A comprehensive survey of Ras mutations in cancer
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SIRT3 is a mitochondrial tumor suppressor: A scientific tale that connects aberrant cellular ROS, the Warburg effect, and carcinogenesis
Marcia C. Haigis, Chu-Xia Deng, Lydia W.S. Finley, Hyun-Seok Kim, and David Gius

Tumor microenvironment complexity: Emerging roles in cancer therapy
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Identification of serum biomarker signatures associated with pancreatic cancer
Christine Wingren, Anna Sandström, Ralf Segersvärd, Anders Carlsson, Roland Andersson, Matthias Lohr, and Carl A. K. Borrebaek

Real-time Raman spectroscopy for in vivo skin cancer diagnosis
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Phosphoproteomics identifies driver tyrosine kinases in sarcoma cell lines and tumors
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AMPKα modulation in cancer progression: Multilayer integrative analysis of the whole transcriptome in Asian gastric cancer
Yon Hui Kim, Han Liang, Xiuping Liu, Ju-Seog Lee, Jae Yong Cho, Jae-Ho Cheong, Hoguen Kim, Min Li, Thomas J. Downey, Matthew D. Dyer, Yongming Sun, Jingtai Sun, Ellen M. Beasley, Hyun Cheol Chung, Sung Hoon No, John N. Weinstein, Chang-Gong Liu, and Garth Powis

Cyclophosphamide creates a receptive microenvironment for prostate cancer skeletal metastasis
Serk In Park, Jinhui Liao, Janice E. Berry, Xin Li, Amy J. Kohan, Megan E. Michalski, Matthew R. Eber, Fabiana N. Soki, David Sadler, Sudha Sud, Sandra Tisdelle, Stephanie D. Daignault, Jeffrey A. Nemeth, Linda A. Snyder, Thomas J. Wronska, Kenneth J. Pienta, and Laurie K. McCauley

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Hepatocyte–Stellate Cell Cross-Talk in the Liver Engenders a Permissive Inflammatory Microenvironment That Drives Progression in Hepatocellular Carcinoma
Cédric Coulouarn, Anne Corlu, Denise Glaise, Isabelle Guénon, Snorri S. Thorgeirsson, and Bruno Clément
Précis: Molecular characterization of the cross-talk between cell types in the liver plays a major role in the progression of hepatocellular carcinoma and may offer novel therapeutic targets for epigenetic modulation.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Parkin Pathway Activation Mitigates Glioma Cell Proliferation and Predicts Patient Survival
Précis: This study provides mechanistic insight into the tumor suppressor function of parkin, a gene that is often mutated in genetic Parkinson disease, but is shown here to play a role in the pathogenesis of gliomas.

KRas Induces a Src/PEAK1/ErbB2 Kinase Amplification Loop That Drives Metastatic Growth and Therapy Resistance in Pancreatic Cancer
Jonathan A. Kelber, Theresa Reno, Sharmeeza Kaushal, Cristina Metlidí, Tracy Wright, Konstantin Stoleto, Jessica M. Weems, Frederick D. Park, Evangeline Mose, Yingchun Wang, Robert M. Hoffman, Andrew M. Lowy, Michael Bouvet, and Richard L. Klemke
Précis: In serving as a novel diagnostic and prognostic biomarker in pancreatic ductal carcinoma, the novel tyrosine kinase PEAK1 may mediate cancer progression and multiple therapy-resistant phenotypes and thus represents an important new therapeutic target.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Dinitroazetidines Are a Novel Class of Anticancer Agents and Hypoxia-Activated Radiation Sensitizers Developed from Highly Energetic Materials
Shoucheng Ning, Mark Bednarski, Bryan Oronsky, Jan Scicinski, Gordon Saul, and Susan J. Knox
Précis: Findings characterize a novel compound based on a highly energetic chemical scaffold that selectively targets hypoxic tumors and enhances the effects of radiotherapy.

Coxsackievirus B3 Is an Oncolytic Virus with Immunostimulatory Properties That Is Active against Lung Adenocarcinoma
Shohei Miyamoto, Hiroyuki Inoue, Takahumi Nakamura, Meiko Yamada, Chika Sakamoto, Yasuo Urata, Yoshihiko Okazaki, Tomotoshi Marumoto, Atsushi Takahashi, Koichi Takayama, Yoichi Nakanishi, Hiroyuki Shimizu, and Kenzaburo Tani
Précis: While oncolytic viruses have failed as yet to realize clinical potential, this study defines a potent virus that by exerting adjuvant immunostimulatory properties may yield a unique and more effective antitumor activity.
Activation of Ras/P13K/ERK Pathway Induces c-Myc Stabilization to Upregulate Argininosuccinate Synthetase, Leading to Argininosuccinate Deiminase Resistance in Melanoma Cells

Wen-Bin Tsai, Isamu Aiba, Yan Long, Hui-Kuan Lin, Lynn Feun, Niramol Savaraj, and Macus Tien Kuo

Precis: Findings offer mechanistic insight into how resistance emerges to arginine deprivation therapy and how inhibitors of the Ras/ERK and PI3K/AKT pathways might restore therapeutic responses.

Mitochondria-Targeted Drugs Synergize with 2-Deoxyglucose to Trigger Breast Cancer Cell Death

Gang Cheng, Jacek Zielonka, Brian P. Dranka, Donna McAllister, A. Craig Mackinnon Jr, Joy Joseph, and Balaraman Kalyanaraman

Precis: This important study may crack the long-standing challenge of how to employ the glycolytic inhibitor 2-deoxyglucose for generalized anticancer therapy, by combining it with mitochondria-targeted cationic compounds that can improve cancer cell cytotoxicity without toxic liabilities to normal tissue.

Smac Mimetic LBW242 Sensitizes XIAP-Overexpressing Neuroblastoma Cells for TNF-α-Independent Apoptosis

Georg Eschenburg, Angelika Eggert, Alexander Schramm, Holger N. Lose, and Patrick Hundsdoerfer

Precis: Smac mimetics offer a potential adjuvant approach to sensitize or resensitize tumors to chemotherapy, as illustrated by this preclinical proof-of-concept study in a commonly deadly type of pediatric cancer.

Epidermal Growth Factor Receptor Variant III Contributes to Cancer Stem Cell Phenotypes in Invasive Breast Carcinoma

Catherine A. Del Vecchio, Kristin C. Jensen, Ryan T. Nitta, A. Hunter Shain, Craig P. Giacomini, and Albert J. Wong

Precis: By identifying breast cancer stem cells that express a variant EGFR receptor, this study has implications for how to improve treatment for patients who harbor this variant receptor.

HER3 is Required for HER2-Induced Preneoplastic Changes to the Breast Epithelium and Tumor Formation

David B. Vaught, Jamie C. Stanford, Christian Young, Donna J. Hicks, Frank Wheeler, Cammie Binehart, Violeta Sánchez, John Koland, William J. Muller, Carlos L. Arteaga, and Rebecca S. Cook

Precis: Findings offer a preclinical proof-of-concept for a new strategy to treat or prevent HER2-amplified breast cancers, which represent nearly 30% of all breast cancers, by targeting an important heterodimeric partner of HER2.

Real-Time Monitoring of Rare Circulating Hepatocellular Carcinoma Cells in an Orthotopic Model by In Vivo Flow Cytometry Assesses Resection on Metastasis

Zhi-Chao Fan, Jun Yan, Guang-Da Liu, Xiao-Ying Tan, Xiao-Fu Weng, Wei-Zhong Wu, Jian Zhou, and Xun-Bin Wei

Precis: In vivo flow cytometry may offer a breakthrough technology to elucidate mechanisms of hematogenous metastasis and to monitor the efficacy of cancer therapy.

ABOUT THE COVER

Interleukin-17 (IL-17) is a key proinflammatory cytokine involved in many inflammatory and autoimmune diseases. Mice with conditional knockout of PTEN tumor suppressor gene developed invasive prostate adenocarcinomas at ages of 9 to 30 weeks. When IL-17 signaling was blocked by knockout IL-17 receptor C (IL-17RC) in the PTEN-null mice, the number and size of prostate tumors were reduced compared to mice that expressed IL-17RC, because IL-17RC knockout reduced cellular proliferation, increased apoptosis, inhibited inflammatory infiltration, and diminished expression of matrix metalloproteinase 7 in the mouse prostates. For details, see article by Zhang and colleagues on page 2589 of this issue.