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856 Metastatic Cells Can Escape the Proapoptotic Effects of TNF-α through Increased Autocrine IL-6/STAT3 Signaling
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865 Monocytic CCR2+ Myeloid-Derived Suppressor Cells Promote Immune Escape by Limiting Activated CD8+ T-cell Infiltration into the Tumor Microenvironment

873 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
Julien Fourcade, Zhaojun Sun, Ornella Pagliano, Philippe Guillaume, Immanuel F. Luescher, Cindy Sander, John M. Kirkwood, Daniel Olive, Vijay Kuchroo, and Hassane M. Zarour

882 Hedgehog Signaling Inhibition Blocks Growth of Resistant Tumors through Effects on Tumor Microenvironment
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
Seng-Ryong Woo, Meghan E. Turnis, Monica V. Goldberg, Jaishree Bankoti, Mark Selby, Christopher J. Nirschl, Matthew L. Bettini, David M. Gravano, Peter Vogel, Chih Long Liu, Stephanie Tangsombatvisit, Joseph F. Grosso, David M. Gravano, Alcides Chaux, Paul J. Utz, Creg J. Workman, Drew M. Pardoll, George Netto, Matthew P. Smeltzer, Alan J. Korman, Charles G. Drake, and Paul J. Utz

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.

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.

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

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.

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, Tzonq-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, Qinqiong 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 I 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.

**TUMOR AND STEM CELL BIOLOGY**

**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, Arnufo 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, Qingxia Wei, Ilkyu Han, Shingo Sato, Ronak Ghanbari-Azarnier, Heather Whetstone, Raymond Poon, Jiayi Hu, Feifei Zheng, Phil Zhang, Wei Shi Wang, Jay S. Wunder, and Benjamin A. Alman

**LETTERS 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 BRAF<sup>V600E</sup>-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.