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Précis: This study paves the way to use circulating tumor cells as a liquid biopsy in cancer patients, providing more effective options to monitor tumor genomes that are prone to change during progression, treatment, and relapse.

Response Classification Based on a Minimal Model of Glioblastoma Growth Is Prognostic for Clinical Outcomes and Distinguishes Progression from Pseudoprogression
Maxwell Lewis Neal, Andrew D. Trister, Sunyoung Ahn, Anne Ballock, Carly A. Bridge, Laura Guyman, Jordan Lange, Rita Sodt, Tyler Cloke, Albert Lai, Timothy F. Cloughesy, Maciej M. Mrugala, Jason K. Rockhill, Russell C. Rockne, and Kristin R. Swanson

Précis: Results describe a novel and simple method to measure the effectiveness of glioblastoma therapies during periods of treatment when timely adjustments may be made to improve patient outcomes.

Précis: This study illustrates how monitoring the biological activity of a factor rather than its expression in cancer patients can provide a more informative metric to predict malignant progression.
Adipocytes Cause Leukemia Cell Resistance to L-Asparaginase via Release of Glutamine

Ehsan A. Ehsanipour, Xia Sheng, James W. Behan, Xingchao Wang, Anna Butturini, Vassilios I. Avramis, and Steven D. Mittelman

Précis: Studies identify mechanisms behind the poor survival of obese leukemia patients through impaired asparaginase response.

Pancreatic Cancer-Associated Stellate Cells Promote Differentiation of Myeloid-Derived Suppressor Cells in a STAT3-Dependent Manner

Thomas A. Mace, Zeenath Ameen, Amy Collins, Sylwia Wojcik, Markus Mair, Gregory S. Young, James R. Fuchs, Tim D. Eubank, Wendy L. Frankel, Tanios Bekaii-Saab, Mark Bloomston, and Gregory B. Lesinski

Précis: A well-known stromal cell population found in pancreatic tumors is found to secrete soluble factors that convert myeloid cells to an immunosuppressive phenotype that promotes tumoral immune escape and progression.

Inhibition of Histone Demethylase JMJD1A Improves Anti-Angiogenic Therapy and Reduces Tumor-Associated Macrophages

Tsuyoshi Osawa, Rika Tsuchida, Masashi Muramatsu, Tepppei Shimamura, Feng Wang, Jun-ichi Suehiro, Yasuharu Kanki, Youichiro Wada, Yasuhiro Yuasa, Hiroyuki Aburatani, Satoru Miyano, Takashi Minami, Tatsuhiko Kodama, and Masahumi Shibuya

Précis: Findings highlight a strategy to target cancer cells resistant to hypoxia and nutrient starvation as an approach to heighten sensitivity to antiangiogenic drugs and to reduce risks of drug resistance and tumor recurrence.

Cowden Syndrome-Related Mutations in PTEN Associate with Enhanced Proteasome Activity

Xin He, Nicholas Arrotta, Deepa Radhakrishnan, Yu Wang, Todd Romigh, and Charis Eng

Précis: The results of this study may help resolve the loose genotype-phenotype correlations that occur in a spectrum of clinical syndromes, marked by germline PTEN mutations, by tracing their common effects to alterations in proteasome activity that are affected both by PTEN protein stability and subcellular localization.

Oncogenic NRAS, Required for Pathogenesis of Embryonic Rhabdomyosarcoma, Relies upon the HMG2–IGF2BP2 Pathway

Zhizhong Li, Yunyu Zhang, Krishnan Ramanujan, Yan Ma, David G. Kirsch, and David J. Glass

Précis: Findings identify the upstream elements controlling a core oncogenic driver in embryonic rhabdomyosarcomas, suggesting novel points to target therapeutic inventions against this aggressive pediatric tumor.

Acquired Resistance to EGFR Inhibitors Is Associated with a Manifestation of Stem Cell–like Properties in Cancer Cells


Précis: In lung cancer, malignant cells with stem cell-like properties appeared as acquired resistance emerged to EGFR inhibitors, reinforcing concerns that while such treatments may be effective initially, they may also promote progression at later times.

Novel HSP90 Inhibitor NVP-HSP990 Targets Cell-Cycle Regulators to Ablate Olig2-Positive Glioma Tumor–Initiating Cells

Jun Fu, Dimpy Koul, Jun Yao, Shuzhen Wang, Ying Yuan, Howard Colman, Erik. P. Sulman, Frederick. F. Lang, and W.K. Alfred Yung

Précis: Findings suggest that HSP90 inhibitors being evaluated in clinical trials may be efficacious against deadly brain tumors that express a particular type of cancer stem-like cell.

Efficacy and Mechanism-of-Action of a Novel Superagonist Interleukin-15: Interleukin-15 Receptor αSu/Fc Fusion Complex in Syngeneic Murine Models of Multiple Myeloma

Wenzin Xu, Monica Jones, Bai Liu, Xiaoyun Zhu, Christopher B. Johnson, Ana C. Edwards, Lin Kong, Emily K. Jeng, Kaiping Han, Warren D. Marcus, Mark P. Rubinstein, Peter R. Rhode, and Hing C. Wong

Précis: Findings offer preclinical proof-of-concept for an engineered T-cell stimulant that mediates antitumor activity against multiple myeloma, rationalizing its clinical evaluation.
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**TUMOR AND STEM CELL BIOLOGY**

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β-Catenin/POU5F1/SOX2 Transcription Factor Complex Mediates IGF-1 Receptor Signaling and Predicts Poor Prognosis in Lung Adenocarcinoma

Chuan Xu, Dan Xie, Shi-Cang Yu, Xiao-Jun Yang, Li-Ru He, Jing Yang, Yi-Fang Ping, Bin Wang, Lang Yang, Sen-Lin Xu, Wei Cui, Qing-Liang Wang, Wen-Juan Fu, Qing Liu, Cheng Qian, You-Hong Cui, Jeremy N. Rich, Hsiang-Fu Kung, Xia Zhang, and Xiu-Wu Bian

Précis: This potentially seminal study reports a novel complex that mediates self-renewal of cancer stem-like cells in lung cancers and perhaps other epithelial tumors.

ABOUT THE COVER

Rapid acquired resistance to antiangiogenic therapies such as bevacizumab limits clinical utility of this approach in highly vascular tumors including glioblastoma multiforme. β1 integrins represent a critical pathway for the promotion of malignant progression and acquired therapy resistance in cancer cells through adhesive interactions with the surrounding tumor microenvironment. Using a multimodal approach, it was found that the β1 integrin subunit was functionally upregulated in patient glioblastoma specimens with acquired resistance to bevacizumab. Knockdown or inhibition of the β1 integrin subunit with neutralizing monoclonal antibodies promoted reversion of malignant phenotype and attenuated in vivo growth of bevacizumab-resistant glioblastoma xenografts. For details, see article by Carbonell and colleagues on page 3145.