Cancer Immunology Research

What We're Reading

Article Recommendations from Our Deputy and Senior Editors

Eradication of triple-negative breast cancer cells by targeting glycosylated PD-L1

Targeting sugars (by Staff Sgt. Christopher Gross via Buckley Air Force Base)

PD-L1 glycosylation was found to be required for binding to PD-1 and immunosuppressive function in triple-negative breast cancer. In TNBC, EGF upregulates the enzyme B3GNT3 that catalyzes PD-L1 glycosylation. Binding of an Ab specific for glycosylated PD-L1 induces internalization and prevents inhibition by PD-1. Coupling this Ab to a cytotoxic drug kills tumor cells expressing glycosylated PD-L1 and bystanders. Targeting glycosylated PD-L1 on TNBC tumors is a potential strategy to enhance immune checkpoint therapy.

Li C-W, . . ., Hung M-C. **Cancer Cell** 2018 Feb 12;33:187–201.e10.

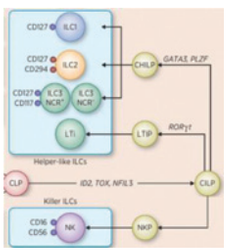
TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

Excluding T cells with TGFβ fences (by Wilson44691 via Wikimedia Commons)

Patients with urothelial cancer who respond to anti–PD-L1 treatment have higher neoantigen and $CD8^+$ T cell levels, whereas nonresponders have more impenetrable tumors surrounded by fibroblasts with strong TGFβ signaling signatures. In a mouse model, addition of anti-TGFβ to anti–PD-L1 therapy enhances $CD8^+$ T-cell infiltration into tumor centers, with concomitant antitumor immunity and tumor regression, highlighting the key role of TGFβ in shaping the tumor microenvironment.

Mariathasan S, . . ., Powles T. **Nature** 2018 Feb 14. doi:10.1038/nature25501.

Natural killer cells control tumor growth by sensing a growth factor



The innate sensors (from B Vallentine et al. Cancer Immunol Res 2015)

PDGF-DD not only acts on tumor and stromal elements to promote tumor growth, but it also is a ligand for the activating NK-cell receptor NKp44. Many human cancers express PDGF-DD. Stimulating human ILC3, ILC1, and NK cells with it increases secretion of IFNγ and TNF and arrests tumor growth *in vitro*. Expression of NKp44 in mice correlates with more effective tumor control and enhances innate antitumor responses in combination with other immunotherapies.

Barrow AD, . . ., Colonna M. **Cell** 2018 Jan 25;172:534–48.e19.

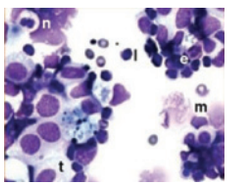
NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting rancer immune control

Recruiting the right skillset (from Library Company of Philadelphia via flickr)

Tumors secrete PGE_2, preventing accumulation of conventional type 1 DCs (cDC1s) in tumors. cDC1s are attracted to tumors by NK-cell production of chemokines XCL1 and CCL5. However, PGE_2 reduces chemokine production by NK cells and downregulates chemokine receptors on cDC1s, impairing migration. Strong NK-, chemokine-, and cDC1-gene signatures correlate with patient survival. These insights into the importance of NK–DC interplay suggest strategies to increase cDC1 infiltration for better cancer control.

Böttcher JP, . . ., Reis eSousa C. **Cell** 2018 Feb 8. doi: 10.1016/j.cell.2018.01.004.

Blocking PD-L1 on myeloid, not tumor, cells is key to developing antitumor immunity

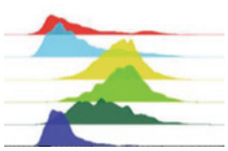


Myeloid cells in tumor digest (from Gros et al. Clin Cancer Res 2012)

The role of PD-L1 on tumor, stroma, and myeloid elements in the tumor microenvironment has remained uncertain. Two papers in *The Journal of Clinical Investigation* determined that the efficacy of PD-L1 blockade relies on the expression of PD-L1 on nontumor myeloid cells such as macrophages and dendritic cells. Expression of PD-L1 on tumor cells had little bearing on the success of blockade in reducing tumor burden in mouse models or clinical responses of patients.

Lin H, . . ., Zou W. **J Clin Invest** 2018 Feb 1;128:805–15.
Tang H, . . ., Fu Y-X. **J Clin Invest** 2018 Feb 1;128:580–8.

The tumour microenvironment creates a niche for the self-renewal of tumour-promoting macrophages in colon adenoma



Macrophage subsets in tumors (from Soncin et al. Fig. 5a)

Adult tissue-resident macrophages develop from the embryonic yolk sac progenitors and need no replenishment from hematopoietic sources. Intestinal tissue-resident macrophages are one of the exceptions, with rapid turnover forcing a constant reliance on circulating blood monocytes. CCR2-independent $F4/80^{hi}$ macrophages within colon tumors, however, are phenotypically similar to the neonatal macrophages, do not rely on circulating monocytes, are possibly maintained by tumor production of CSF1, and are supportive of tumor progression.

Soncin I, . . ., Ruedl C. **Nat Commun** 2018 Feb 8. doi:10.1038/s41467-018-02834-8.

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