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831 The Dark Side of Mast Cell–Targeted Therapy in Prostate Cancer
Paola Pittoni and Mario Paolo Colombo

836 Regulation of Cancer Progression by \( \beta \)-Endorphin Neuron
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841 Twenty-Third Annual Pezcoller Symposium: Engineering Influences in Cancer Research
Peter Friedl, Jeff Hubbell, David Livingston, and Enrico Mihi

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845 N-Myc Regulates Expression of the Detoxifying Enzyme Glutathione Transferase \( \text{GSTP1} \), a Marker of Poor Outcome in Neuroblastoma

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854 Hyperpolarized \( ^{13} \text{C} \) Spectroscopy Detects Early Changes in Tumor Vasculature and Metabolism after \( \text{VEGF} \) Neutralization
Sarah E. Bohndiek, Mikko I. Kettunen, De-en Hu, and Kevin M. Brindle

MICROENVIRONMENT AND IMMUNOLOGY

865 Metastatic Cells Can Escape the Proapoptotic Effects of TNF-\( \alpha \) through Increased Autocrine IL-6/\( \text{STAT3} \) Signaling
Shun Li, Ni Wang, and Pnina Brodt

Précis: This study defines an IGF-1–driven mechanism of cancer cell survival that is critical for metastatic colonization of the liver, suggesting that IGF-1 receptor antagonists currently in clinical trials may have particular utility in treating colon cancers and other cancers that metastasize frequently to liver.

876 Monocytic CCR2\(^{\dagger} \) Myeloid-Derived Suppressor Cells Promote Immune Escape by Limiting Activated CD8 T-cell Infiltration into the Tumor Microenvironment
Alexander M. Leesokhin, Mias Tobias M. Hohl, Shigehisa Kitano, Carina Cortez, Daniel Hirschhorn-Cymerman, Francesca Avogadri, Gabrielle A. Rizzuto, John J. Lazarus, Eric G. Pamer, Alan N. Houghton, Taha Merghoub, and Jedd D. Wolchok

Précis: 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 CD8 T cells into the tumor microenvironment, perhaps unwittingly contributing to immune escape.

887 CD8\(^{\dagger} \) T Cells Specific for Tumor Antigens Can Be Rendered Dysfunctional by the Tumor Microenvironment through Upregulation of the Inhibitory Receptors \( \text{BTLA} \) and \( \text{PD-1} \)
Julien Fourcade, Zhaojun Sun, Ornella Pagliano, Philippe Guillaume, Immanuel F. Luescher, Cindy Sander, John M. Kirkwood, Daniel Olive, Vijay Kuchroo, and Hassane M. Zaro

Précis: 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.

897 Hedgehog Signaling Inhibition Blocks Growth of Resistant Tumors through Effects on Tumor Microenvironment
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

Précis: Regulation of the monocarboxylate transporter MCT1 is crucial in cancer metabolism. p53 regulates MCT1 expression, affecting tumor metabolism and cell death.

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-Jang Yan, Jong-Wei Hsu, Tzu-Hua Lin, Wei-Si Zeng, James Messing, Tzong-Jeng Sheu, Bo-Ying Bao, Willis X. Li, Edward Messing, and Yi-Fen Lee

Précis: Findings suggest that vitamin D prevents cancer by stimulating a positive feedback signaling loop from the vitamin D receptor to the DNA repair machinery, increasing its efficiency.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Resistance to Selective BRAF Inhibition Can Be Mediated by Modest Upstream Pathway Activation

Fei Su, William D. Bradley, Qingqiong Wang, Hong Yang, Lizhong 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

Précis: Findings address the present clinical challenge to prevent or reverse acquired resistance to mutant BRAF inhibition, which can produce powerful but only transient therapeutic responses in melanoma.

Potentiation of the Novel Topoisomerase I Inhibitor Indenoisoquinoline LMP-400 by the Cell Checkpoint and Chk1-Chk2 Inhibitor AZD7762

Sheena M. Aris and Yves Pommier

Précis: 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.

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

Précis: 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.

Immune Inhibitory Molecules LAG-3 and PD-1 Synergistically Regulate T-cell Function to Promote Tumoral Immune Escape


Précis: 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

Précis: 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.

Myc Posttranscriptionally Induces HIF1α Protein and Target Gene Expression in Normal and Cancer Cells

Megan R. Doe, Janice M. Ascano, Mandeep Kaur, and Michael D. Cole

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

Précis: This study identifies the lactate transporter MCT1 as a critical mediator of p53-driven metabolic controls on glycolysis and respiration, and thus also potentially critical for supporting malignant progression of p53-deficient cancers.

Resistance to Selective BRAF Inhibition Can Be Mediated by Modest Upstream Pathway Activation

Fei Su, William D. Bradley, Qingqiong Wang, Hong Yang, Lizhong 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

Précis: Findings address the present clinical challenge to prevent or reverse acquired resistance to mutant BRAF inhibition, which can produce powerful but only transient therapeutic responses in melanoma.

Potentiation of the Novel Topoisomerase I Inhibitor Indenoisoquinoline LMP-400 by the Cell Checkpoint and Chk1-Chk2 Inhibitor AZD7762

Sheena M. Aris and Yves Pommier

Précis: 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.
### 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

**Précis:** 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.

### Dysregulation of Ezrin Phosphorylation Prevents Metastasis and Alters Cellular Metabolism in Osteosarcoma

Ling Ren, Sung-Hyeok Hong, Qing-Rong Chen, Joseph Briggs, Jessica Cassavaugh, Satish Srinivasan, Michael M. Lizardo, Arnulfo Mendoza, Ashley Y. Xia, Narayan Avadhani, Javed Khan, and Chand Khanna

**Précis:** This study offers mechanistic insights into the role of a pivotal regulator of metastasis that links the plasma cell membrane to the actin cytoskeleton, and that may act in part by linking metabolic and respiratory capacity to metastatic capability.

### Hedgehog and Notch Signaling Regulate Self-Renewal of Undifferentiated Pleomorphic Sarcomas

Chang Ye Yale Wang, Qingsxia Wei, Ilkyu Han, Shingo Sato, Ronak Ghanbari-Azarnier, Heather Whetstone, Raymond Poon, Jiayi Hu, Feifei Zheng, Phil Zhang, Weishi Wang, Jay S. Wunder, and Benjamin A. Alman

**Précis:** Findings suggest not only novel treatment strategies for a soft tumor subtype seen almost exclusively in the elderly, but also possible insights into its enigmatic origins of development, which have been historically controversial.

### Mammary Gland Selective Excision of c-Jun Identifies Its Role in mRNA Splicing

Sanjay Katiyar, Xuanmao Jiao, Sankar Addya, Adam Ertel, Yolanda Covarrubias, Vanessa Rose, Mathew C. Casimiro, Jie Zhou, Michael P. Lisanti, Talat Nasim, Paolo Fortina, and Richard G. Pestell

**Précis:** This study suggests strategies to overcome resistance to MEK kinase inhibitors, which are presently being evaluated in clinical trials.

### 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

### 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 BRAF \(^{V600E}\)-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.
Cancer Research

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