### Microenvironment and Immunology

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<th>Page</th>
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<td>865</td>
<td>Metastatic Cells Can Escape the Proapoptotic Effects of TNF-α through Increased Autocrine IL-6/STAT3 Signaling</td>
<td>Shun Li, Ni Wang, and Pnina Brodt</td>
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<td><strong>Précis:</strong> This study defines an IGF-I-driven mechanism of cancer cell survival that is critical for metastatic colonization of the liver, suggesting that IGF-I receptor antagonists currently in clinical trials may have particular utility in treating colon cancers and other cancers that metastasize frequently to liver.</td>
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<td><strong>Précis:</strong> The cytokine GM-CSF, which is used to enhance white cell counts in many cancer patients, also expands a population of immune-suppressive monocytic cells that can block the entry of activated antitumor T cells into the tumor microenvironment, perhaps unwittingly contributing to immune escape.</td>
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<td>887</td>
<td>CD8+ T Cells Specific for Tumor Antigens Can Be Rendered Dysfunctional by the Tumor Microenvironment through Upregulation of the Inhibitory Receptors BTLA and PD-1</td>
<td>Julien Fourcade, Zhaojun Sun, Ornella Pugliano, Philippe Guillaume, Immanuel F. Luescher, Cindy Sander, John M. Kirkwood, Daniel Olive, Vijay Kuchroo, and Hassane M. Zarour</td>
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<td><strong>Précis:</strong> This study extends knowledge concerning how an important inhibitory class of co-receptor molecules on T cells acts to block their specific cytotoxic activity against tumor cells, thereby deepening insights into how to reverse this key mechanism of immune escape in tumors for therapeutic benefit.</td>
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<td>897</td>
<td>Hedgehog Signaling Inhibition Blocks Growth of Resistant Tumors through Effects on Tumor Microenvironment</td>
<td>Emanuela Heller, Michelle A. Hurchla, Jingyu Xiang, Xinning Su, Sara Chen, Jochen Schneider, Kyu-Sang Joeng, Marcos Vidal, Leah Goldberg, Hongju Deng, Mary C. Hornick, Julie L. Prior, David Piwnica-Worms, Fanxin Long, Ross Caugh, and Katherine N. Weilbaecher</td>
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<td><strong>Précis:</strong> This study describes an MRI imaging method that can be used to noninvasively monitor vascular disruption and normalization following VEGF blockade, addressing a clinical need to rapidly evaluate the likely impact of antiangiogenic therapy in patients.</td>
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MOLECULAR AND CELLULAR PATHOBIOLOGY

Regulation of Monocarboxylate Transporter MCT1 Expression by p53 Mediates Inward and Outward Lactate Fluxes in Tumors
Romain Boidot, Frédérique Végran, Aline Meulle, Aude Le Breton, Chantal Dessy, Pierre Sonveaux, Sarah Lizard-Nacol, and Olivier Feron

PREVENTION AND EPIDEMIOLOGY

A Positive Feedback Signaling Loop between ATM and the Vitamin D Receptor Is Critical for Cancer Chemoprevention by Vitamin D
Huei-Ju Ting, Sayeda Yasmin-Karim, Shian-Jiang Yan, Jong-Wei Hsu, Tzu-Hua Lin, Wei-Si Zeng, James Messing, Tsong-Jeng Sheu, Bo-Ying Bao, Willis X. Li, Edward Messing, and Yi-Fen Lee

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Resistance to Selective BRAF Inhibition Can Be Mediated by Modest Upstream Pathway Activation
Fei Su, William D. Bradley, Qinqiong Wang, Hong Yang, Lihong Xu, Brian Higgins, Kenneth Kolinsky, Kathryn Packman, Min Jung Kim, Kerstin Trunzer, Richard J. Lee, Kathleen Schostack, Jade Carter, Thomas Albert, Soren Germer, Jim Rosinski, Mitchell Martin, Mary Ellen Simcox, Brian Lestini, David Heimbrook, and Gideon Bollag

Precis: This study provides a proof-of-concept that a combination therapy composed of non-camptothecin topoisomerase 1 inhibitors plus checkpoint kinase inhibitors can trigger synergistic cancer cell deaths.

Myc Posttranscriptionally Induces HIF1 Protein and Target Gene Expression in Normal and Cancer Cells
Megan R. Doe, Janice M. Ascano, Mandeep Kaur, and Michael D. Cole

Precis: Myc overexpression is linked to induction of a core regulator of tumor hypoxia, highlighting a previously unrecognized effector pathway for oncogenic transformation by Myc.

Potential Control of Hedgehog Signaling in Osteosarcoma Cells by miR-20a Encoded by the miR-17–92 Cluster Increases the Metastatic Potential of Osteosarcoma Cells by Regulating Fas Expression
Gangzong Huang, Kazumasa Nishimoto, Zhichao Zhou, Dennis Hughes, and Eugenie S. Kleinerman

Precis: Findings provide insights into the means by which bone cancers gain access to the lung, by modulating expression of a microRNA program that permits cancer cell survival in the lung microenvironment.

Fluxes in Tumors Mediate Inward and Outward Lactate Transporter MCT1 Expression by p53
Romain Boidot, Frédérique Végran, Aline Meulle, Aude Le Breton, Chantal Dessy, Pierre Sonveaux, Sarah Lizard-Nacol, and Olivier Feron

Precis: Findings demonstrate a novel role for hedgehog signaling in osteoclast function and demonstrate that hedgehog inhibitors reduce tumor burden through direct effects on tumor cells, osteoclasts, and stromal cells within the tumor microenvironment.

Immune Inhibitory Molecules LAG-3 and PD-1 Synergistically Regulate T-cell Function to Promote Tumoral Immune Escape
Seng-Ryong Woo, Meghan E. Turnis, Monica V. Goldberg, Jaishree Bankoti, Mark Selby, Christopher J. Nirischl, Matthew L. Bettini, David M. Gravano, Peter Vogel, Chih Long Liu, Stephanie Tsangoumbatvisit, Joseph F. Grosso, George Netto, Matthew P. Smeltzer, Alcides Chaux, Paul J. Utz, Creg J. Workman, Drew M. Pardoll, George Netto, Matthew P. Smeltzer, Alcides Chaux, Paul J. Utz, Creg J. Workman, Drew M. Pardoll, Alan J. Korman, Charles G. Drake, and Dario A.A. Vignali

Precis: Analogous to combination strategies for targeted drugs, this study shows how combination strategies for immunotherapeutic antibodies that target important negative regulatory immune receptors can produce powerful antitumor effects, in essence, by correcting immune escape.

Antigen-Specific CD4 T Cells Regulate Function of Myeloid-Derived Suppressor Cells in Cancer via Retrograde MHC Class II Signaling
Srinivas Nagaraj, Allison Nelson, Je-in Youn, Pingyan Cheng, David Quiceno, and Dmitry I. Gabrilovich

Precis: This report addresses a controversy regarding how myeloid-derived suppressor cells suppress the activity of CD4 T cells in cancer, revealing a forward feedback loop in which activated, tumor antigen–specific forms of these T cells may augment the immunosuppressive effects of myeloid-derived suppressor cells.
Histone Deacetylase Inhibition Increases Levels of Choline Kinase α and Phosphocholine Facilitating Noninvasive Imaging in Human Cancers
Mounia Beloueche-Babari, Vaitha Arunan, Helen Troy, Robert H. te Poele, Anne-Christine Wong Te Fong, L. Elizabeth Jackson, Geoffrey S. Payne, John R. Griffiths, Ian R. Judson, Paul Workman, Martin O. Leach, and Yuen-Li Chung

Precis: Noninvasive biomarkers offer critical tools for clinical trials of targeted drugs, as illustrated in this study providing mechanistic support for the use of phosphocholine as a candidate noninvasive biomarker for imaging the pharmacodynamic response to HDAC inhibitors.

Letter to the Editor
Impact of Epithelial Organization on Myc Expression and Activity—Letter
Johanna I. Partanen and Juha Klefstrom

Impact of Epithelial Organization on Myc Expression and Activity—Response
David Simpson Senthil Muthuswamy, and William P. Tansey

CORRECTIONS
Correction: Endoglin Regulates Cancer–Stromal Cell Interactions in Prostate Tumors

Correction: Sirtuin 1 Is Upregulated in a Subset of Hepatocellular Carcinomas where It Is Essential for Telomere Maintenance and Tumor Cell Growth

Correction: Long Noncoding RNA HOTAIR Regulates Polycomb-Dependent Chromatin Modification and Is Associated with Poor Prognosis in Colorectal Cancers

ABOUT THE COVER
Vemurafenib recently achieved FDA approval for treating patients with metastatic melanoma harboring the BRAF V600E mutation. The BRAFV600E-driven uncontrolled proliferation is effectively blocked by vemurafenib, reflected in the remarkable regressions observed in the clinic. However, most patients eventually relapse, and in many instances, progression is associated with reactivation of ERK signaling, as observed by high levels of ERK phosphorylation in tumor biopsies taken at progression. The cover shows an example of a tumor biopsy taken at progression. Su and colleagues identify a novel KRAS mutation that mediates the acquired resistance of melanoma cells to vemurafenib. Both MAPK and PI3K pathways are active despite the presence of drug. Combinations of vemurafenib with either MEK or AKT inhibitors are able to overcome this resistance, providing hope that these combinations could mitigate disease relapse in patients. For details, see the article by Su and colleagues on page 969 of this issue.