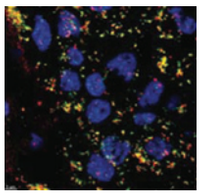
Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from our Deputy and Senior Editors

Insights and resources for investigating breast cancer interactions with immune cells



Breast cancer cells responding to MDSCs (from Wu et al. Cancer Res 2018)

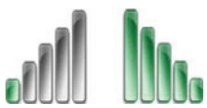
Wu et al. show that CD11c$^+$ myeloid cells in breast tumors produce IL1β in response to interactions with tumor cell TGFβ, an inflammatory signature with a poor prognosis, but blocking either cytokine inhibits tumor progression. Azizi et al. use high-dimensional single-cell analysis to compare breast tumor T and myeloid cells to cells in other tissues. T cells do not have a limited number of discrete activation states but operate in a continuum. Michea et al.'s complementary study focuses on the differences in DC subsets between luminal and triple-negative breast tumors and shows how distinct microenvironments affected different DC subsets.

Wu T-C, . . ., Palucka K. **Cancer Res** 2018 Jul 16. DOI: 10.1158/0008-5472.CAN-18-0413.

Azizi E, . . ., Pe'er D. **Cell** 2018 Aug 23. doi: 10.1016/j.cell.2018.05.060.

Michea P, . . ., Soumelis V. **Nat Immunol** 2018 Jul 16;19:885–97.

When it pays to have strong TCR signals and when the influence of TCR wanes



Different signal strengths (from D. Edmundson Jr, Computing Concepts, LLC)

How important is TCR signal strength to specific immune responses? Snook et al. find that the strength of TCR signals affects CD4$^+$ T-cell fate: strong signals lead to development of T_H1 cells, whereas lower strength leads to development of memory and follicular T_H cells. Richard et al. analyzed single-cells and find that the frequency of CD8$^+$ T cell activation is increased by stronger TCR signals, but crossing the cell's activation threshold gives similar effector function for high- and low-affinity stimulation.

Richard AC, . . ., Griffiths GM. **Nat Immunol** 2018 Jul 16;19:849–58.

Snook JP, . . ., Williams MA. **Sci Immunol** 2018 Jul 20;3:eaas9103.

Reprogramming human T-cell function and specificity with non-viral genome targeting

Rapid and efficient engineered assembly (by Siyuuj via Wikimedia Commons)

A CRISPR-Cas9 targeting system allowed for efficient insertion of over one kilobase of DNA at specific sites in primary human T cells, without affecting their function or viability. Using this platform, a pathogenic mutation was corrected that improved cell function, and T cells with TCRs engineered with a desired tumor antigen specificity were generated and showed effective antitumor responses. This provides a useful technique for rapidly and efficiently engineering immune cells for therapeutic purposes.

Roth TL, . . ., Marson A. **Nature** 2018 Jul 11;559:405–9.

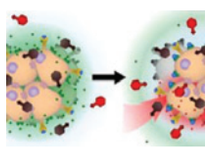
MHC proteins confer differential sensitivity to CTLA-4 and PD-1 blockade in untreated metastatic melanoma

MHC class is key to checkpoint responses (from Locker Singapore)

Immune checkpoint blockade with combination anti–CTLA-4 and anti–PD-1 has benefited patients with advanced melanoma more than either therapy alone. Low, or complete lack of, MHC class I on tumor cells is a key predictor of anti–CTLA-4 resistance in patients, whereas tumor cell MHC class II expression and a pre-existing IFNγ response can predict anti–PD-1 responsiveness. Thus, the benefits of immune checkpoint blockade may be partly attributable to distinct antigen presentation pathways and the antitumor responses induced.

Rodig SJ, . . ., Hodi FS. **Sci Transl Med** 2018 Jul 18;10:eaar3342.

Immune-based mechanisms of tumor resistance



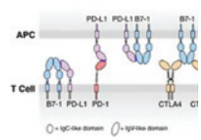
Breaking adenosine-based resistance to checkpoint blockade (from Chen et al. Cancer Discovery 2018)

Chen et al. find that blocking PD-1/PD-L1 interactions in solid tumors can induce resistance through upregulation of CD38 on tumor cells, resulting in suppression of T cells. Combining CD38 blockade with anti–PD-L1 improves antitumor responses. Calcinotto et al. find that the mechanism for resistance to androgen-deprivation therapy in prostate cancer relies on the IL23 produced by MDSCs, which sustains androgen receptor signaling in prostate tumor cells. Inactivation of IL23 restores sensitivity to deprivation therapy in mice.

Chen L, . . ., Gibbons DL. **Cancer Discov** 2018 Jul 16. DOI: 10.1158/2159-8290.CD-17-1033.

Calcinotto A, . . ., Alimonti A. **Nature** 2018 Jun 27;559:363–9.

Biological consequences of *cis* vs. *trans* binding of PD-1 and its ligands to their binding partners



Cis interference (from Chaudhri et al. Cancer Immunol Res 2018)

Interaction of PD-1 on T cells and PD-L1 on APCs or tumor cells inhibits T-cell responses. Zhao et al. find that PD-1 is co-expressed with PD-L1 on tumor cells and tumor-infiltrating APCs, which allows for binding *in cis*. This interaction blocks T-cell PD-1 binding *in trans* and prevents inhibitory signaling. Chaudhri et al. show that B7-1 also binds PD-L1, but only *in cis*. This B7-1/PD-L1 *cis* interaction can competitively block PD-1 binding. Thus, competition for binding to PD-L1 *in cis* and *in trans* needs to be considered when developing immunotherapies.

Zhao Y, . . ., Hui E. **Cell Reports** 2018; 24:379–90.

Chaudhri A, . . ., Freeman G. **Cancer Immunol Res** 2018 Jun 5; DOI: 10.1158/2326-6066.CIR-17-0316.

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Cancer Immunol Res 2018;6:989.