Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

Augmenting immunotherapy impact by lowering tumor TNF cytotoxicity threshold

Overcoming ICB resistance (by EliasSch via Pixabay)

Tumor resistance to immune checkpoint blockade (ICB) is associated with loss of responsiveness to IFNγ. CRISPR-Cas9 screens of *IFNGR1* knockout melanoma cells cocultured with antigen-specific $CD8^+$ T cells identified TRAF2 (involved in the TNFα pathway) as a candidate to enhance T-cell killing. T cells induce RIPK1-mediated death in *TRAF2*-knockout tumor cells, which correlates with robust growth inhibition of *TRAF2* knockout tumors after adoptive cell therapy. Inhibition of the TRAF2/cIAP complex increases melanoma susceptibility to $CD8^+$ T cells and augments the efficacy of checkpoint blockade.

Vredevoogd DW, . . ., Peeper DS. **Cell** 2019 Jul 25;178:585–99.E15.

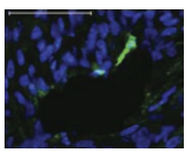
Engineering nanoparticles to locally activate T cells in the tumor microenvironment

Laser targeting (by Pang Kakit via Wikimedia Commons)

Suppressive tumor microenvironments (TMEs) inhibit cytotoxic T-lymphocyte influx and immune checkpoint blockade. Metalloproteinases in the TME and draining lymph nodes can release anti–PD-L1 containing a photosensitizer from a tumor-permeable protected nanoparticle (S-αPDL1/ICG@NP). Subsequent treatment with near-infrared (NIR) lasers triggers the release of reactive oxygen species within the tumor, which increases inflammatory cytokines, dendritic cell maturation, and $CD8^+$ T-cell infiltration. The activated nanoparticles are better inhibitors of tumor growth and metastasis dissemination compared to conventional PD-L1 antibody, suggesting a promising approach for immunotherapy.

Wang D, . . ., Li Y. **Sci Immunol** 2019 Jul 12;4:eaau6584.

Oncogenic kinase inhibition limits Batf3-dependent dendritic cell development and antitumor immunity

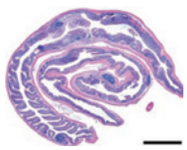


Fluorescent DCs in GIST (from Medina et al. J Exp Med 2019)

$Batf3^+CD103^+CD11b^-$ DCs mediate tumor antigen–specific, $CD8^+$ T-cell cross-priming, and DC activation is key to the effectiveness of the protein kinase inhibitor imatinib. Treatment of human and mouse gastrointestinal stromal tumors (GISTs) with imatinib for different durations varies the antitumor $CD8^+$ T-cell response. Chronic imatinib reduces the macrophage-reliant GM-CSF production of γδ T cells, which is needed for DC maturation and activation. Therefore, maintaining an environment conducive to DC maturation and activation should be considered when treating with imatinib in order to promote antitumor activity in GISTs.

Medina BD, . . ., DeMatteo RP. **J Exp Med** 2019 Jun 3;216:1359–76.

Editing of the gut microbiota reduces carcinogenesis in mouse models of colitis-associated colorectal cancer

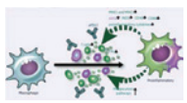


Inflammation-induced colon tumors (from Zhu et al. J Exp Med 2019)

Gut microbiota can enhance the likelihood of colorectal cancer through production of toxins and perpetuation of inflammation. Oral tungstate (which interferes with necessary enterobacterial metalloenzymes) manipulates microbiota composition by specific reduction of Gammaproteobacteria populations (but not obligate anaerobes) during colonic inflammation. Selectively controlling Enterobactericeae reduces inflammation intensity, toxin production, and tumor development in both injury and genetic models of chronic inflammation. Thus, targeting gut microbes that promote CRC could reduce the frequency of malignant polyp formation.

Zhu W, . . ., Winter SE. **J Exp Med** 2019 Jul 29. DOI: 10.1084/jem.20181939.

Anti–PD-L1 treatment results in functional remodeling of the macrophage compartment

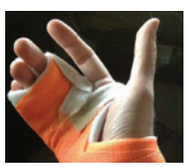


Repolarizing tumor-associated macrophages (from Xiong et al. Cancer Res 2019)

Tumor burden can correlate with a suppressive tumor-associated macrophage (TAM) phenotype. Treating MC38 or EMT6 murine tumors with anti–PD-L1 increases IFNγ production, redirects TAM polarization to be pro-inflammatory, and enhances T-cell proliferation and activation. Suppressive activity of TAMs can also be modulated by agonist CD40 mAbs to increase M1 polarization by depletion of TAMs with anti-CSF1R. As the response to anti–PD-L1 is affected by TAM numbers and suppressive activity, combining one or both of these reagents with anti–PD-L1 in macrophage-rich tumors could expand the proportion of patients that respond to immunotherapy.

Xiong H, . . ., Cubas R. **Cancer Res** 2019 Apr 1;79:1493–506.

Stabilized MHC class I to rapidly screen for antigen-specific peptides



Stabilizing useful structures (by pixlaw via Wikimedia Commons)

Libraries of peptide-MHC class I complexes are useful for characterizing T-cell responses. Two studies have created libraries by overcoming the instability of empty MHC class I complexes with disulfide-stabilized (DS) MHC-I molecules. Using peptide-DS MHC multimers, Saini et al. rapidly screened T cells infiltrating melanomas for neoantigen reactivity. Moritz et al. utilized a peptide-DS MHC library to assess reactivity of affinity-matured TCRs, including off-target self-reactivity. Thus, stable, "empty" MHC molecules easily loaded with peptide can facilitate analysis of TCR interactions with peptide-MHC.

Saini SK, . . ., Hadrup SR. **Sci Immunol** 2019 Jul 19;4:eaau9039.

Moritz A, . . ., Maurer D. **Sci Immunol** 2019 Jul 19;4:eaav0860.

Cancer Immunology Research

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

Cancer Immunol Res 2019;7:1383.