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## WHAT WE’RE READING

1. A Sampling of Highlights from the Literature

## CANCER IMMUNOLOGY AT THE CROSSROADS

2. Lighting a Fire: Can We Harness Pyroptosis to Ignite Antitumor Immunity?  
   Zhibin Zhang, Ying Zhang, and Judy Lieberman

## RESEARCH ARTICLES

8. The Prognostic Role of Macrophage Polarization in the Colorectal Cancer Microenvironment  
   Juha P. Väyrynen, Koichiro Haruki, Mai Chan Lau, Sara A. Väyrynen, Rong Zhong, Andressa Dias Costa, Jennifer Borowsky, Melissa Zhao, Kenji Fujiyoshi, Kota Arima, Tyler S. Twombly, Junako Kishikawa, Simeng Gu, Saina Aminmozaffari, Shanshan Shi, Yoshifumi Baba, Naohiko Akimoto, Tomotaka Ugai, Annacarolina Da Silva, Jennifer L. Guerriero, Miaowei Song, Kana Wu, Andrew T. Chan, Reiko Nishihara, Charles S. Puchs, Jeffrey A. Meyerhardt, Andrew T. Chan, Reiko Nishihara, Charles S. Puchs, Jeffrey A. Meyerhardt, Marios Giannakis, Shuji Ogino, and Jonathan A. Nowak

   Macrophage polarization state, rather than overall density, in the colorectal cancer microenvironment is associated with cancer-specific survival independent of potential confounding factors, with M1-like and M2-like macrophage phenotypes exhibiting distinct prognostic roles.

20. Retinoic Acid Synthesis Deficiency Fosters the Generation of Polymorphonuclear Myeloid-Derived Suppressor Cells in Colorectal Cancer  
   Hong-Wei Sun, Jing Chen, Wen-Chao Wu, Yan-Yan Yang, Yi-Tuo Xu, Xing-Juan Yu, Hai-Tian Chen, Zilian Wang, Xiao-Jun Wu, and Limin Zheng

   A defect in ADH1-mediated retinoic acid synthesis contributes to the accumulation of polymorphonuclear (PMN)-MDSCs in colorectal cancer. The data highlight how restoring retinoic acid signaling could abrogate the generation of PMN-MDSCs and improve antitumor responses.

34. A CRISPR Screen Reveals Resistance Mechanisms to CD3-Bispecific Antibody Therapy  
   Si-Qi Liu, Alyssa Grantham, Casey Landry, Brian Granda, Rajiv Chopra, Srinivas Chakravarty, Sabine Deutsch, Markus Vogel, Katie Russo, Katherine Seiss, William R. Tschantz, Tomas Rejtar, David A. Ruddy, Tianceng Hu, Kimberly Aardalen, Joel P. Wagner, Glenn Dranoff, and Joseph A. D’Alessio

   A genome-wide CRISPR screen was developed to understand cancer cell–derived resistance mechanisms to CD3-bispecific antibodies. The screen identifies IFNγ signaling being pivotal for responsiveness to CD3 bispecifics, and deficiency in core fucosylation as causing resistance to the therapeutic flotetuzumab.

50. A Bispecific Antibody Antagonizes Prosurvival CD40 Signaling and Promotes Vg9Vd2 T cell–Mediated Antitumor Responses in Human B-cell Malignancies  
   Iris de Weerdt, Roeland Lameris, George L. Scheffer, Jana Vree, Renate de Boer, Anita G. Stam, Rieneke van der Ven, Mark-David Levin, Steven T. Pals, Rob C. Roovers, Paul W.H.I. Parren, Tanja D. de Grujilj, Arnon P. Kater, and Hans J. van der Vliet

   The generation of a CD40-specific Vg9Vd2 T-cell engager, which abrogates prosurvival CD40 signaling, is described. This bispecific antibody unleashes Vg9Vd2 T cell–mediated responses against both leukemia and multiple myeloma in vitro and in vivo.

62. CD28 Costimulatory Domain–Targeted Mutations Enhance Chimeric Antigen Receptor T-cell Function  
   Justin C. Boucher, Gongbi Li, Hiroshi Kotani, Maria L. Cabral, Dylan Morrissey, Sue Bom Lee, Kristen Spitler, Nolan J. Beatty, Estelle V. Cervantes, Bishwas Shrestha, Bin Yu, Asamuzzaman Kazi, Xuefeng Wang, Said M. Sebti, and Marco L. Davila

   CD28 mutations enhance CAR T-cell function by reducing expression of exhaustion-related genes. These data highlight considerations for CAR design that could improve antitumor responses.
The Cerebroventricular Environment Modifies CAR T Cells for Potent Activity against Both Central Nervous System and Systemic Lymphoma


In the clinic, CD19-CAR T cells are administered IV and are not used specifically to treat CNS lymphoma. The authors show a single ICV infusion of CD19-CAR T cells completely eradicates both CNS and systemic lymphoma in mice.

Activin A Promotes Regulatory T-cell–Mediated Immunosuppression in Irradiated Breast Cancer

Mara De Martino, Camille Daviaud, Julie M. Diamond, Jeffrey Kraynak, Amandine Alard, Silvia C. Formenti, Lance D. Miller, Sandra Demaria, and Claire Vanpouille-Box


Improved T-cell Receptor Diversity Estimates Associate with Survival and Response to Anti-PD-1 Therapy

Dante S. Bortone, Mark G. Woodcock, Joel S. Parker, and Benjamin G. Vincent

Inaccurate TCR diversity estimates from RNA sequencing data have made the relationship between diversity and immunotherapy responses unclear. Improved estimation of diversity uncovers the association between diversity and responses of melanoma patients treated with PD-1 inhibition.

Sialylation of CD55 by ST3GAL1 Facilitates Immune Evasion in Cancer

Wen-Der Lin, Tan-Chi Fan, Jung-Tung Hung, Hui-Ling Yeo, Sheng-Hung Wang, Chu-Wei Kuo, Kay-Hooi Khoo, Li-Mei Pai, John Yu, and Alice L. Yu

Silencing of the ST3GAL1 glycosyltransferase in breast cancer cells reduces O-sialylation of CD55, enhancing C3 deposition and susceptibility to complement- and antibody-dependent cytotoxicity. These findings suggest ST3GAL1 inhibition could be a strategy to block breast cancer immune evasion.

Acknowledgment to Reviewers

ABOUT THE COVER

The prognostic value of tumor-associated macrophages (TAM) remains to be fully elucidated. By combining multiplex immunofluorescence with digital analysis and machine learning, Väärynen et al. show that TAM subsets have distinct prognostic roles in patients with colorectal cancer. Total intraepithelial and stromal TAM densities are not prognostic. Rather, TAM polarization is key, with M2-like TAMs correlating with worse cancer-specific survival. Interestingly, a survival benefit is not seen when assessing M1-like TAMs in the tumor stromal region, although high M1:M2 density ratio is associated with better survival. The study highlights the importance of utilizing multiplex analysis to more accurately determine the prognostic value of immune-cell subsets, as total population assessment or single-marker analysis may mask underlying associations. Read more in this issue on page 8. Original image from Supplementary Fig. S3B. Artwork by Lewis Long.