Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Differential regulation of PD-L1 expression by immune and tumor cells in NSCLC and the response to treatment with atezolizumab (anti–PD-L1)

Differential regulation (from pxhere.com)

High PD-L1 expression in non–small cell lung cancers on either tumor or immune cells allows for responsiveness to PD-L1 blockade. PD-L1 expression is controlled by different mechanisms: tumor cells have epigenetically dysregulated methylation and increases in PD-L1 copy number, but immune cell expression is in response to the IFNγ from activated T cells. Cancers with high PD-L1 on tumor cells are fibrotic with few immune cells in them, but high expression on immune cells in tumors correlates with a rich infiltration of $CD8^+$ T cells.

Kowanetz M, . . ., Hegde PS. **Proc Natl Acad Sci USA** 2018 Oct; 115:E10119–E10126.

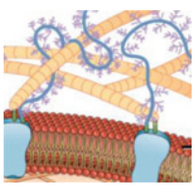
A cancer cell program promotes T-cell exclusion and resistance to checkpoint blockade

Resistance program master is CDK4/6 (from maxpixel.net)

Single-cell analysis of 33 melanoma specimens reveals intrinsic determinants of "cold" tumors that prevent T-cell infiltration and promote immune evasion. This resistance program is re-engaged when patients no longer respond to checkpoint blockade. Patients with tumors strongly expressing the program have the worst response to checkpoint blockade and the poorest survival. CDK4/6 acts as a master regulator of the program, which comprises a repression of cell–cell interactions and immune evasion. Because inhibiting CDK4/6 enhances checkpoint blockade's efficacy in a murine model, targeting such resistance programs has potential to complement immunotherapies.

Jerby-Arnon L, . . ., Regev A. **Cell** 2018 Nov; 175:984–97.

TGF-β–associated extracellular matrix genes link cancer-associated fibroblasts to immune evasion and immunotherapy failure



Extracellular matrix signature and tumor progression (by CNX Open Stax via WikiMedia Commons)

A dysregulated set of extracellular matrix (ECM) genes is overexpressed across tumor types and associates with tumorigenesis. ECM overexpression correlates with cancer-associated fibroblasts, microsatellite instability, and immunologically active tumors (perhaps as an adaptive mechanism for immune evasion). TGFβ is activated, and this state predicts nonresponsiveness to anti–PD-1. Thus, tumors overexpressing ECM genes may be setting up an immunosuppressive state that could be reversed through inhibition of TGFβ and immune checkpoints.

Chakravarthy A, . . ., De Carvalho DD. **Nat Commun** 2018 Nov. DOI: 10.1038/s41467-018-06654-8.

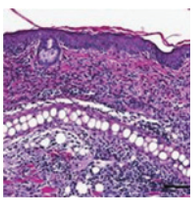
Defining T-cell states associated with response to checkpoint immunotherapy in melanoma

High-dimensional definition (by csanhuezalobos via github.com)

To better clarify the types of T cells in melanomas, biopsies from checkpoint blockade–treated patients were subjected to high-dimensional RNA sequencing. $CD8^+$ T cells clustered into two large camps: primarily enriched in expression of memory, activation, and cell survival genes, or enriched in genes associated with exhaustion. The active/memory states ($TCF7^+$) predict positive clinical outcomes. Exhausted cells express TIM3 and CD39, whose chromatin is made accessible in the exhausted cells. Given that memory-like cells are associated with response to checkpoint blockade, developing treatments that increase these cells over the $CD39^+TIM3^+$ T cells could enhance immunotherapy.

Sade-Feldman M, . . ., Hacohen N. **Cell** 2018 Nov; 175:998-1013.e20.

IFNγ-activated dermal lymphatic vessels inhibit cytotoxic T cells in melanoma and inflamed skin



Inflamed skin (from Fig 4 in R.S. Lane et al. in J Exp Med 2018)

Peripheral tissues employ mechanisms that suppress immune responses to avoid tissue damage. PD-L1 is readily expressed by lymphatic and blood endothelial cells in skin exposed to the antitumor or antiviral IFNγ from $CD8^+$ T cells. PD-L1 expression limits $CD8^+$ T cell cytotoxicity in melanoma and during inflammation. Thus, tumor cells have co-opted a tissue-protective strategy that limits the damage to tissue from an antiviral response, while also diminishing the effectiveness of cytotoxic antitumor responses.

Lane RS, . . ., Lund AW. **J Exp Med** 2018 Dec; 215:3057–74.

High-dimensional analysis delineates myeloid and lymphoid compartment remodeling during successful immune-checkpoint cancer therapy

Productive branch-points during checkpoint blockade (by L. Miller)

Immune cell populations in a murine tumor model are altered by checkpoint blockade. Through the use of two different high-dimensional methods, CyTOF for protein and single-cell RNAseq for gene expression, changes in both lymphoid myeloid populations could be followed in "pseudotime." This combination of assessments provides insight into why combination checkpoint blockade is so efficacious and implicates circulating monocytes as the myeloid cells that undergo a functional branch-point after checkpoint blockade to enhance antitumor responses.

Gubin MM, . . ., Artyomov MN. **Cell** 2018 Nov; 175:1014–30.

Cancer Immunology Research

A Sampling of Highlights from the Literature: Article Recommendations from Our Deputy and Senior Editors

Cancer Immunol Res 2019;7:1.