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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

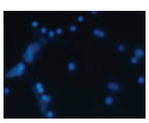
Tumoural activation of TLR3–SLIT2 axis in endothelium drives metastasis

Endothelial SLIT2 expression contributes to metastasis (by Pleiotrope via Wikimedia Commons)

How endothelial cells aid in the dissemination of cancer is not well-known. By assessing highly and poorly metastatic tumors, Tavora et al. identify the specific compartment within the endothelium that contributes to metastases based on expression of *Slit2*. Expression of SLIT2 protein by endothelial cells, in addition to its receptor, promotes migration and invasion of lung and breast cancer cells, and *Slit2* deletion in endothelial cells, but not tumor cells, reduces metastasis in mouse models. Mechanistically, tumor-derived double-stranded RNA triggers endothelial SLIT2 protein expression via TLR3 signaling. The data highlight an important role of endothelial cells in facilitating metastases and how the expression of *Slit2*, as well as its cellular source, can dictate disease progression.

Tavora B, . . ., Tavazoie SF. ***Nature*** *2020 Sep 30;586:299–304.*

Interleukin-17–induced neutrophil extracellular traps mediate resistance to checkpoint blockade in pancreatic cancer

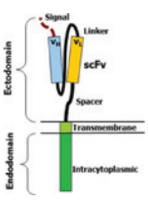


IL17 can trigger "NETosis" (by Ltumanovskaya via Wikimedia Commons)

Pancreatic ductal adenocarcinoma (PDAC) has an immunosuppressive tumor microenvironment (TME) that contributes to therapy resistance. Zhang et al. find that IL17 plays a pivotal role in maintaining immune suppression in the PDAC TME by recruiting neutrophils and subsequent induction of neutrophil extracellular traps (NET) via their upregulation of peptidyl arginine deiminase type IV (Padi4). At the same time, $CD8^+$ T-cell recruitment and activation are decreased when IL17 is present. By blocking IL17 signaling, tumors are sensitized to immune checkpoint blockade, an effect dependent on $CD8^+$ T cells. In patients, high IL17 and PADI4 expression correlates with poor prognosis, thus, blocking IL17 could boost antitumor responses in PDAC.

Zhang Y, . . ., McAllister F. J ***Exp Med*** *2020 Aug 28;217:e20190354.*

Single-cell analyses identify brain mural cells expressing CD19 as potential off-tumor targets for CAR-T immunotherapies

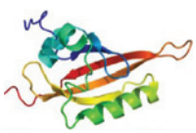


CD19-directed CAR T cells could also target mural brain cells (by Mxpule via Wikimedia Commons)

Neurologic toxicities are a known adverse event associated with chimeric antigen receptor (CAR) T-cell therapy, but the mechanisms underlying these are not well known. CD19 is typically considered a B cell–specific marker, and its targeting has been the basis for some CAR T-cell therapies. Parker et al., through single-cell RNA sequencing, show that CD19 is also expressed in human brain mural cells, which have a vital role in maintaining the integrity of the blood–brain barrier. CD19 expression by brain mural cells occurs during their development and is maintained across the brain. These data show how mural cell CD19 expression could account for, or at least contribute to, the neurotoxicities associated with CD19-directed therapies.

Parker KR, . . ., Satpathy AT. ***Cell*** *2020 Oct 1;183:126–42.E17.*

IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression



AHR promotes tumor growth (by Emw via Wikipedia)

The aryl hydrocarbon receptor (AHR), which regulates immune function, is a transcription factor activated by ligands such as tryptophan derivatives. Using a pan-tissue AHR signature, Sadik et al. identify IL4I1 as a potent AHR-activating enzyme. IL4I1, like IDO1, catabolizes tryptophan, but it generates indole-3-pyruvic acid, which gives rise to AHR ligands. IL4I1 is highly expressed in primary and metastatic human tumors, with its expression positively correlating with myeloid-derived suppressor cells and regulatory T cells. This effect of IL4I1 enhances chronic lymphocytic leukemia progression in mice. IL4I1 expression is increased together with IDO1 expression after immune checkpoint blockade (ICB), and this may induce resistance to ICB and to combination ICB and IDO inhibition.

Sadik A, . . ., Opitz CA. ***Cell*** *2020 Sep 3;182:1252–70.E34.*

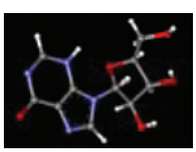
Functional genomic landscape of cancer-intrinsic evasion of killing by T cells

Picturing the genomic landscape of immune evasion (by Larisa Koshkina via publicdomainpictures.net)

A comprehensive understanding of the genes and pathways that allow cancer cells to evade the immune system is still lacking. Using a genome-wide CRISPR screen, Lawson et al. identify a core set of 182 cancer cell–intrinsic genes associated with evasion from killing by CTLs across a panel of six mouse cancer cell lines. Analysis of the dataset reveals discrete functional modules of genes that mediate resistance to killing by CTLs. One module shows that the autophagy pathway mediates cancer cell evasion of CTL-induced cytotoxicity by IFNγ and TNF. The data strengthen our understanding of the interplay between cancer and the immune system.

Lawson KA, . . ., Moffat J. ***Nature*** *2020 Sep 23;586:120–6.*

Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy



Inosine from gut bacteria can enhance ICB (by MarinaVladivostok via Wikimedia Commons)

Certain species of intestinal bacteria are associated with increased immune checkpoint blockade (ICB) efficacy; what mediates these effects is unclear. Mager et al. show that ICB efficacy in mouse models of colorectal cancer is enhanced by intestinal *Bifidobacterium pseudolongum, Lactobacillus johnsonii*, and *Olsenella* species, all of which are found in human intestines. *B. pseudolongum* mediates its effects through production of inosine, which enters the blood and promotes Th1 cell differentiation. The ICB-enhancing effect of inosine is context dependent, requiring costimulation, and also occurs in models of bladder cancer and melanoma, suggesting new avenues for developing ICB-enhancing therapies.

Mager LF, . . ., McCoy KD. ***Science*** *2020 Sep 18;369:1481–9.*