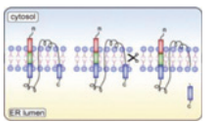
Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from our Deputy and Senior Editors

Identification of non-mutated neoantigens presented by TAP-deficient tumors



Identifying unmutated neoantigens (from Fig. 1 of Marijt et al., J Exp Med 2018)

TAP-deficient tumor cells generate non-mutated antigens derived from N-terminal signal peptides or C-terminal tail peptides, to which multiple individuals can have reactive T cells. These T cells are activated by peptides from TAP-deficient tumors of diverse tissue origins. Targeting these antigens does not harm critical organs expressing the intact protein, thereby providing a therapeutic opportunity for TAP-deficient tumors that escape immune surveillance.

Marijt KA, . . ., van Hall T. **J Exp Med** 2018 Aug 16. DOI: 10.1084/jem.20180577.

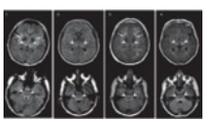
Phosphoproteomic analysis of chimeric antigen receptor signaling reveals kinetic and quantitative differences that affect cell function

Strong activation signals can affect downstream cellular effects (by Krish Dulal via Wikimedia Commons)

Signal strength trumps signal type. Head-to-head comparison of the downstream phosphorylation patterns in T cells activated by CARs containing either CD28 or 4-1BB signal domains suggested they are almost identical. However, the CD28 domains led to stronger TCR signals that led to faster and larger magnitude downstream phosphorylation, leading to more effector differentiation and less memory formation, making the cells less effective at eliminating axenografted lymphoma in a mouse model.

Salter AI, . . ., Riddell SR. **Sci Signal** 2018 Aug 21;11:eaat6753.

Major role for IL1 in CAR T-cell CRS and neurotoxicity

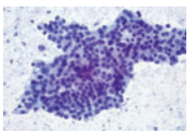


Neurotoxicity after CAR T-cell therapy (from Fig. 2 of Santomasso et al., CD 2018)

Two teams developed new mouse models to examine the cytokine-release syndrome (CRS) experienced by patients treated with CAR T cells. Both find that IL6 and IL1 from monocytes and macrophages are the major effectors of the toxicity. Giavridis et al. developed a CAR that produced IL1Ra (IL1 receptor antagonist), which obviated CRS without diminishing T-cell antitumor efficacy. The Norelli group's model recapitulates aspects of the neurotoxicity associated with human CRS and finds that, although IL6 and IL1 from macrophages are both involved in CRS, blocking signals from the IL1R alone can prevent neurotoxicity. Santomasso et al. evaluate this in treated patients and show that the neurotoxic effects are likely due, in part, from nervous system–specific production of IL6, IL8, IP10, and MCP1. Seizures appear likely due to excitatory agonists present in the cerebrospinal fluid, and are mediated by quinolinic acid and glutamate-activated NMDA and AMPA receptors.

Norelli M, . . ., Bondanza A. **Nat Med** 2018 May 28;24:739–48.
Giavridis T, . . ., Sadelain M. **Nat Med** 2018 May 28;24:731–8.
Santomasso BD, . . ., Brentjens RJ. **Cancer Discov** 2018 Aug 1;8:958–71.

Unresolved endoplasmic reticulum stress engenders immune-resistant, latent pancreatic cancer metastases



Pancreatic adenocarcinoma (by Ed Uthman via Wikimedia Commons)

A mouse model was developed to examine why dormant micrometastases arise in PDA and become active after resection of pancreatic ductal adenocarcinomas. Hosts with PDA contain disseminated cancer cells (DCCs) that do not express cytokeratin or MHC class I, which is needed for an adaptive immune response. These DCCs are experiencing a cell autonomous ER stress response promoting a dormant state. If the stress response is resolved by expression of XBP1s and T cells are also depleted, class I and cytokeratin are re-expressed, and micrometastases grow into macrometastases.

Pommier A, . . ., Fearon DT. **Science** 2018 Jun 15;360:eaao4908.

High-dimensional single cell analysis identifies stemlike cytotoxic CD8$^+$ T cells infiltrating human tumors

High-dimensional single-cell analysis of TILs (from Fig. 1 of Brummelman et al., J Exp Med 2018)

Tumor-infiltrating CD8$^+$ T cell subsets have not yet been fully defined. Brummelman et al. used high-dimensional single-cell analysis of tumors, blood, and normal tissues from 53 patients with non–small cell lung cancer to identify specific CD8$^+$ T cell subsets enriched in the tumor microenvironment. A subset of CXCR5$^+$TIM-3$^-$ partially exhausted CD8$^+$ T cells expressing PD-1 and TIGIT were found and shown to have stem-like characteristics, including self-renewability and multipotency, while also maintaining effector potential. As disease progresses, this subset disappears and outcomes worsen.

Brummelman J, . . ., Lugli E. **J Exp Med** 2018 Aug 28. DOI: 10.1084/jem.20180684.

Exosomal PD-L1 contributes to immunosuppression and is associated with anti–PD-1 response

Release of exosomes expressing PD-L1 (by John Liu via Wikimedia Commons)

A mechanism of immune evasion is tumor cell upregulation of PD-L1, which interacts with PD-1 to deliver suppressive signals to T cells. Chen et al. demonstrate metastatic melanoma releases exosomes expressing PD-L1, which increases after exposure to IFNγ, and can suppress anti-tumor responses and facilitate tumor growth. Assessment of exosomal PD-L1 stratified melanoma patients into responders and non-responders to PD-1 blockade, highlighting that this may be useful as a biomarker for predicting outcomes with anti–PD-1 therapy.

Chen G, . . ., Guo W. **Nature** 2018 Aug 8;560:382–386.

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Cancer Immunol Res 2018;6:1121.