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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 PATHOBIOLGY

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 Kausbal, Cristina Metildi, Tracy Wright, Konstantin Stoletov, Jessica M. Weems, Frederick D. Park, Evangeline Mose, Yingchun Wang, Robert M. Hoffman, Andrew M. Lowy, Eric Coulouarn, Anne Corlu, Denise Glaise, Isabelle Guénon, Snorri S. Thorgeirsson, and Bruno Clément

Précis: In serving as a novel diagnostic and prognostic marker 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.

Therapeuctics, 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, Toshihiko Okazaki, Tomotoshi Marumoto, Atsushi Takahashi, Koichi Takayama, Yoichi Nakahishi, 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.

Loss of Cell-Surface Laminin Anchoring Promotes Tumor Growth and Is Associated with Poor Clinical Outcomes

Armin Akhavan, Obi L. Grifflih, Liliana Soroceanu, Dmitri Leonoudakis, Maria Gloria Luciani-Torres, Anneleen Daemen, Joe W. Gray, and John L. Muschler

Précis: Defects in the cell surface anchoring of laminin in cancer cells of diverse origin is common and strongly associated with aggressive phenotypes, suggesting a common tethering point to understand how laminin in the tumor microenvironment directs malignant progression, as well as how novel generalized therapies might be directed to this aspect.

Interleukin-17 Promotes Formation and Growth of Prostate Adenocarcinoma in Mouse Models

Quyang Zhang, Sen Liu, Dongxia Ge, Qingsong Zhang, Yun Xue, Zhenggang Xiong, Asim B. Abdel-Mageed, Leann Myers, Steven M. Hill, Brian G. Rowan, Oliver Sartor, Jonathan Melamed, Zhenbang Chen, and Zongbing You

Précis: Findings in a mouse model of prostate cancer indicate that proinflammatory cytokine IL-17 drives the transition of premalignant lesions to frank adenocarcinoma, suggesting a molecular mechanism to underpin the concept that reducing prostate inflammation could help prevent emergence of this disease.

Mitochondrial Bcl-2 Family Dynamics Define Therapy Response and Resistance in Neuroblastoma

Kelly C. Goldsmith, Michelle Gross, Susan Peirce, Dema Luyindula, Xueyuan Liu, Annette Vu, Michael Slozberg, Bong Guo, Huaqing Zhao, C. Patrick Reynolds, and Michael D. Hogarty

Précis: Mitochondrial profiling reveals that acquired therapy resistance in neuroblastoma is due to repression at the level of Bak/Bax-mediated apoptosis, and this may offer a basis to stratify patients who could benefit most from treatment with Bcl-2/Bcl-xL antagonists.
### Activation of Ras/Pi3K/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 Egger, Alexander Schramm, Holger N. Lose, and Patrick Hundsdorfer

**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 Rinehart, 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.
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