

CANCER IMMUNOLOGY RESEARCH

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Weixi Zhao and Qi Xie
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REVIEW

- 1373 Fueling T-cell Antitumor Immunity: Amino Acid Metabolism Revisited
Chenfeng Han, Minmin Ge, Ping-Chih Ho, and Lianjun Zhang

RESEARCH ARTICLES

- 1383 Glioblastoma Cell-Derived lncRNA-Containing Exosomes Induce Microglia to Produce Complement C5, Promoting Chemotherapy Resistance
Ziwei Li, Xiangqi Meng, Pengfei Wu, Caijun Zha, Bo Han, Lulu Li, Nan Sun, Tengfei Qi, Jie Qin, Yangong Zhang, Kaifu Tian, Shupeng Li, Changxiao Yang, Lejia Ren, Jianguang Ming, Pandeng Wang, Yifei Song, Chuanlu Jiang, and Jinquan Cai
The authors find glioblastoma cells transfer the long noncoding RNA lnc-TALC to microglia via exosomes. lnc-TALC activates an ENO1/p38 MAPK pathway that results in C5 production, which promotes chemotherapy resistance. The data identify novel therapeutic strategies for glioblastoma.
See related Spotlight, p. 1372

- 1400 Effective Treatment of Established Bone Metastases Can Be Achieved by Combinatorial Osteoclast Blockade and Depletion of Granulocytic Subsets
Aude-Hélène Capietto, Seunghyun Lee, David Clever, Emily Eul, Haley Ellis, Cynthia X. Ma, and Roberta Faccio
Established tumors in bone can be refractory to osteoclast blockade and are protected from chemotherapeutic agents. The data highlight that bone metastases can be effectively treated by combining osteoclast blockade and anti-Gr1 to deplete Gr1⁺ cell subsets.

- 1413 The SETDB1-TRIM28 Complex Suppresses Antitumor Immunity
Jianhuang Lin, Daqiang Guo, Heng Liu, Wei Zhou, Chen Wang, Iris Müller, Andrew V. Kossenkov, Ronny Drapkin, Benjamin G. Bitler, Kristian Helin, and Rugang Zhang
Using a CRISPR-Cas9 screen, the authors identify the SETDB1-TRIM28 complex as a promising epigenetic target to simultaneously activate cGAS-STING signaling and upregulate PD-L1 expression to enhance the antitumor effects of anti-PD-L1 immune checkpoint blockade.

- 1425 CAR T-cell Entry into Tumor Islets Is a Two-Step Process Dependent on IFN γ and ICAM-1
Chahrazade Kantari-Mimoun, Sarah Barrin, Lene Vimeux, Sandrine Haghiri, Claire Gervais, Sandy Joaquina, Joerg Mittelstaet, Nadine Mockel-Tenbrinck, Ali Kinkhabwala, Diane Damotte, Audrey Lupo, Mathilde Sibony, Marco Alifano, Elisabetta Dondi, Nadège Bercovici, Alain Trautmann, Andrew D. Kaiser, and Emmanuel Donnadieu
An IFN γ - and ICAM-1-dependent mechanism is used by CAR T cells to infiltrate tumors. The data provide a deeper understanding of CAR T-cell biology that can be used to improve treatment efficacy.

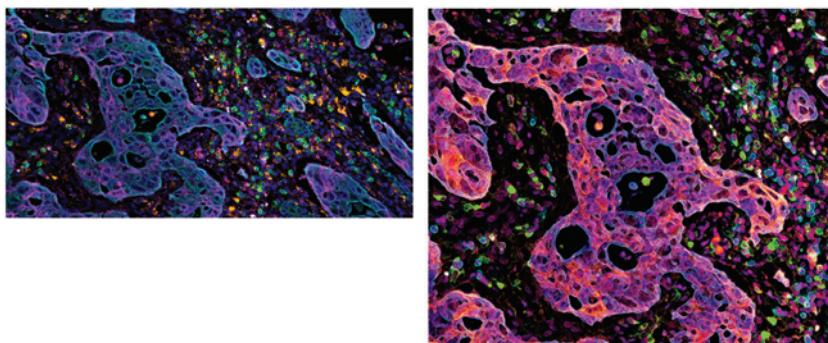
- 1439 PD-1/PD-L1-Associated Immunoarchitectural Patterns Stratify Pancreatic Cancer Patients into Prognostic/Predictive Subgroups
Eva Karamitopoulou, Andreas Andreou, Aurélie Pahud de Mortanges, Marianne Tinguey, Beat Gloor, and Aurel Perren
Four PD-1/PD-L1 expression patterns are identified in samples from patients with MSS pancreatic cancer. Each pattern correlates with distinct immune composition and other tumor microenvironment features, as well as with patient outcomes, highlighting the heterogeneity of immunologic responses.

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<p>1451 Conditional PD-1/PD-L1 Probody Therapeutics Induce Comparable Antitumor Immunity but Reduced Systemic Toxicity Compared with Traditional Anti-PD-1/PD-L1 Agents</p> <p>Hikmat H. Assi, Chihunt Wong, Kimberly A. Tipton, Li Mei, Ken Wong, Jennifer Razo, Chanty Chan, Bruce Howng, Jason Sagert, Michael Krimm, Linnea Diep, Andrew Jang, Margaret T. Nguyen, Nicole Lapuyade, Victoria Singson, Ruth Villanueva, Madan Paidhungat, Shouchun Liu, Vangipuram Rangan, Olga Vasiljeva, James W. West, Jennifer H. Richardson, Bryan Irving, Dylan Daniel, Marcia Belvin, and W. Michael Kavanaugh</p> <p>Checkpoint inhibitor immunotherapy can be associated with severe immune-related adverse events that can limit therapeutic efficacy. The authors show that Probody therapeutics effectively localize checkpoint inhibition to sites of tumor growth, thereby reducing toxicities and maintaining therapeutic efficacy.</p>	<p>1476 CD137 Costimulation Counteracts TGFβ Inhibition of NK-cell Antitumor Function</p> <p>Mariona Cabo, Sara Santana-Hernández, Marcel Costa-García, Anna Rea, Roberto Lozano-Rodríguez, Michelle Ataya, Francesc Balaguer, Manel Juan, María C. Ochoa, Silvia Menéndez, Laura Comerma, Ana Rovira, Pedro Berraondo, Joan Albanell, Ignacio Melero, Miguel López-Botet, and Aura Muntasell</p> <p>TGFβ directly inhibits cytotoxic T and NK lymphocytes in the tumor microenvironment. In this study, CD137 is identified as an actionable target for enhancing NK-cell persistence and function by counteracting TGFβ suppression.</p>
<p>1465 Monitoring PD-1 Phosphorylation to Evaluate PD-1 Signaling during Antitumor Immune Responses</p> <p>Xia Bu, Vikram R. Juneja, Carol G. Reynolds, Kathleen M. Mahoney, Melissa T. Bu, Kathleen A. McGuire, Seth Maleri, Ping Hua, Baogong Zhu, Sarah R. Klein, Edward A. Greenfield, Philippe Armand, Jerome Ritz, Arlene H. Sharpe, and Gordon J. Freeman</p> <p>Reagents for specifically detecting PD-1 signaling are lacking. Here, an antibody for phosphorylated (phospho)-PD-1 was developed and can effectively detect T-cell PD-1 signaling after binding PD-L1. Data highlight the potential use of phospho-PD-1 to track PD-1-based immunotherapy responses.</p>	<p>1491 $\gamma\delta$ T Cells Support Antigen-Specific $\alpha\beta$ T cell-Mediated Antitumor Responses during BCG Treatment for Bladder Cancer</p> <p>Niannian Ji, Neelam Mukherjee, Zhen-Ju Shu, Ryan M. Reyes, Joshua J. Meeks, David J. McConkey, Jonathan A. Gelfond, Tyler J. Curiel, and Robert S. Svatek</p> <p>$\gamma\delta$ T cells are shown to be required for boosting antitumor responses of conventional antigen-specific T cells during BCG treatment of bladder cancer. Rapamycin enhances BCG efficacy, supporting the use of the combination for treating bladder cancer.</p>

ABOUT THE COVER

Pancreatic ductal adenocarcinoma (PDAC) is considered immunologically “cold,” and treatment with immune checkpoint blockade targeting PD-1/PD-L1 is only effective in a subset of patients. Karamitopoulou et al. use an automated system, in addition to next-generation sequencing, to analyze the tumor microenvironment (TME) from patients with microsatellite-stable (MSS) and -instable (MSI) PDAC. Distinct patterns of PD-1/PD-L1 expression that correlate with different patient outcomes and characteristics of the TME, including immune composition and cell proximity, are identified. These data provide a deeper understanding of the PDAC TME and its heterogeneity and could aid in treatment decisions for patients with PDAC. Read more in this issue on page 1439. Original image from Fig. 4. Artwork by Lewis Long.



doi: 10.1158/2326-6066.CIR-9-12-CVR