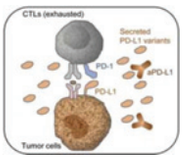
Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Extracellular PD-L1 mechanisms of resistance



Interference from extracellular decoy PD-L1 (from B. Gong et al., J Exp Med 2019)

Extracellular PD-L1 contributes to resistance to anti–PD-L1 therapy. Poggio et al. find that some tumor cells release PD-L1 in exosomes. This interferes with T-cell activation, promoting tumor progression. Gong et al. identify transmembrane-minus PD-L1 splice variants secreted in lung cancer patients. This secreted form acts as a decoy for anti–PD-L1, causing resistance to immunotherapy that is overcome by use of anti–PD-1. Thus, noncellular PD-L1 exists in multiple forms that can interfere with antitumor immunity.

Gong B, . . ., Katayama R. **J Exp Med** 2019 Mar 14. DOI: 10.1084/jem.20180870.

Poggio M, . . ., Blelloch R. **Cell** 2019 Apr;117:414–27.

Hepatocytes direct the formation of a pro-metastatic niche in the liver

Laying the groundwork for a new niche (by J.D. Harlan via IGB Training and Education Center)

Pancreatic cancers induce the production of IL6 from fibroblasts in the primary tumor. IL6 circulates to the liver, where it binds the IL6 receptor on hepatocytes and, through STAT3, initiates hepatocyte production of SAA proteins. Myeloid (Ly6G$^+$) cells accumulate and immunosuppress the pro-metastatic site, which can sustain cancer cells that escaped the primary site. Thus, primary tumors help prepare metastatic sites via immune manipulation.

Lee JW, . . ., Beatty GL. **Nature** 2019 Mar;567:249–52.

Neoepitope discovery with chimeric peptide-MHC proteins that reverse-signal

Useful chimeras developed (from iamagardian via WikiMedia)

Chimeric peptide-MHC (pMHC) reporter constructs can identify the neoepitopes binding TCRs during an immune response. Kisielow et al. devised libraries of pMHC class II–TCR chimeras that signal via TCR complexes in reporter hybridomas when activated by cognate TCRs. Joglekar et al. describe a system in which libraries of single-chain pMHC class I are coupled to CAR-like structures with TCRζ-CD28 domains on reporter cells. Li et al. take advantage of the "reverse" trogocytosis of TCRs onto the reporter cells to identify the TCRs that see particular antigens. These systems provide high-throughput screens and epitope identification with wide-scale potential.

Kisielow J, . . ., Kopf M. **Nat Immunol** 2019 Mar 11. DOI: 10.1038/s41590-019-0335-z

Joglekar AV, . . ., Baltimore D. **Nat Methods** 2019 Jan 28;16:191–8

Li G, . . ., Baltimore D. **Nat Methods** 2019 Jan 28;16:183–90.

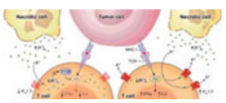
CAR T cell trogocytosis and cooperative killing regulate tumor antigen escape

Transfer of surface molecules after contact (by MusicMoon via flickr)

Cancer patients can relapse after CAR T-cell therapy due to target-antigen loss or low antigen density on tumor cells. CAR T cells can trogocytose target antigens from tumors, decreasing tumor antigen density and promoting T-cell exhaustion or the killing of T cells expressing the trogocytosed protein. Modifying the CAR construct to account for low antigen density, as well as dual-targeting and higher CAR T-cell doses, can reduce tumor escape.

Hamieh M, . . ., Sadelain M. **Nature** 2019 Mar 27. DOI: 10.1038/s41586-019-1054-1.

Different flavors of T-cell exhaustion



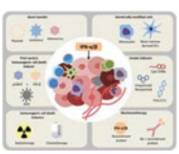
Potassium-mediated T-cell suppression (from Gurusamy et al. Cancer Immunol Res 2017)

Exhausted T cells can still proliferate, have stem-like properties, and facilitate the clearance of tumors, and multiple mechanisms come into play. Miller et al. find that exhausted CD8$^+$ T cells can be either progenitor- ("stem-like") or terminally exhausted phenotypes, with distinct persistence, ability to control tumors, and responsiveness to immune checkpoint blockade. Vodnala et al. show that increased potassium in the tumor microenvironment alters persistence and multipotency of TCF7-expressing CD8$^+$ T cells. Their metabolic reprogramming and altered histone acetylation at effector and exhaustion loci limit effector function while preserving stemness.

Miller BC, . . ., Haining WN. **Nat Immunol** 2019 Feb 18;20:326–36.

Vodnala SK, . . ., Restifo NP. **Science** 2019 Mar 29;363:eaau0135.

Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response



Type I interferons induced by multiple cancer therapies (from Medrano et al. Oncotarget 2017)

Myeloid cells can affect the efficacy of chemotherapy. A KEP transgenic breast cancer model shows that CSF-1$^+$ macrophages infiltrate tumors and anti–CSF-1R reduces this population. When combined with chemotherapy, both survival and Ly6C$^+$ myeloid cells, with elevated CD80/86 and reduced CCR2 and CX3CR1 expression, increase. Macrophages and neutrophils from dual-treated animals had altered transcriptional profiles and are enriched in genes for type I IFN signaling. Targeting both cell types in addition to chemotherapy increases antitumor responses.

Salvagno C, . . ., de Visser KE. **Nat Cell Biol** 2019 Mar 18. DOI: 10.1038/s41556-019-0298-1.

Cancer Immunology Research

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

Cancer Immunol Res 2019;7:695.