### WHAT WE'RE READING

#### A Sampling of Highlights from the Literature

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### CANCER IMMUNOLOGY AT THE CROSSROADS

#### Immune Escape during Breast Tumor Progression

Carlos R. Gil Del Alcazar, Maša Aleković, and Kornelia Polyak

### PRIORITY BRIEF

#### Inhibition of the SRC Kinase HCK Impairs STAT3-Dependent Gastric Tumor Growth in Mice


Myeloid-specific HCK activity promotes gastric tumor development by enhancing macrophage polarization and production of STAT3-stimulatory ligands, which enhance STAT3 signaling in tumor epithelial and immune cells. Reduction or inhibition of HCK activity reduces STAT3-dependent tumor growth.

### RESEARCH ARTICLES

#### Cancer-Associated Fibroblasts Promote Immunosuppression by Inducing ROS-Generating Monocytic MDSCs in Lung Squamous Cell Carcinoma


Lung cancer-derived fibroblasts produce CCL2, which recruits suppressive CCR2⁺ myeloid cells to the tumor microenvironment, where they suppress CD8⁺ T-cell function. Use of various inhibitors shows that this suppression can be reversed, highlighting possible druggable targets.

451 **Interferon-Induced IDO1 Mediates Radiation Resistance and Is a Therapeutic Target in Colorectal Cancer**

Baosheng Chen, David M. Alvarado, Micah Iticovici, Nathan S. Kau, Haeseong Park, Parag J. Parikh, Dinesh Thotala, and Matthew A. Ciorba

Inhibition of the immune-metabolic enzyme IDO1 enhances radiation sensitivity in colorectal cancer and is radioprotective to the normal small intestine in mice. IDO1 inhibitors may increase radiation therapy effectiveness in humans with colorectal cancer while reducing intestinal toxicity.

465 **CD73 Blockade Promotes Dendritic Cell Infiltration of Irradiated Tumors and Tumor Rejection**

Erik Wennerberg, Sheila Spada, Nils-Petter Rudqvist, Claire Lhuillier, Sylvia Gruber, Qiuying Chen, Fengli Zhang, Xi K. Zhou, Steven S. Gross, Silvia C. Formenti, and Sandra Demaria

Radiation-induced adenosine production is identified as a barrier that limits radiotherapy-induced antitumor immune responses. Antibodies to CD73 that block adenosine generation could be used in combination with radiotherapy and immune checkpoint blockade to improve response to radiation therapy.

479 **Fatty Acid Oxidation Controls CD8⁺ Tissue-Resident Memory T-cell Survival in Gastric Adenocarcinoma**

Run Lin, Hui Zhang, Yue J. Yuan, Qiong He, Jiawen Zhou, Shuhua Li, Yu Sun, Daniel Y. Li, Hai-Bo Qiu, Wei Wang, Zhehong Zhuang, Bin Chen, Yonghui Huang, Chuwei Liu, Yingzhao Wang, Shirong Cai, Zunfu Ke, and Weiling He

Tissue-resident memory T cells (Trm) protect against local infection and tumor formation. In gastric adenocarcinoma, Trm are associated with better patient survival and fatty acid availability, and are crucial for Trm persistence and antitumor effects.
Metabolome of Pancreatic Juice Delineates Distinct Clinical Profiles of Pancreatic Cancer and Reveals a Link between Glucose Metabolism and PD-1 Cells

Nina Cortese, Giovanni Capretti, Marialuisa Barbagallo, Alessandra Rigamonti, Panteleimon G. Takis, Giovanni F. Castino, Debora Vignali, Massimo Roncalli, Paola Cappello, Francesco Novelli, Paolo Monti, Alessandro Zerbi, Paola Allavena, Alberto Mantovani, and Federica Marchesi

Metabolomics performed on pancreatic juice from pancreatic ductal adenocarcinoma patients identifies metabolic variables correlating with outcome and immune infiltration of tumors. Obtaining a metabolic profile could aid in the stratification of patients for more tailored immunotherapies.

Inhibition of SHP-1 Expands the Repertoire of Antitumor T Cells Available to Respond to Immune Checkpoint Blockade

Jeremy P. Snook, Ashleigh J. Soedel, H. Atakan Ekiz, Ryan M. O'Connell, and Matthew A. Williams

Checkpoint blockade enhances high-affinity T-cell responses to melanoma, but some patients do not benefit. Targeting SHP-1 expands the repertoire of T cells available to respond to treatment and induces antitumor activity from low-affinity T cells.

Improved Antitumor Efficacy of Chimeric Antigen Receptor T Cells that Secrete Single-Domain Antibody Fragments

Yushu Joy Xie, Michael Dougan, Jessica R. Ingram, Novalia Pishesha, Tao Fang, Noor Momin, and Hilde L. Ploegh

CAR T cells that target the tumor microenvironment are designed to secrete immune-modulating single-domain antibodies that can engage the innate immune system, cause epiteptide spreading, and evade checkpoint immunosuppression by the tumor.

γδ T-cell Receptors Derived from Breast Cancer-Infiltrating T Lymphocytes Mediate Antitumor Reactivity


Proinflammatory γδ T cells infiltrate triple-negative breast cancers and are positioned in close proximity to tumor cells. T cells engineered to express paired TCR/γδTCR chains are tumor reactive against an array of tumor types.

Proteogenomics Uncovers a Vast Repertoire of Shared Tumor-Specific Antigens in Ovarian Cancer

Qingchuan Zhao, Jean-Philippe Laverdure, Joel Lanoix, Chantal Durette, Caroline Côté, Eric Bonneil, Céline M. Laumont, Patrick Gendron, Krystel Vincent, Mathieu Courcelles, Sébastien Lemieux, Douglas G. Millar, Pamela S. Ohashi, Pierre Thibault, and Claude Perreault

By exploring all open reading frames of all genomic regions, 103 ovarian cancer-specific antigens are identified. Most would not be detected by traditional methods, highlighting a pipeline that can be used to identify novel target antigens.
ABOUT THE COVER

Cancer-associated fibroblasts (CAFs) are a major component of the tumor stroma and can promote tumorigenesis and treatment resistance. However, the mechanisms behind how CAFs do this are not fully understood in lung squamous cell carcinoma (LSCC). By evaluating primary human LSCCs, Xiang et al. demonstrate interactions between CAFs and myeloid cells in the tumor microenvironment (TME). Lung CAFs produce CCL2, which recruits CCR2⁺ myeloid cells to the TME and promotes their polarization into a myeloid-derived suppressor cell (MDSC) phenotype. This results in suppression of CD8⁺ T-cell responses. Reduction of reactive oxygen species in CAF-induced MDSCs reverses the suppression of CD8⁺ T-cell proliferation and function, highlighting possible druggable targets to boost antitumor responses in LSCC. Read more in this issue on page 436. Original image from Fig. 1D. Artwork by Lewis Long.