Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Restriction of PD-1 function by *cis*-PD-L1/CD80 interactions is required for optimal T cell responses

Capping PD-L1 with cis CD80 blocks inhibition (by Trounce via Wikimedia Commons)

PD-L1 and CD80 only interact in *cis*. Dendritic cells (DCs) can express excessive amounts of CD80, which is necessary for costimulation of antitumor T cells. However, another role that CD80 plays is to tie up any PD-L1 expressed on the DC surface. In doing so, PD-1 on T cells is prevented from engaging its ligand PD-L1 on DCs, allowing for CD28 costimulation and thus, the consequent activation of specific T cells can commence.

Sugiura D, . . ., Okazaki T. **Science** 2019 May 10;364:558–66.

Cancer cell stemness and the antitumor immune response

Toxic stems keep controls at bay (E. Aardvark via Wikimedia Commons)

Miao and colleagues developed an inducible epidermal squamous cell carcinoma model and find that cancer stem cells responding to TGFβ can evade immune responses through upregulation of CD80, which then binds to CTLA-4 on T cells, dampening the response. Miranda and colleagues find other mechanisms to explain how cancer stem cells can keep tumors "cold", which include increased expression of immune checkpoints, decreased type I IFN signaling, and reduced expression of endogenous retroviruses.

Miao Y, . . ., Fuchs E. **Cell** 2019 April 25. DOI: 10.1016/j.cell.2019.03.025.

Miranda A, . . ., Nelson BH. **Proc Natl Acad Sci U S A** 2019 Apr 30;116:9020–9.

Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4$^+$ T Cell Immunity

Releasing cDC2s (by E. Alcinoe via OpenPhoto)

Migratory conventional dendritic cells (cDC2s) in tumor draining lymph nodes were identified by single-cell analysis from the heterogeneous myeloid population as critical for the proliferation of conventional CD4$^+$ T cells. cDC2s can only fully prime CD4$^+$ T cells if regulatory T cells are depleted or if anti–CTLA-4 treatment is given. Human tumors also have extensive heterogeneity among myeloid cells, and patients whose tumors had more cDC2s and fewer Tregs had the best prognoses, suggesting usefulness as a biomarker.

Binnewies M, . . ., Krummel MF. **Cell** 2019 Apr 18;177:556–71.

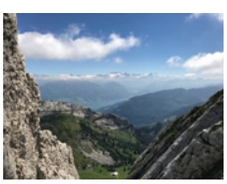
CD8$^+$ T cells regulate tumour ferroptosis during cancer immunotherapy

Allies with iron-dependent death (by E. Serrao via Flickr)

An iron-dependent form of cell death, ferroptosis, results from the accumulation of lipid peroxidation in tumor cells. CD8$^+$ T cells secrete IFNγ, which decreases the amount of two subunits of a cystine transporter necessary to fend off this accumulation in tumor cells. Mice depleted of cystine or cysteine have enhanced responses to immune checkpoint blockade (ICB), and patients whose tumors have intact cystine transport have poorer prognoses. Patient response to ICB correlated with reduced expression of the transporters and more IFNγ-producing CD8$^+$ T cells.

Wang W, . . ., Zou W. **Nature** 2019 May 1;569:270–4.

Human tumor-associated macrophage and monocyte transcriptional landscapes reveal cancer-specific reprogramming, biomarkers, and therapeutic targets



Comparing landscapes (from LJ Miller)

Biomarkers of TAMs associated with survival, recruitment, and metastasis are identified by differential gene expression. Breast and endometrial tumors secrete undetermined factors that stimulate a regulatory loop whereby tumor cells secrete CSF1 and TNFα inducing TAMs to express SIGLEC1 and CCL8, attracting not only more monocytes but also stimulating tumor cells to make more CSF1 and TNFα, as well as inducing cancer cell motility.

Cassetta L, . . ., Pollard JW. **Cancer Cell** 2019 Apr 15;35:588–602.

Immunogenic neoantigens derived from gene fusions stimulate T cell responses

Fusions stimulate responses (by N. Hotsuma via Flickr)

A patient with an HPV$^-$ metastatic squamous cell carcinoma (SCC) responded completely to anti–PD-1. T cells recognized and were activated by a neoepitope formed by a fusion of two genes in the cancer cells. T-cell clones specific for this fusion-derived epitope increased with anti–PD-1 therapy, then decreased as the tumor regressed and stabilized at low numbers. Other patients' T cells were found to recognize other immunostimulatory fusion neoepitopes. Analysis of data sets from patients who received PD-1 blockade revealed that the frequency of fusions predicted to be immunogenic declined in responders, suggestive of immunoediting.

Yang W, . . ., Morris LGT. **Nat Med** 2019 Apr 22;25:767–75.

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Cancer Immunol Res 2019;7:853.