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CANCER IMMUNOLOGY AT THE CROSSROADS
422 Immune Escape during Breast Tumor Progression
Carlos R. Gil Del Alcazar, Maša Alecković, and Kornelia Polyak

PRIORITY BRIEF
428 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
436 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. Ciocirba
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, Quying 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, Yujie Yuan, Qiong He, Jianwen 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, Zuifu 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.
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493 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, Paolo Cappello, Francesca Gavazzi, Cristina Ridolfi, Gennaro Nappo, Greta Donisi, Marco Erreni, Roberta Avigni, 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.

506 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.

518 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 Hidde 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 epitope spreading, and evade checkpoint immunosuppression by the tumor.

530 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 TCRγ/δT chains are tumor reactive against an array of tumor types.

544 Proteogenomics Uncovers a Vast Repertoire of Shared Tumor-Specific Antigens in Ovarian Cancer
Qingchuan Zhao, Jean-Philippe Laverdure, Joel Lanoix, Chantal Durette, Caroline Côté, Éric 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.

556 Immunosuppressive Mediators Impair Proinflammatory Innate Lymphoid Cell Function in Human Malignant Melanoma
Giuseppe Ercolano, Andrea García-Garijo, Bérengère Salomé, Alejandra Gomez-Cadena, Giulia Vanoni, Beatris Mastelic-Gavillet, Angela Ianaro, Daniel E. Speiser, Pedro Romero, Sara Trabanelli, and Camilla Jandus

Innate lymphoid cells (ILCs) reside in epithelial tissues where melanomas arise. ILC1s are enriched in melanoma-bearing patients and animals but display impaired cytokine production partially due to adenosine and kynurenine produced by the tumor microenvironment.

565 LncRNA AK036396 Inhibits Maturation and Accelerates Immunosuppression of Polymorphonuclear Myeloid-Derived Suppressor Cells by Enhancing the Stability of Ficolin B
Xinyu Tian, Yu Zheng, Kai Yin, Jie Ma, Jie Tian, Yue Zhang, Lingxiang Mao, Huaxi Xu, and Shengjun Wang

Knockdown of a lncRNA or its target, ficolin B, inhibits the immunosuppressive capacity of PMN-MDSCs and delays tumor progression in mice. H-ficolin, the human ortholog of ficolin B, is elevated in patients with lung cancer, suggesting clinical relevance.

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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.