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, Dashyan 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 Mottoma, Serena Zucchiga, Lucia Pattarini, Lorena Zentilin, Giulia Ruozzi, Miguel Mano, Milena Sinigaglia, Federica Maione, Guido Serini, Enrico Giraudo, Federico Russolino, 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.
TWIST1 Is an ERK1/2 Effector That Promotes Invasion and Regulates MMP-1 Expression in Human Melanoma Cells
Michele B. Weiss, Ethan V. Abel, Melanie M. Mayberry, Kevin J. Basile, Adam C. Berger, and Andrew E. Aplin

Précis: Findings define the mechanism of action of a core regulator of EMT in tumor cell invasion through its action in a previously unrecognized signaling cascade that may have general implications in cancer.

p38 MAPK in Myeloma Cells Regulates Osteoclast and Osteoblast Activity and Induces Bone Destruction
Jin He, Zhiquiang Liu, Yuhuan Zheng, Jianfei Qian, Haiyan Li, Yong Lu, Jingda Xu, Bangxian Hong, Mingjun Zhang, Pei Lin, Zhen Cai, Robert Z. Orloski, Larry W. Kwak, Qing Yi, and Jing Yang

Précis: Findings suggest that p38 MAPK inhibitors developed clinically should be repositioned to evaluate their use in treating osteolytic bone lesions in myeloma, with potentially broader implications to treat bone metastasis occurring in various cancers.

Genetically Mediated Nf1 Loss in Mice Promotes Diverse Radiation-Induced Tumors Modeling Second Malignant Neoplasms
Grace Choi, Brian Huang, Emile Pinarbası, Steve E. Braunstein, Andrew E. Horvai, Scott Kogan, Smita Bhatia, Bruce Faddegon, and Jean L. Nakamura

Précis: A mouse model of second malignant neoplasms reveals that loss of the Nf1 gene drives genotoxin-induced tumorigenesis in multiple tissue types. Concordant with this mouse model, genetically-mediated Nf1 loss also occurs in human second malignant neoplasms.

miR-23b Represses Proto-oncogene Src Kinase and Functions as Methylation-Silenced Tumor Suppressor with Diagnostic and Prognostic Significance in Prostate Cancer

Précis: This study documents the diagnostic, prognostic, and functional significance of microRNA-23b as a tumor suppressor gene in prostate cancer.

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.I. 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**

**6477**

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

Nelson E. Brown, Rinath Jeselsohn, Teeru Bihani, Miaofen G. Hu, Parthena Foltopoulou, Charlotte Kupershawser, 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.

**6490**

**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. Schedin, and Paul S. MacLean

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

**6492**

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

6524

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

Yan Feng, Ye Wang, Zuojuan 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 bactericidal factor secreted by macrophages, PMNs, and colonocytes contributes to colon cancer suppression by activating a novel pathway of apoptosis in colon cancer cells.

**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.
Cancer Research

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