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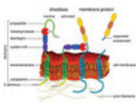
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Resistance to PD1 blockade in the absence of metalloprotease-mediated LAG3 shedding

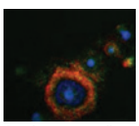


The ADAM metalloproteases mediate LAG3 shedding (by Ktuebi via Wikimedia Commons)

Not all tumors respond to immunotherapy, and the mechanisms behind therapy resistance are not fully understood. Andrews et al. highlight the role of LAG3 signaling in $CD4^+$ T cells in resistance to anti–PD-1. Metalloproteases ADAM10 and ADAM17 regulate LAG3 expression and shedding, and a mouse model with a noncleavable mutant LAG3 on T cells interfered with the ability of conventional $CD4^+$ T cells to provide $CD8^+$ T-cell help, thus limiting antitumor responses to PD-1 blockade. In cancer patients, high LAG3 and low ADAM10 expression on conventional $CD4^+$ T cells correlates with worse prognosis and disease progression. The data highlight how LAG3 shedding can impact the efficacy of immunotherapy.

Andrews LP, . . ., Vignali DAA. ***Science Immunol*** *2020 Jul 17;5:eabc2728.*

Resistance to natural killer cell immunosurveillance confers a selective advantage to polyclonal metastasis

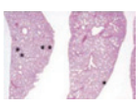


Circulating tumor cell clusters can seed polyclonal metastases (by Ryan Jeffs via Wikimedia Commons)

Mechanisms behind the seeding of metastases are not fully understood. Lo et al. show that polyclonal tumor cell clusters metastasize more efficiently than their monoclonal counterparts and have decreased sensitivity to NK cell–mediated cytotoxicity. Tumor cell profiling shows that clusters express adhesion and epithelial genes associated with decreased expression of activating NK-cell ligands. Because NK cells can suppress monoclonal tumor cell seeding, there is a selection for seeding by polyclonal tumor cell clusters that can evade immune surveillance.

Lo HC, . . ., Zhang XHF. ***Nat Cancer*** *2020 Jun 1;1:709–22.*

The disabled homolog 2 controls pro-metastatic activity of tumor-associated macrophages



Knockout of Dab2 reduces lung metastasis in mice (from Fig. 2A of Marigo and Trovato et al., Cancer Discov 2020)

Tumor-associated macrophages (TAMs) contribute to the remodeling of the extracellular matrix and tumor progression and metastasis. Marigo and Trovato et al. show that DAB2 (disabled homolog 2) is upregulated in TAMs localized at the tumor invasive front and supports their protumoral functions, including aiding in tumor cell invasiveness, dissemination, and seeding of metastasis. $DAB2^+$ TAMs promote invasion by a mechano-sensing mechanism requiring the transcription factor YAP (Yes-associated protein). In patients, $DAB2^+$ TAMs correlate with poor prognosis, suggesting their presence may serve as a useful biomarker.

Marigo I, . . ., Bronte V. ***Cancer Discov*** *2020 Jul 10. DOI: 10.1158/2159-8290.CD-20-0036.*

Pyroptosis, an "inflamed" player in antitumor immunity

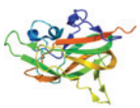
Pyroptosis can ignite antitumor responses (by Oscar via Wikimedia Commons)

Pyroptosis is a form of pro-inflammatory programmed cell death. Wang et al. develop a system that effectively delivers and activates antibody–drug conjugates into tumor cells, and delivery of the pore-forming protein gasdermin A3 induces pyroptosis, which in turn triggers antitumor responses and enhances efficacy of immune checkpoint blockade. Zhang and colleagues show cancer cells often have reduced gasdermin E or loss-of-function mutations. Expression of gasdermin E increases TAM phagocytosis of tumor cells and increases the presence of cytolytic NK cells and $CD8^+$ T cells, which creates a positive feedback loop as killer cell–produced granzyme B also induces pyroptosis in a caspase-independent manner.

Wang Q, . . ., Liu Z. ***Nature*** *2020 Mar 11;579:421–6.*

Zhang Z, . . ., Lieberman J. ***Nature*** *2020 Mar 11;579:415–20.*

Neuropilin-1 is a T cell memory checkpoint limiting long-term antitumor immunity



Expression of NRP1 contributes to cancer progression and spread (by Emw via Wikimedia Commons)

Generation of long-term memory T-cell responses can be compromised in cancer and contributes to lack of durable responses to immune checkpoint blockade (ICB). Liu et al. show that NRP1 (neuropilin-1) is upregulated on tumor-infiltrating $CD8^+$ T cells, and that genetic deletion of NRP1 in $CD8^+$ T cells protects mice from tumor re-challenge and also renders tumors more sensitive to ICB. NRP1 promotes terminal exhaustion in tumor-infiltrating $CD8^+$ T cells and is associated with impaired TCR signaling. The data bring attention to the potential of targeting NRP1 to promote the generation of durable and efective antitumor immunity.

Liu C, . . ., Vignali DAA. ***Nat Immunol*** *2020 Jul 13. DOI: 10.1038/s41590-020-0733-2.*

An oncogenic alteration creates a microenvironment that promotes tumor progression by conferring a metabolic advantage to regulatory T cells

RHOA mutations result in Tregs getting a metabolic jolt (by Aivarcs via Wikimedia Commons)

Immunotherapy has been of limited benefit in gastric cancer (GC). By profiling the immune landscape of GC, Kumagai et al. identify a subset with a high frequency of regulatory T cells (Tregs) and few effectors. These tumors have mutations in *RHOA*, activating PI3K–AKT–mTOR signaling with increased free fatty acid production, which feeds Tregs in the tumor microenvironment (TME). Tumors with this profile are resistant to anti–PD-1, but combination with Treg-targeting therapies or PI3K inhibitors sensitizes them to treatment. These data illustrate a metabolic advantage promoting Treg accumulation in the TME that may be targetable.

Kumagai S, . . ., Nishikawa H. ***Immunity*** *2020 Jul 14;53:187–203.e8.*