BREAKING ADVANCES

Highlights from Recent Cancer Literature

EPIGENOME CONSORTIUM

A Blueprint for an International Cancer Epigenome Consortium. A Report from the AACR Cancer Epigenome Task Force

Stephan Beck, Bradley E. Bernstein, Robert M. Campbell, Joseph F. Costello, Dashyant Dhanak, Joseph R. Ecker, John M. Greally, Jean-Pierre Issa, Peter W. Laird, Kornelia Polyak, Benjamin Tycko, and Peter A. Jones, for the AACR Cancer Epigenome Task Force

REVIEWS

Role of Chemokines and Chemokine Receptors in Shaping the Effector Phase of the Antitumor Immune Response

Katarzyna Franciszkiewicz, Alexandre Boissonnas, Marie Boutet, Christophe Combadière, and Fathia Mami-Chouaib

TLRs as miRNA Receptors

Müller Fabbri

Cytokine Stimulation of Epithelial Cancer Cells: The Similar and Divergent Functions of IL-4 and IL-13

Miranda A. Hallett, Katherine T. Venmar, and Barbara Fingleton

PRIORITY REPORT

Paracrine Hedgehog Signaling Drives Metabolic Changes in Hepatocellular Carcinoma


Précis: Myofibroblasts in the microenvironment of liver carcinoma rely on Hedgehog signals, suggesting new diagnostic and therapeutic targets to exploit in this disease.

INTEGRATED SYSTEMS AND TECHNOLOGIES

An Integrated Genome-Wide Approach to Discover Tumor-Specific Antigens as Potential Immunologic and Clinical Targets in Cancer

Qing-Wen Xu, Wei Zhao, Yue Wang, Maureen A. Sartor, Dong-Mei Han, Jixin Deng, Bakesh Ponnala, Jiang-Ying Yang, Qing-Yun Zhang, Guo-Qing Liao, Yi-Mei Qu, Lu Li, Fang-Fang Liu, Hong-Mei Zhao, Yan-Hui Yin, Wei-Feng Chen, Yu Zhang, and Xiao-Song Wang

Précis: This important paper reports an integrated technology to uncover the cancer-specific antigen genome as a reservoir for novel immunological and clinical targets.

Evolutionary Approaches to Prolong Progression-Free Survival in Breast Cancer

Ariosto S. Silva, Yoonseok Kam, Zayar P. Khin, Susan E. Minton, Robert J. Gillies, and Robert A. Gatenby

Précis: This work challenges the paradigm of maximum tolerated dose for drug treatment in cancer by proposing a combination strategy to burden chemoresistant cells with a chronic futile efflux of noncytotoxic drugs, with only the minimal chemotherapy dose needed to block tumor growth.

MICROENVIRONMENT AND IMMUNOLOGY

Neuropilin-1 Identifies a Subset of Bone Marrow Gr1+ Monocytes That Can Induce Tumor Vessel Normalization and Inhibit Tumor Growth

Alessandro Carrer, Silvia Moimas, Serena Zacchigna, Lucia Pattarini, Lorena Zentilin, Giulia Ruoci, Miguel Mano, Milena Sinigaglia, Federica Maione, Guido Serini, Enrico Giraudo, Federico Bussolino, and Mauro Giacca

Précis: Neuropilin-1 expressing monocytes (NEM) are able to stabilize the tumor vasculature, thereby improving tumor oxygenation and reducing tumor malignancy, invasiveness, and resistance to chemotherapy.
### Molecular and Cellular Pathobiology

#### Polyploidization of Murine Mesenchymal Cells Is Associated with Suppression of the Long Noncoding RNA H19 and Reduced Tumorigenicity

Ofer Shoshani, Hassan Massalha, Nir Shani, Sivan Kagan, Orly Ravid, Shalom Madar, Luba Trakhtenbrot, Dena Leshkowitz, Gideon Rechavi, and Dov Zipori

**Précis:** Findings reveal a critical link between a noncoding RNA and the polyploid character and low tumorigenicity of mesenchymal stromal cells.

#### Loss of PPP2R2A Inhibits Homologous Recombination DNA Repair and Predicts Tumor Sensitivity to PARP Inhibition

Peter Kalev, Michal Simicek, Iria Vazquez, Sebastian Munck, Liping Chen, Thomas Soin, Natasha Danda, Wen Chen, and Anna Sablina

**Précis:** Findings suggest that downregulation of a PP2A family phosphatase in tumors may predict therapeutic responses to a promising new class of anticancer agents currently in clinical trials.

### Therapeutics, Targets, and Chemical Biology

#### Systemic Delivery of Salmonella typhimurium Transformed with IDO shRNA Enhances Intratumoral Vector Colonization and Suppresses Tumor Growth

Céline A. Blache, Edwin R. Manuel, Teodora I. Kaltcheva, Andrea N. Wong, Joshua D.J. Ellenhorn, Bruce R. Blazar, and Don J. Diamond

**Précis:** IDO blockade can leverage hypoxia-targeting infections that recruit neutrophils with powerful tumor-killing capacity, further expanding the broad acting modifier effects of IDO on adaptive and innate mechanisms of immune escape in tumors.

#### Modulation of the ATPase and Transport Activities of Broad-Acting Multidrug Resistance Factor ABCC10 (MRP7)

Ekaterina V. Malofeeva, Natalya Domanitskaya, Mariya Gudima, and Elizabeth A. Hopper-Borge

**Précis:** Findings suggest that the approved multikinase inhibitor sorafenib may enhance chemotherapeutic efficacy of drugs that are effluxed by an important mediator of drug resistance in cancer cells.
**TUMOR AND STEM CELL BIOLOGY**

**Cyclin D1 Activity Regulates Autophagy and Senescence in the Mammary Epithelium**

Nelson E. Brown, Rinath Jeselsohn, Teeru Bihani, Miaofen G. Hu, Parthena Foltopoulou, Charlotte Kupershaw, and Philip W. Hinds

**Précis:** Mammary epithelial cells expressing a kinase defective cyclin D1 survive due to an upregulation of autophagy, which if blocked, results in senescence.

**Obesity and Overfeeding Affecting Both Tumor and Systemic Metabolism Activates the Progesterone Receptor to Contribute to Postmenopausal Breast Cancer**

Erin D. Giles, Elizabeth A. Wellberg, David P. Astling, Steven M. Anderson, Ann D. Thor, Sonali Jindal, Aik-Choon Tan, Pepper S. Scheditz, and Paul S. MacLean

**Précis:** Striking findings may help explain why obese postmenopausal women have relatively increased risks of breast cancer.

**The CRTC1-NEDD9 Signaling Axis Mediates Lung Cancer Progression Caused by LKB1 Loss**

Yan Feng, Ye Wang, Zuo Yuan Wang, Zhaoyuan Fang, Fei Li, Yijun Gao, Hongyan Liu, Tian Xiao, Fuming Li, Yang Zhou, Qiwei Zhai, Xiaolong Liu, Yihua Sun, Nabeel Bardeesy, Kwok-kin Wong, Haiquan Chen, Zhi-qi Xiong, and Hongbin Ji

**Précis:** Results decipher the mechanism through which mutation of the tumor suppressor LKB1 in lung cancer leads to progression and metastasis, offering mechanistic insights into how to attack these processes.

**Host Immune Defense Peptide LL-37 Activates Caspase-Independent Apoptosis and Suppresses Colon Cancer**


**Précis:** Findings suggest that a bacteriocidal factor secreted by macrophages, PMNs, and colonocytes contributes to colon cancer suppression by activating a novel pathway of apoptosis in colon cancer cells.

**Correction:** The Kynurenine Pathway in Brain Tumor Pathogenesis

**Correction:**

The authors corrected a mistake in their previous publication regarding the role of the kynurenine pathway in brain tumor pathogenesis. The corrected version clarifies the findings and implications of their research in this area.

**ABOUT THE COVER**

Obesity increases the risk for breast cancer after menopause. Animal studies reveal that obesity and ovariectomy-induced overfeeding converge to promote progesterone receptor (PR)-positive mammary tumors as shown by high nuclear PR immunohistochemical staining. Elevated PR expression positively correlated with tumor expression of glycolytic and lipogenic enzymes, glucose uptake, and proliferation markers. A similar relationship between PR expression and metabolic capacity was observed in tumors from postmenopausal women. Metformin treatment during the window of weight gain following ovariectomy caused PR downregulation and tumor regression. For details, see article by Giles and colleagues on page 6490.