Cancer Immunology Research

A Sampling of Highlights from the Literature

Article Recommendations from Our Deputy and Senior Editors

MHC-II neoantigens shape tumour immunity and response to immunotherapy

Helpful CD4s (by Ashlee Galloway, U.S. Dept. of Defense)

Immunotherapy is beneficial to only a subset of patients for reasons not yet fully understood. A new predictive algorithm identifies MHC-II neoantigens important for induction of $CD8^+$ T-cell antitumor responses. Tumors need to coexpress both MHC-I and MHC-II neoantigens for optimal efficacy of immune checkpoint therapy and neoantigen-specific cancer vaccines leading to elimination of tumors in preclinical models (including ones that lack MHC-II). Thus, $CD4^+$ and $CD8^+$ T-cell responses in both the lymph node and tumor microenvironment are key to successful immunotherapy treatment.

Alspach E, . . ., Schreiber RD. **Nature** 2019 Oct;574:696–701.

Oncolytic viruses engineered to enforce leptin expression reprogram tumor-infiltrating T cell metabolism and promote tumor clearance

Boosting T-cell metabolism (modified from moritz320 via Pixabay)

Responses to oncolytic viruses are limited by immunosuppressive tumor microenvironments (TMEs). Oncolytic vaccinia virus (OVV) slightly delays tumor growth by increasing accumulation of non-exhausted, yet metabolically deficient, $CD8^+$ T cells recruited to the TME. Leptin revitalizes the metabolism of $CD8^+$ T cells, resulting in T cell–mediated delays in tumor growth. Leptin-producing OVV improves the efficacy of OVV therapy by increasing functional, memory $CD8^+$ T cells, inducing long-term antitumor immunity.

Rivadeneira DB, . . ., Delgoffe GM. **Immunity** 2019 Sep;51:548–60.e4.

Tumor heterogeneity and mutational burden affect diversity and effectiveness of T-cell response

Clonality and heterogeneity (by Jean Beaufort via PublicDomainPictures)

The relationship between tumor clonal heterogeneity and T-cell clonal expansion is controversial. Wolf et al. examine melanoma in a controlled system in which intratumoral heterogeneity and immunity are compared independent of mutational burden, revealing complex relationships between tumor clonal heterogeneity, mutational burden, and antitumor response. Joshi et al. track the T-cell repertoire in patients with non–small cell lung cancer (NSCLC). The expansion of TCR clones and their diversity and relatedness reflect the local diversity of mutations at any one NSCLC tumor site. Blood obtained at the time of tumor resection is informative for tracking and monitoring relevant neoepitope-specific T cells.

Wolf Y, . . ., Samuels Y. **Cell** 2019 Sep;179:219–35.
Joshi K, . . ., Chain B. **Nat Med** 2019 Oct;25:1549–59.

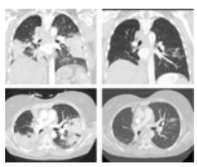
Multiplexed activation of endogenous genes by CRISPRa elicits potent antitumor immunity

Increasing tumor antigens enhances immune targeting (by Linnaea Mallette via PublicDomainPictures)

CRISPR technology can be used to boost antitumor responses. Wang et al. developed MAEGI (multiplexed activation of endogenous genes as an immunotherapy) as a versatile and scalable treatment modality to fight cancer. This strategy capitalizes on CRISPR activation (CRISPRa) using inactive Cas9 to increase expression of specific endogenous tumor genes that are presented as tumor antigens. When MAEGI is delivered *in vivo* via an adeno-associated virus, antitumor responses were enhanced in both prophylactic and therapeutic models. This strategy thus has the potential to complement current treatment strategies.

Wang G, . . ., Chen S. **Nat Immunol** 2019 Oct;20:1494–505.

Two effective inhibitors of mutant KRAS synergize with targeted inhibitors and immune checkpoint blockade

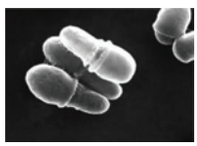


KRAS inhibitor–induced tumor regression (from J. Hallin et al. Cancer Discov 2019)

Specific inhibition of the driver mutation $KRAS^{G12C}$ has been limited by its high affinity for GTP/GDP and the lack of a clear binding pocket. Two inhibitors, MRTX849 by Hallin et al. and AMG 510 by Canon et al., have been developed that covalently bind the cysteine mutation and block KRAS signaling (ERK and S6), subsequently delaying the growth of various $KRAS^{G12C}$ -driven tumor models and inducing partial responses in lung cancer patients. The activity of the KRAS inhibitors can be enhanced by concurrent administration of RTK, SHP2, mTOR, MEK, PD-1, and CDK4/6 inhibitors, and KRAS inhibition can potentially lead to enhanced antitumor immunity and improved responses to checkpoint blockade.

Hallin J, . . ., Christensen JG. **Cancer Discov** 2019 Oct 28. DOI: 10.1158/2159-8290.CD-19-1167.
Canon J, . . ., Lipford JR. **Nature** 2019 Nov;575:217–23.

The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL



Malassezia predominates in pancreatic tumors (by Janice Haney Carr via PIXNIO)

The complement system has emerged as an important component of the TME and tumor promotion. Fungi are found in pancreatic tumors, but the community of fungi in pancreatic tumors differs from that found in gut and normal pancreas. Tumors express a mannose-binding lectin that is cross-linked by fungi glycans to activate the complement cascade. Tumors also express the C3aR, and both the lectin and the C3aR are required for fungal-induced progression.

Aykut B, . . ., Miller G. **Nature** 2019 Oct;574:264–7.

Downloaded from cancerimmunolres.aacrjournals.org on January 25, 2021. © 2019 American Association for Cancer Research.

AACR American Association for Cancer Research

Cancer Immunology Research

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

Cancer Immunol Res 2019;7:1901.

Updated version Access the most recent version of this article at:
http://cancerimmunolres.aacrjournals.org/content/7/12/1901

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
http://cancerimmunolres.aacrjournals.org/content/7/12/1901.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerimmunolres.aacrjournals.org on January 25, 2021. © 2019 American Association for Cancer Research.