WHAT WE'RE READING

167 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

168 Revolutionizing Cancer Immunology: The Power of Next-Generation Sequencing Technologies
Meromit Singer and Ana C. Anderson

PRIORITY BRIEFS

174 A Synthetic DNA, Multi-Neoantigen Vaccine Drives Predominately MHC Class I CD8⁺ T-cell Responses, Impacting Tumor Challenge
Elizabeth K. Duperret, Alfredo Perales-Puchalt, Regina Stoltz, Hiranjith G.H., Nitin Mandloi, James Barlow, Amitabha Chaudhuri, Niranjan Y. Sardesai, and David B. Weiner
A multi-neoantigen DNA cancer vaccine was designed and tested against multiple tumor types. The vaccine was efficiently delivered and elicited CD8⁺ T-cell responses, highlighting how this platform could be used to target a variety of neoantigens in cancer.

183 Antagonism of IAPs Enhances CAR T-cell Efficacy
Jessica Michie, Paul A. Beavis, Andrew J. Freeman, Stephijn J. Vervoort, Kelly M. Ramsbottom, Vignesh Narasimhan, Emily J. Lelliott, Najoua Lalaoui, Robert G. Ramsay, Ricky W. Johnstone, John Silke, Phillip K. Darcy, Ilia Voskoboinik, Conor J. Kearney, and Jane Oliaro
Antagonizing “inhibitor of apoptosis proteins” (IAPs) with the clinical SMAC-mimetic, birinapant, enhances the antitumor activity of CAR T cells in a TNF-dependent, perforin-independent manner. The data illustrate the potential for this combination therapy to enhance antitumor efficacy.

RESEARCH ARTICLES

193 Intracellular Activation of Complement C3 Leads to PD-L1 Antibody Treatment Resistance by Modulating Tumor-Associated Macrophages
Haoran Zha, Xinxin Wang, Ying Zhu, Diangang Chen, Xiaohai Han, Fei Yang, Jianbao Gao, Chunyan Hu, Chi Shu, Yi Feng, Yulong Tan, Jinyu Zhang, Yongsheng Li, Yisong Y. Wan, Bo Guo, and Bo Zhu
Intracellular activation of complement C3 by tumor cells was found to suppress CD8⁺ T-cell responses by modulating tumor-associated macrophages. The data suggest that a combined strategy of PD-L1 blockade with C3 targeting may enhance antitumor immunity.

208 CD16⁺ NKG2A⁺ Natural Killer Cells Infiltrate Breast Cancer–Draining Lymph Nodes
Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, and Anne Caignard
NK cells infiltrating breast cancer–draining lymph nodes express activating NK receptors, the inhibitory NKG2A receptor, and PD-1 and are capable of degranulation and tumor cell lysis. These findings support potential therapeutic development targeting these cells.

219 An Antibody Designed to Improve Adoptive NK-Cell Therapy Inhibits Pancreatic Cancer Progression in a Murine Model
Jaemin Lee, Tae Heung Kang, Wonbeak Yoo, Hyunjik Choi, Seongyea Jo, Sungyoun Ko, Sang-Rae Lee, Sun-Ick Kim, Ji-Su Kim, Duck Cho, Janghwan Kim, Jeong-Yoon Kim, Eun-Soo Kwon, and Seokho Kim
Antagonizing “inhibitor of apoptosis proteins” (IAPs) with the clinical SMAC-mimetic, birinapant, enhances the antitumor activity of CAR T cells in a TNF-dependent, perforin-independent manner. The data illustrate the potential for this combination therapy to enhance antitumor efficacy.

230 A Mechanism of Resistance to Antibody-Targeted Immune Attack
Dalal S. Aldeghaither, David J. Zahavi, Joseph C. Murray, Elana J. Fertig, Garrett T. Graham, Yong-Wei Zhang, Allison O’Connell, Junfeng Ma, Sandra A. Jablonski, and Louis M. Weiner
Antibody targeting of the EGFR on tumor cells is a form of immunotherapy that works by inducing NK-cell killing through antibody–NK-cell interactions. Resistance develops via the downregulation of the interaction molecules; thus, NK cells are not activated.

244 Mouse PVRIG Has CD8⁺ T Cell–Specific Coinhibitory Functions and Dampens Antitumor Immunity
Expression of PVRIG, an immune checkpoint target, is upregulated on activated and tumor-infiltrating CD8⁺ T cells in mice. Disrupting the PVRIG (receptor)/PVRL2 (ligand) pathway using PVRIG-deficient mice or monoclonal antibodies inhibited tumor growth.

See related article, p. 257.
PVRIG and PVRL2 Are Induced in Cancer and Inhibit CD8+ T-cell Function
Sarah Whelan, Eran Ophir, Maya F. Kotturi, Ofer Levy, Sudipto Ganguly, Ling Leung, Ilan Vaknin, Sandeep Kumar, Liat Dassa, Kyle Hansen, David Bernados, Benjamin Murter, Abba Soni, Janis M. Taube, Amanda Nickles Fader, Tian-Li Wang, Ie-Ming Shih, Mark White, Drew M. Pardoll, and Spencer C. Liang

PVRIG acts as an immune checkpoint in human tumors that express its ligands. A PVRIG antagonistic antibody, COM701, may be useful as monotherapy or combined with other immunotherapies. COM701 is in clinical trials for patients with solid tumors.

See related article, p. 244.

Late-Stage Tumor Regression after PD-L1 Blockade Plus a Concurrent OX40 Agonist
Fanny Polesso, Andrew D. Weinberg, and Amy E. Moran

PD-L1 blockade with concurrent OX40 agonism enhanced frequency and functionality of antigen-specific CD8+ T cells in mouse models of large tumors. Th1 skewing, CD8+ T cell metabolism, and antitumor immunity were augmented, and tumor regression was promoted.

Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function
Paul E. Clavijo, Jay Friedman, Yvette Robbins, Ellen C. Moore, Ernest Smith, Maurice Zauderer, Elizabeth E. Evans, and Clint T. Allen

Neutralization of Semaphorin4D within the tumor microenvironment inhibited recruitment and function of myeloid-derived suppressor cells, sensitizing carcinomas to CTLA-4 or PD-1 blockade. Semaphorin4D mAb may be useful as an adjuvant for immune checkpoint immunotherapies.

LncRNA-MM2P Identified as a Modulator of Macrophage M2 Polarization
Ji Cao, Rong Dong, Li Jiang, Yanling Gong, Meng Yuan, Jiaqiong You, Wen Meng, Zhanlei Chen, Ning Zhang, Qixinie Weng, Hong Zhu, Qiaojun He, Meidan Ying, and Bo Yang

A long noncoding RNA (lncRNA), called lncRNA-MM2P, is specifically expressed in M2 macrophages, and its knockdown prevents polarization. This lncRNA could serve as a marker for protumoral tumor-associated macrophages and highlights the role of lncRNAs in macrophage polarization.

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ABOUT THE COVER

Complement is known to play a role in antitumor immunity. However, specific complement molecules can be enriched in the tumor microenvironment where they can regulate the function of tumor and immune cells to promote tumor progression, and thus, interfere with immune-checkpoint blockade efficacy. Zha et al. show that expression and activation of complement C3 in murine tumor cells created an immunosuppressive milieu by facilitating the accumulation and suppressive function of tumor-associated macrophages, mediated by signaling through the C3a receptor. Deletion of C3 in the tumor cells enhanced the efficacy of checkpoint blockade, illustrating the potential of targeting tumor cell-derived complement to boost responses to immune-checkpoint blockade. Read more in this issue on page 193. Original image from Fig. 1D. Artwork by Lewis Long.