

IN THE SPOTLIGHT

- 473** Tales of Antigen Evasion from CAR Therapy
Michel Sadelain
See related articles, pp. 498 and 509.

CANCER IMMUNOLOGY MINIATURES

- 474** Myelodysplastic Syndrome Revealed by Systems Immunology in a Melanoma Patient Undergoing Anti-PD-1 Therapy
Allison R. Greenplate, Douglas B. Johnson, Mikael Roussel, Michael R. Savona, Jeffrey A. Sosman, Igor Puzanov, P. Brent Ferrell Jr, and Jonathan M. Irish
It has become crucial to understand immunotherapy-induced changes to the immune system. Mass cytometry allowed the in-depth monitoring of multiple immune subsets during a patient's therapy, detecting an emerging myelodysplasia and providing insights into the therapeutic response.
- 481** Possible Interaction of Anti-PD-1 Therapy with the Effects of Radiosurgery on Brain Metastases
Ahmed K. Alomari, Justine Cohen, Alexander O. Vortmeyer, Anne Chiang, Scott Gettinger, Sarah Goldberg, Harriet M. Kluger, and Veronica L. Chiang
Patients undergoing stereotactic radiosurgery for brain metastases may show unexpected effects in the lesions after treatment with antibodies to PD-1. Assessments of clinical and radiologic changes need accurate interpretation in this growing patient population.

RESEARCH ARTICLES

- 488** Environmental and Genetic Activation of Hypothalamic BDNF Modulates T-cell Immunity to Exert an Anticancer Phenotype
Run Xiao, Stephen M. Bergin, Wei Huang, Andrew M. Slater, Xianglan Liu, Ryan T. Judd, En-Ju D. Lin, Kyle J. Widstrom, Steven D. Scoville, Jianhua Yu, Michael A. Caligiuri, and Lei Cao
Housing mice in enriched environments with multiple stimuli modulated T-cell immunity and inhibited cancer progression. Enhanced immunity was mediated by hypothalamic BDNF, supporting the concept that manipulating a single gene in the brain can improve cancer immunotherapy.

- 498** T Cells Expressing CD19/CD20 Bispecific Chimeric Antigen Receptors Prevent Antigen Escape by Malignant B Cells
Eugenia Zah, Meng-Yin Lin, Anne Silva-Benedict, Michael C. Jensen, and Yvonne Y. Chen
Bispecific chimeric antigen receptors (CARs) have been systematically optimized to simultaneously target two clinically relevant antigens, CD19 and CD20, presenting a clinically applicable solution to antigen escape and facilitating the rational design of receptors with higher-level complexities.
See related Spotlight, p. 473.
- 509** Preserved Activity of CD20-Specific Chimeric Antigen Receptor-Expressing T Cells in the Presence of Rituximab
Gregory A. Rufener, Oliver W. Press, Philip Olsen, Sang Yun Lee, Michael C. Jensen, Ajay K. Gopal, Barbara Pender, Lihua E. Budde, Jeffrey K. Rossow, Damian J. Green, David G. Maloney, Stanley R. Riddell, and Brian G. Till
Most patients with B-cell lymphoma are treated with mAbs to CD20, which might interfere with subsequent chimeric antigen receptor (CAR) T cells against CD20. However, function was preserved in vivo in the presence of clinically relevant rituximab concentrations and only modestly impaired in vitro.
See related Spotlight, p. 473.
- 520** Autophagy Inhibition Dysregulates TBK1 Signaling and Promotes Pancreatic Inflammation
Shenghong Yang, Yu Imamura, Russell W. Jenkins, Israel Cañadas, Shunsuke Kitajima, Amir Aref, Arthur Brannon, Eiji Oki, Adam Castoreno, Zehua Zhu, Tran Thai, Jacob Reibel, Zhirong Qian, Shuji Ogino, Kwok K. Wong, Hideo Baba, Alec C. Kimmelman, Marina Pasca Di Magliano, and David A. Barbie
Autophagy inhibition has been proposed for treatment of KRAS-driven cancer, but this strategy resulted in a protumorigenic feedback loop that activated TBK1 and induced PD-L1 expression. Therapeutic approaches that counteract this feedback may be necessary to limit pancreatic dysplasia.
- 531** Antibody-Mediated Phosphatidylserine Blockade Enhances the Antitumor Responses to CTLA-4 and PD-1 Antibodies in Melanoma
Bruce D. Freemark, Jian Gong, Dan Ye, Michael J. Gray, Van Nguyen, Shen Yin, Michaela M.S. Hatch, Christopher C.W. Hughes, Alan J. Schroit, Jeff T. Hutchins, Rolf A. Brekken, and Xianming Huang
Blocking phosphatidylserine (PS) with antibodies reprograms the tumor microenvironment from immunosuppressive to immunosupportive and reactivates innate and adaptive antitumor immunity. Combining PS targeting with immune checkpoint blockade improved the therapeutic efficacy of both approaches in two preclinical tumor models.

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541 Augmentation of CAR T-cell Trafficking and Antitumor Efficacy by Blocking Protein Kinase A Localization

Kheng Newick, Shaun O'Brien, Jing Sun, Veena Kapoor, Steven Maceyko, Albert Lo, Ellen Puré, Edmund Moon, and Steven M. Albelda

Insertion of the small transgene RIAD augmented the efficacy of CAR T cells in solid tumors by blocking the inhibitory activity of PKA. This reduced immunosuppression by adenosine and PGE₂, while enhancing CAR T cells trafficking into tumors.

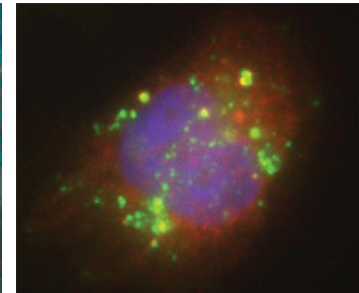
552 Altered Expression and Splicing of *ESRP1* in Malignant Melanoma Correlates with Epithelial–Mesenchymal Status and Tumor-Associated Immune Cytolytic Activity

Jun Yao, Otavia L. Caballero, Ying Huang, Calvin Lin, Donata Rimoldi, Andreas Behren, Jonathan S. Cebon, Mien-Chie Hung, John N. Weinstein, Robert L. Strausberg, and Qi Zhao

Epithelial tumors are thought to recapitulate an epithelial–mesenchymal transition during the transformation process. By assessing ESRP1 transcripts in melanomas, associations were found between more mesenchymal states, immune cytolytic activity, and checkpoint expression that may have implications for immunotherapy.

ABOUT THE COVER

When tumors contain the oncogenic form of KRAS, their progression is aided by autophagy, a process by which cellular protein and organelles are degraded by the cell and become a source of energy. Thus, inhibiting autophagy is being considered as a treatment for these tumors. However, Yang and colleagues found that blocking autophagy in the pancreas permitted the accumulation of activated TBK1, a situation that increased protumorigenic inflammation. By blocking autophagy at the level of TBK1 with the inhibitor CYT387, chemokine production and granulocyte recruitment were also inhibited and KRAS-induced dysplasia was decreased. The cover art (left) is based on a figure in the original article (right; Fig. 2C). It shows the accumulation of phosphorylated TBK1 in autophagosomes when autophagy is inhibited. Artwork by Lewis Long. Read more starting on page 520 of this issue of *Cancer Immunology Research*.



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