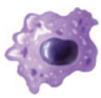
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature
Article Recommendations from Our Deputy and Senior Editors

Reprogramming of tumor-associated macrophages in the microenvironment



Macrophages can be reprogrammed to promote antitumor responses (by Noah Smith via Wikimedia Commons).

Multiple factors contribute to the suppression that occurs in the tumor microenvironment (TME) and this could potentially be alleviated through various mechanisms. Chen et al. find that high potassium in the TME inhibits antitumor responses from tumor-associated macrophages (TAM) via alteration of their metabolism. Blocking this metabolic switch enables TAMs to mount effective antitumor responses. Chryplewicz et al. find that TAMs in glioma are reprogrammed to a proinflammatory phenotype, along with other antitumor remodeling of the TME and tumor vasculature, after treatment with VEGF inhibitors and imipramine (tricyclic anti-depressant). These studies provide insight into multiple mechanisms of TAM suppression and potential targets that can be used to boost antitumor responses.

Chen S, . . ., Wang D. ***Cell Metab*** *2022 September 13. DOI:10.1016/j.cmet.2022.08.016.*
Chryplewicz A, . . ., Hanahan D. ***Cancer Cell*** *2022 September 15;40:1111–27.E9.*

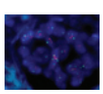
Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

Dietary intake can affect microbiota and immunity (by the NCI via Wikimedia Commons).

Dietary intake can affect antitumor immunity and response to immunotherapy. In a prospective study, Simpson et al. evaluated dietary patterns and microbial signatures of different patient populations and how these factors related to response to neoadjuvant immune checkpoint inhibition. Distinct differences between response groups were observed not only in microbial composition but also in immune-related adverse events. Specific diets, as well as certain microbial compositions, were associated with better treatment outcomes. The data highlight the crossroads of cancer-intrinsic and -extrinsic factors with patient lifestyle, and how these factors together can shape responses to treatment.

Simpson RC, . . ., Long GV. ***Nat Med*** *2022 September 12. DOI:10.1038/s41591-022-01965-2.*

Targeted immunotherapy against distinct cancer-associated fibroblasts overcomes treatment resistance in refractory HER2+ breast tumors

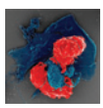


Immunotherapy can overcome resistance to HER2-targeted therapy (from IrinaPaw via Wikimedia Commons).

HER2-specific antibodies such as trastuzumab are used to treat HER2$^+$ breast cancer, but not all patients respond and some that do ultimately relapse. Using orthogonal approaches, including analysis of tumor tissue and transcriptomic data from trastuzumab-treated patients with HER2$^+$ breast cancer and a fully humanized immunocompetent model of HER2$^+$ breast cancer, Rivas et al. find that a population of TGFβ-activated cancer-associated fibroblasts (CAF) and low IL2 activity associate with trastuzumab resistance. Targeting IL2 to fibroblast activation protein-α (FAP)–expressing cells restores tumor responsiveness to trastuzumab by enhancing NK cell–mediated antibody-dependent cytotoxicity, highlighting the therapeutic potential of targeting stromal components in the tumor microenvironment.

Rivas EI, . . ., Calon A. ***Nat Commun*** *2022 September 9;13:5310.*

Regulatory T cells are associated with poor response in CAR T cell recipients



A Treg subpopulation of CAR T cells drives therapeutic resistance (from NIH via Flickr).

Using single-cell profiling methods, two groups have identified subpopulations of CD19-targeting CAR T cells with T regulatory (Treg)–cell phenotypes associated with poor response in patients with B-cell lymphoma. Good et al. find a higher proportion of circulating CD4$^+$Helios$^-$ Treg CAR T cells in patients with progressive disease who received axicabtagene ciloleucel (axi-cel), highlighting their potential as a biomarker prognostic for progression at day 7 post infusion. Haradhvala et al. similarly identify CAR$^+$ Treg cells in blood and infusion products for patients nonresponsive to either axi-cel or tisagenlecleucel, and validate their role in mouse models of CAR T-cell treatment. The studies provide new insight into therapeutic resistance to CAR T-cell therapy.

Good Z, . . ., Mackall CL. ***Nat Med*** *2022 September 12;28:1860–71.*
Haradhvala NJ, . . ., Maus MV. ***Nat Med*** *2022 September 12;28:1848–59.*

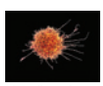
A covalent inhibitor of K-Ras(G12C) induces MHC class I presentation of haptenated peptide neoepitopes targetable by immunotherapy

Covalent K-Ras (G12C) inhibitor provides a new target for immunotherapy (from Rawpixel).

MHC class I presentation of tumor-specific peptides derived from intracellular proteins provides a target for anticancer therapy. Zhang et al. have identified a new class of therapeutically targetable MHC class I epitopes: covalently modified intracellular proteins. K-Ras(G12C) covalently conjugated to the K-Ras(G12C)-specific inhibitor ARS1620 can undergo antigen processing and presentation on MHC class I. ARS1620-specific antibodies can recognize MHC class I–restricted ARS1620-peptides. Incorporating such an antibody into a bispecific T-cell engager (BiTE) induces T-cell responses against K-Ras(G12C) tumor cells, suggesting a new strategy for cancer immunotherapy.

Zhang Z, . . ., Craik CS. ***Cancer Cell*** *2022 September 12;40:1060–69.e7.*

BACH2 restricts NK cell maturation and function, limiting immunity to cancer metastasis



NK cells are key component of the antitumor immune response (from NIAID via Wikimedia Commons).

Understanding the factors that regulate the maturation and function of natural killer (NK) cells is important for understanding the antitumor immune response. Imianowski et al. show that the transcriptional regulator BACH2 is expressed in developing and mature NK cells and is a negative regulator of NK-cell maturation and function, keeping NK cells quiescent under conditions of IL15 stimulation. In mice lacking BACH2 in NK cells, the NK cells show increased cytotoxicity and enhanced ability to limit metastasis to the lungs in two preclinical models. The data provide new avenues for potential therapeutic modulation of NK cell–mediated antitumor immunity.

Imianowski CJ, . . ., Roychoudhuri R. ***J Exp Med*** *2022 September 30;219:e20211476.*

doi: 10.1158/2326-6066.CIR-10-11-WWR