11.*