

CANCER IMMUNOLOGY RESEARCH

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Natalia Jaeger and Marco Colonna
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- 601 **Repertoire Remodeling through CD4⁺ T-cell Depletion**
Winnie Yao and Ansuman T. Satpathy
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PRIORITY BRIEF

- 602 **Robust Antitumor Immunity in a Patient with Metastatic Colorectal Cancer Treated with Cytotoxic Regimens**
Venkatesh Rajamanickam, Carmen Ballesteros-Merino, Kimberly Samson, David Ross, Brady Bernard, Bernard A. Fox, Eric Tran, Pippa Newell, and Thomas Duhon
Metastatic colorectal cancers usually have low immune infiltration and poor prognosis. This report of a patient with a strong tumor antigen-specific CD8⁺ T-cell response following cytotoxic regimens suggests these treatments have potential to prime the immune system.

RESEARCH ARTICLES

- 612 **$\gamma\delta$ T Cells in Merkel Cell Carcinomas Have a Proinflammatory Profile Prognostic of Patient Survival**
Nicholas A. Gherardin, Kelly Waldeck, Alex Caneborg, Luciano G. Martelotto, Shiva Balachander, Magnus Zethoven, Pasquale M. Petrone, Andrew Pattison, James S. Wilmott, Sergio M. Quiñones-Parra, Fernando Rossello, Atara Posner, Annie Wong, Alison M. Weppler, Kerwin F. Shannon, Angela Hong, Peter M. Ferguson, Valerie Jakrot, Jeanette Raleigh, Athena Hatzimihalis, Paul J. Neeson, Paolo Deleso, Meredith Johnston, Margaret Chua, Juergen C. Becker, Shahneen Sandhu, Grant A. McArthur, Anthony J. Gill, Richard A. Scolyer, Rodney J. Hicks, Dale I. Godfrey, and Richard W. Tothill
The data show many Merkel cell carcinomas have prominent $\gamma\delta$ T-cell infiltrates. These unconventional T cells recognize MHC-like ligands and have a proinflammatory gene-expression profile that is associated with improved patient survival, suggesting potential prognostic and therapeutic utility.
See related Spotlight, p. 600

- 624 **Transient Depletion of CD4⁺ Cells Induces Remodeling of the TCR Repertoire in Gastrointestinal Cancer**
Hiroyasu Aoki, Satoshi Ueha, Shigeyuki Shichino, Haru Ogiwara, Kohei Shitara, Manami Shimomura, Toshihiro Suzuki, Tetsuya Nakatsura, Makiko Yamashita, Shigehisa Kitano, Sakiko Kuroda, Masashi Wakabayashi, Makoto Kurachi, Satoru Ito, Toshihiko Doi, and Kouji Matsushima
Analysis of the blood-tumor overlapping TCR repertoire reveals that transient depletion of CD4⁺ cells causes beneficial remodeling of the TCR repertoire and contributes to the expansion of CD8⁺ tumor-reactive clones in patients with cancer.
See related Spotlight, p. 601

- 637 **Alternative Splicing of the Inhibitory Immune Checkpoint Receptor SLAMF6 Generates a Dominant Positive Form, Boosting T-cell Effector Functions**
Emma Hajaj, Elad Zisman, Shay Tzaban, Sharon Merims, Jonathan Cohen, Shiri Klein, Shoshana Frankenburg, Moshe Sade-Feldman, Yuval Tabach, Keren Yizhak, Ami Navon, Polina Stepensky, Nir Hacohen, Tamar Peretz, André Veillette, Rotem Karni, Galit Eisenberg, and Michal Lotem
Alternative splicing of SLAMF6 generates two isoforms with opposing effects on T-cell activation; immune checkpoint blockade enriches for the shorter agonistic isoform in T cells, and switching SLAMF6 splicing using antisense oligonucleotides leads to improved antitumor T-cell responses.


- 651 **Chronic Adrenergic Stress Contributes to Metabolic Dysfunction and an Exhausted Phenotype in T Cells in the Tumor Microenvironment**
 Guanxi Qiao, Minhui Chen, Hemn Mohammadpour, Cameron R. MacDonald, Mark J. Bucsek, Bonnie L. Hylander, Joseph J. Barbi, and Elizabeth A. Repasky
T-cell exhaustion impacts immunotherapy efficacy. How T-cell exhaustion is regulated remains incompletely understood. Here, the sympathetic stress response is shown to regulate the development of T-cell exhaustion by modulating CD8⁺ T-cell metabolism and function in the TME.

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665 Chemotherapy Induces Tumor-Associated Macrophages that Aid Adaptive Immune Responses in Ovarian Cancer

Owen Heath, Chiara Berlato, Eleni Maniati, Anissa Lakhani, Colin Pegrum, Panoraia Kotantaki, Samar Elorbany, Steffen Böhm, Simon T. Barry, Alessandro Annibaldi, Desmond P. Barton, and Frances R. Balkwill

Neoadjuvant chemotherapy is shown to reduce the density of tumor-associated macrophages (TAM). In addition, chemotherapy reduces M2-related markers and increases proinflammatory signaling in TAMs, including inflammasome activation, thus highlighting an opportunity to improve antitumor responses.

682 Pro- and Antitumorogenic Capacity of Immunoproteasomes in Shaping the Tumor Microenvironment

Hanna Leister, Maik Luu, Daniel Staudenraus, Aleksandra Lopez Krol, Hans-Joachim Mollenkopf, Arjun Sharma, Nils Schmeer, Leon N. Schulte, Wilhelm Bertrams, Bernd Schmeck, Markus Bosmann, Ulrich Steinhoff, and Alexander Visekruna

Data demonstrate that the immunoproteasome is essential for shaping the tumor microenvironment. Opposing pro- and antitumor functions of the immunoproteasome are identified, highlighting the importance of understanding its role in different cancer types.

693 Virus-Like Particle-Drug Conjugates Induce Protective, Long-lasting Adaptive Antitumor Immunity in the Absence of Specifically Targeted Tumor Antigens

AC

Rhonda C. Kines, Cynthia D. Thompson, Sean Spring, Zhenyu Li, Elisabet de los Pinos, Stephen Monks, and John T. Schiller

AU-011 is composed of an HPV VLP conjugated to photoactivatable IRDye-700DX. Their broad, tumor-tropic nature combined with light-induced cytotoxic activity induces tumor immunogenic cell death, boosts antitumor immunity, and elicits long-term antitumor immunity.

707 Targeting Triple-Negative Breast Cancer with Combination Therapy of EGFR CAR T Cells and CDK7 Inhibition

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Lin Xia, Zaozao Zheng, Jun-yi Liu, Yu-jie Chen, Jiancheng Ding, Guo-sheng Hu, Ya-hong Hu, Suling Liu, Wen-xin Luo, Ning-shao Xia, and Wen Liu

CAR T-cell resistance can occur due to multiple factors. EGFR CAR T-cell treatment induces expression of an immune-suppressive gene set. Interruption of transcriptional activity using a "unite-and-conquer" strategy sensitizes refractory TNBC to treatment and reduced tumor growth.

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ABOUT THE COVER

The effects of neoadjuvant chemotherapy (NACT) on innate antitumor immunity are not fully understood. Heath et al. find that NACT promotes tumor-associated macrophages (TAM) to acquire an antitumor phenotype in high-grade serous ovarian cancer (HGSOC). Although TAM density is reduced with NACT, the treatment also decreases expression of M2-related markers while increasing proinflammatory pathways, including the inflammasome. These TAMs are found to be important for disease-free and overall survival in orthotopic HGSOC models. The data highlight the potential of targeting tumor-promoting TAMs whilst augmenting the activity of antitumor TAMs to boost therapeutic responses in the context of NACT. Read more in this issue on page 665. Original image from Fig. 1C. Artwork by Lewis Long.

