March 1, 2024 | Volume 12 | Number 3

CANCER IMMUNOLOGY RESEARCH
TABLE OF CONTENTS

WHAT WE'RE READING

281 **A Sampling of Highlights from the Literature**

CANCER HALLMARKS PERSPECTIVE

282 **A Metabolic Axis of Immune Intractability**
Dominique C. Hinshaw, Meet Patel, and Lalita A. Shevde

PRIORITY BRIEF

287 **Intragenic Rearrangement Burden Associates with Immune Cell Infiltration and Response to Immune Checkpoint Blockade in Cancer**
Han Zhang, Sanghoon Lee, Renee R. Muthakana, Binfeng Lu, David N. Boone, Daniel Lee, and Xiao-Song Wang

IGRs are an ill-studied class of cryptic genomic rearrangements. The authors suggest that IGR burden is a pivotal contributor to immune infiltration and a new genetic biomarker for immunotherapy response in TMB-low, IGR-dominant tumors, and in platinum-exposed tumors.

RESEARCH ARTICLES

296 **T-cell States, Repertoire, and Function in Classical Hodgkin Lymphoma Revealed through Single-Cell Analyses**
Xiufen Chen, Jovian Yu, Girish Venkataraman, Sonali M. Smith, Mengjie Chen, Alan Cooper, Sravya Tumuluru, Joshua D. Brody, James Godfrey, and Justin Kline

The authors report single-cell phenotyping of the cHL environment, finding clonal expansion of $CD8^+$ T cells and Treg cells. Moreover, conventional T cells retain effector function upon restimulation, arguing against an irreversibly dysfunctional T-cell state in cHL.

308 **Immune-Related Colitis Is Associated with Fecal Microbial Dysbiosis and Can Be Mitigated by Fecal Microbiota Transplantation**
Arielle Elkrief, Nicholas R. Waters, Natalie Smith, Angel Dai, John Slingerland, Nathan Aleynick, Binita Febles, Pooja Gogia, Nicholas D. Socci, Melissa Lumish, Paul A. Giardina, Jamie E. Chaft, Juliana Eng, Robert J. Motzer, Robin B. Mendelsohn, Kate A. Markey, Mingqiang Zhuang, Yanyun Li, Zhifan Yang, Travis J. Hollmann, Charles M. Rudin, Marcel R.M. van den Brink, Jinru Shia, Susan DeWolf, Adam J. Schoenfeld, Matthew D. Hellmann, N. Esther Babady, David M. Faleck, and Jonathan U. Peled

By combining an observational analysis of biospecimens and a case series of fecal transplantation, the authors provide evidence for the hypothesis that the intestinal microbiome contributes to the pathophysiology of irColitis and can be remitted with FMT.

322 **FcγRIIB Is an Immune Checkpoint Limiting the Activity of Treg-Targeting Antibodies in the Tumor Microenvironment**
David A. Knorr, Lucas Blanchard, Rom S. Leidner, Shawn M. Jensen, Ryan Meng, Andrew Jones, Carmen Ballesteros-Merino, Richard B. Bell, Maria Baez, Alessandra Marino, David Sprott, Carlo B. Bifulco, Brian Piening, Rony Dahan, Juan C. Osorio, Bernard A. Fox, and Jeffrey V. Ravetch

Antibodies designed to deplete tumor-infiltrating Tregs have shown limited efficacy in patients so far. The authors identify FcγRIIB as an immune checkpoint limiting the activity of Treg-targeting antibodies in the TME and Fc-engineering strategies to overcome this limitation.

334 **Neutralizing Antibodies Impair the Oncolytic Efficacy of Reovirus but Permit Effective Combination with T cell–Based Immunotherapies**
Christianne Groeneveldt, Priscilla Kinderman, Lisa Griffioen, Olivia Rensing, Camilla Labrie, Diana J.M. van den Wollenberg, Rob C. Hoeben, Matt Coffey, Houra Loghmani, Els M.E. Verdegaal, Marij J.P. Welters, Sjoerd H. van der Burg, Thorbald van Hall, and Nadine van Montfoort

The authors show that Reo-specific NAbs hamper the oncolytic function of Reo but not its T cell–attracting capacity. Since preexisting NAbs are prevalent, this suggests Reo should be used with T cell–based immunotherapies for optimal efficacy.

TABLE OF CONTENTS

350 **LILRB3 Supports Immunosuppressive Activity of Myeloid Cells and Tumor Development**
Ryan Huang, Xiaoye Liu, Jaehyup Kim, Hui Deng, Mi Deng, Xun Gui, Heyu Chen, Guojin Wu, Wei Xiong, Jingjing Xie, Cheryl Lewis, Jade Homsi, Xing Yang, Chengcheng Zhang, Yubo He, Qi Lou, Caroline Smith, Samuel John, Ningyan Zhang, Zhiqiang An, and Cheng Cheng Zhang

LILRB3 is an inhibitory receptor expressed by myeloid cells. The authors show galectin-4 and galectin-7 bind LILRB3, promoting the immunosuppressive function of myeloid cells. Blocking LILRB3 reduces immunosuppression and promotes antitumor immunity, suggesting a potential new immunotherapeutic approach.

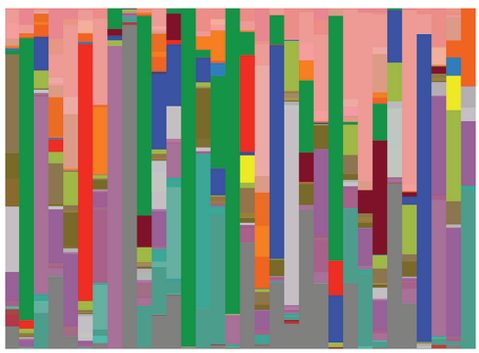
363 **An NFAT1-C3a-C3aR Positive Feedback Loop in Tumor-Associated Macrophages Promotes a Glioma Stem Cell Malignant Phenotype**
Yaochuan Zhang, Yifu Song, Xiaoliang Wang, Mengwu Shi, Yibin Lin, Dongxia Tao, and Sheng Han

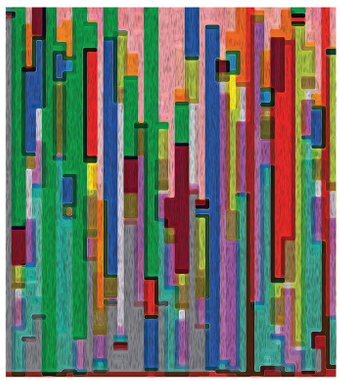
An NFAT1–complement system feedback loop is identified and shown to induce M2-like polarization of tumor-associated macrophages. Data highlight how these macrophages promote the malignant phenotype of glioma and provide insights into potential complement-associated targets to improve antitumor immunity.

ABOUT THE COVER

Treatment with immune checkpoint inhibitors can yield durable responses for patients with various types of cancer, but many patients experience immune-related colitis (irColitis) as a result of the treatment. Through fecal microbiota profiling of 18 patients with irColitis, Elkrief et al. show that fecal microbial dysbiosis, in particular an enrichment in Proteobacteria at the time of active symptoms, is associated with irColitis. Healthy-donor fecal microbiota transplantation led to clinical improvement in irColitis symptoms in four of five patients. The data indicate a role for fecal microbiota in the pathophysiology of irColitis and suggest that preventing or restoring fecal microbial dysbiosis could provide a way to mitigate this immune-related adverse event.

Read more in this issue on page 308. Original image from Fig. 2A. Artwork by Lewis Long.





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