

CANCER IMMUNOLOGY RESEARCH

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WHAT WE'RE READING

- 363** A Sampling of Highlights from the Literature

IN THE SPOTLIGHT

- 364** HIF1 α or HIF2 α : Enhancing CD8⁺ T-cell Fitness for Antitumor Immunity

Jin Chen

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CANCER IMMUNOLOGY AT THE CROSSROADS

- 365** Gut Microbiota and Antitumor Immunity: Potential Mechanisms for Clinical Effect
Erez N. Baruch, Jingjing Wang, and Jennifer A. Wargo

RESEARCH ARTICLES

- 371** DGKA Mediates Resistance to PD-1 Blockade
Lingyi Fu, Sen Li, WeiWei Xiao, Kuai Yu, Shuo Li, Sujing Yuan, Jianfei Shen, Xingjun Dong, Ziqian Fang, Jianeng Zhang, Siyu Chen, Wende Li, Hua You, Xiaojun Xia, Tiebang Kang, Jing Tan, Gong Chen, An-Kui Yang, YuanHong Gao, and Penghui Zhou
DGKA-mediated re-exhaustion of invigorated tumor-specific T cells is an important mechanism of resistance to PD-1 blockade. Inhibition of DGKA displays dual effects on T-cell invigoration and tumor cell growth and enhances the efficacy of anti-PD-1 therapy.
- 386** Antitumor T-cell Immunity Contributes to Pancreatic Cancer Immune Resistance
Reham Ajina, Zoe X. Malchiodi, Allison A. Fitzgerald, Annie Zuo, Shangzi Wang, Maha Moussa, Connor J. Cooper, Yue Shen, Quentin R. Johnson, Jerry M. Parks, Jeremy C. Smith, Marta Catalfamo, Elana J. Fertig, Sandra A. Jablonski, and Louis M. Weiner
T-cell antitumor responses can drive immune evasion and suppression in the pancreatic cancer tumor microenvironment. Targeting JAK/STAT signaling using ruxolitinib can overcome these immunosuppressive mechanisms, as well as improve anti-PD-1 efficacy.

- 401** Modified Hypoxia-Inducible Factor Expression in CD8⁺ T Cells Increases Antitumor Efficacy



Pedro Veliça, Pedro P. Cunha, Nikola Vojnovic, Iosifina Petrina Foskolou, David Bargiela, Milos Gojkovic, Helene Rundqvist, and Randall S. Johnson

In this study, ectopic expression of FIH-insensitive HIF2 α enhances human CD8⁺ T-cell cytolytic function *in vitro* and in a xenograft model. Modifying HIF expression may provide a way to enhance the antitumor efficacy of adoptive T-cell therapy.

See related Spotlight, p. 364

- 415** Arginase Therapy Combines Effectively with Immune Checkpoint Blockade or Agonist Anti-OX40 Immunotherapy to Control Tumor Growth

Mark D. Badaeux, Annah S. Rolig, Giulia Agnello, Danlee Enzler, Melissa J. Kasiewicz, Leslie Priddy, Jason F. Wiggins, Alexander Muir, Mark R. Sullivan, Jessica Van Cleef, Christopher Daige, Matthew G. Vander Heiden, Venkatesh Rajamanickam, James E. Wooldridge, William L. Redmond, and Scott W. Rowlinson

Arginine deprivation is commonly thought to be immunosuppressive. However, this study demonstrates that this is not always the case. Here, arginine deprivation in combination with different immunotherapies can enhance antitumor responses elicited by these immunotherapies.

- 430** Enhancing the Generation of Eomes^{hi} CD8⁺ T Cells Augments the Efficacy of OX40- and CTLA-4-Targeted Immunotherapy

Dana A. Emerson, Annah S. Rolig, and William L. Redmond

Combined anti-OX40/anti-CTLA-4 therapy boosts Eomes^{hi} CD8⁺ T-cell numbers and tumor regression. ITK blockade synergizes with anti-OX40/anti-CTLA-4 to augment the generation of Eomes^{hi} CD8⁺ T cells and enhance antitumor efficacy, suggesting this approach could improve cancer immunotherapy.

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441 Modifications to the Framework Regions Eliminate Chimeric Antigen Receptor Tonic Signaling

Elisa Landoni, Giovanni Fucá, Jian Wang, Venkat R. Chirasani, Zhiyuan Yao, Elena Dukhovlinova, Soldano Ferrone, Barbara Savoldo, Lee K. Hong, Peishun Shou, Silvia Musio, Francesco Padelli, Gaetano Finocchiaro, Miriam Droste, Brian Kuhlman, Abdijapar Shamshiev, Serena Pellegatta, Nikolay V. Dokholyan, and Gianpietro Dotti
Structural analysis demonstrates that the instability of the scFv causes CAR self-aggregation and tonic signaling. Amino acid substitutions or humanization of the framework regions abrogates the tonic signaling and enhances the functionality of CAR-T cells.

454 Targeting PIM1-Mediated Metabolism in Myeloid Suppressor Cells to Treat Cancer

Gang Xin, Yao Chen, Paytsar Topchyan, Moujtaba Y. Kasmani, Robert Burns, Peter J. Volberding, Xiaopeng Wu, Alexandra Cohn, Yiliang Chen, Chien-Wei Lin, Ping-Chih Ho, Roy Silverstein, Michael B. Dwinell, and Weiguo Cui
Myeloid-derived suppressor cells (MDSC) are a barrier to successful anti-PD-L1 therapy. The authors show that PIM1 facilitates CD36-mediated fatty acid uptake via the PPAR γ pathway, promoting MDSC immunosuppressive activity, and that PIM1 inhibition overcomes resistance to anti-PD-L1 therapy.

470 Immunosuppressive Myeloid Cells Induce Nitric Oxide-Dependent DNA Damage and p53 Pathway Activation in CD8⁺ T Cells

Adam N.R. Cartwright, Shengbao Suo, Soumya Badrinath, Sushil Kumar, Johannes Melms, Adrienne Luoma, Archis Bagati, Assieh Saadatpour, Benjamin Izar, Guo-Cheng Yuan, and Kai W. Wucherpfennig
Myeloid-derived suppressor cells (MDSC) inhibit T cell-mediated tumor immunity. The data show that MDSCs do not block early steps of T-cell activation but rather induce nitric oxide-dependent DNA damage and subsequent p53 pathway activation in T cells.

CORRECTION

486 Correction: CD28 Costimulatory Domain-Targeted Mutations Enhance Chimeric Antigen Receptor T-cell Function

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ABOUT THE COVER

Immune checkpoint blockade is efficacious in some cancers, but resistance to therapy can occur, and the mechanisms behind this are still not fully understood. Fu et al. find that T-cell exhaustion contributes to therapy resistance. By evaluating T cell-intrinsic diacylglycerol kinase alpha (Dgka), it is revealed that Dgka plays a major role in regulating T-cell exhaustion in the tumor microenvironment of solid tumors by modulating T-cell intracellular signaling. Dgka also mediates tumor cell signaling and growth, highlighting a dual tumor-immune role. Inhibition of Dgka prolongs T-cell antitumor responses and, thus, increases efficacy of anti-PD-1 therapy against solid tumors. The study reveals that inhibition of Dgka has dual effects on T-cell invigoration and tumor cell growth and that when it is combined with immune checkpoint blockade, antitumor responses are enhanced. Read more in this issue on page 371. Original image from Fig. 7A. Artwork by Lewis Long.

