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**MICROENVIRONMENT AND IMMUNOLOGY**

865  Metastatic Cells Can Escape the Proapoptotic Effects of TNF-α through Increased Autocrine IL-6/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  Monocyte CCR2+ Myeloid-Derived Suppressor Cells Promote Immune Escape by Limiting Activated CD8 T-cell Infiltration into the Tumor Microenvironment
Alexander M. Lesokhin, Tobias M. Hohl, Shigehisa Kitano, Cinzia Cortese, Daniel Hirschhorn-Cymerman, Francesca Avogadri, Gabrielle A. Rizzuto, John J. Lazarus, Eric G. Pamer, Alan N. Houghton, Taha Merghoub, and Jedd D. Wolchok

 précis: This cytokine GM-CSF, which is used to enhance white cell counts in many cancer patients, also expands a population of immune-suppressive monocytes that can block the entry of activated antitumor T cells into the tumor microenvironment, perhaps unwittingly contributing to immune escape.

887  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 Pugliano, Philippe Guillaume, Immanuel F. Luescher, Cindy Sander, John M. Kirkwood, Daniel Olive, Vijay Kuchroo, and Hassane M. Zarour

 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**

939 Regulation of Monocarboxylate Transporter MCT1 Expression by p53 Mediates Inward and Outward Lactate Fluxes in Tumors

Romain Boidot, Frédérique Védran, Aline Meulle, Aude Le Breton, Chantal Dessy, Pierre Sonveaux, Sarah Lizard-Nacol, and Olivier Feron

**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.

949 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.

958 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, 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

**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.

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

Fei Su, William D. Bradley, Qiongqing Wang, Hong Yang, Lihzong 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.

979 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:** Analogous to combination strategies for targeted drugs, this study demonstrates a novel role for hedgehog inhibitors reducing tumor burden through direct effects on tumor cells, osteoclasts, and stromal cells within the tumor microenvironment.

**PREVENTION AND EPIDEMIOLOGY**

948 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 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**

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

Fei Su, William D. Bradley, Qiongqing Wang, Hong Yang, Lihzong 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.
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.

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 Cassavanga, Satish Srinivasan, Michael M. Lizardo, Arnulfio Mendoza, Ashley Y. Xia, Narayan Avadhani, Javed Khan, and Chand Khanna

Precis: 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

Precis: 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.

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 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.
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