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BREAKING ADVANCES

3645 Highlights from Recent Cancer Literature

REVIEW

3647 MET-Mediated Resistance to EGFR Inhibitors: An Old Liaison Rooted in Colorectal Cancer Stem Cells
Carla Boccaccio, Paolo Luraghi, and Paolo M. Comoglio

PRIORITY REPORT

3652 Antimetastatic Effects of Blocking PD-1 and the Adenosine A2A Receptor
Deepak Mittal, Arabella Young, Kimberley Stannard, Michelle Yong, Michele W.L. Teng, Bertrand Allard, John Stagg, and Mark J. Smyth
Précis: These findings provide a preclinical rationale for a generalized combination strategy for cancer immunotherapy that warrants immediate clinical exploration.

INTEGRATED SYSTEMS AND TECHNOLOGIES

3659 Novel Strategies to Enforce an Epithelial Phenotype in Mesenchymal Cells
Ana-Maria Dragoi, Rachel Swiss, Beile Gao, and Hervé Agaisse
Précis: A novel functional assay for E-cadherin expression was used in a genetic screen to identify candidate therapeutic targets to block or reverse EMT as a generalized strategy for treatment of metastatic solid tumors.

3673 Mechanisms of Resistance to Intermittent Androgen Deprivation in Patients with Prostate Cancer Identified by a Novel Computational Method
Jason D. Morken, Aaron Packer, Rebecca A. Everett, John D. Nagy, and Yang Kuang
Précis: The novel computational method described in this study may help clinicians to reestablish treatment sensitivity in their patients with advanced prostate cancer by targeting the relevant mechanism in a personalized manner.

MICROENVIRONMENT AND IMMUNOLOGY

3684 Ly-49 Family Receptors Are Required for Cancer Immunosurveillance Mediated by Natural Killer Cells
Megan M. Tu, Ahmad Bakur Mahmoud, Andrew Wight, Amelia Mottashed, Simon Bélanger, Mir Munir A. Rahim, Elías Abou-Samra, and Andrew P. Makrigiannis
Précis: These results offer a genetic proof establishing the integral role of Ly-49 receptors in tumoral immune surveillance by natural killer cells.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3695 Slug Promotes Survival during Metastasis through Suppression of Puma-Mediated Apoptosis
Seaho Kim, Jiahong Yao, Kimita Suyama, Xia Qian, Bin-Zhi Qian, Sanmay Bandyopadhyay, Olivier Loudig, Carlos De Leon-Rodriguez, Zhen Ni Zhou, Jeffrey Segall, Fernando Macian, Larry Norton, and Rachel B. Hazan
Précis: An important pathway of cell survival in cancer cells antagonizes a proapoptotic molecule first identified as a p53 target, with potential implications for a general targeting principle against metastatic disease.

3707 A Rare Polymorphic Variant of NBS1 Reduces DNA Repair Activity and Elevates Chromosomal Instability
Yuki Yamamoto, Mamiko Miyamoto, Daisuke Tatsuda, Michiaki Kubo, Hitoshi Nakagama, Yusuke Nakamura, Hitoshi Satoh, Koichi Matsuda, Toshiki Watanabe, and Tsutomu Ohta
Précis: These findings address the long-running debate concerning whether the chromosomal instability of cancer cells is cause or consequence of malignant development, offering findings that support a role in causation.

3716 Netrin-1 Promotes Medulloblastoma Cell Invasiveness and Angiogenesis, and Demonstrates Elevated Expression in Tumor Tissue and Urine of Patients with Pediatric Medulloblastoma
Tomoshige Akino, Xueze Han, Hironao Nakayama, Brendan McNeish, David Zurakowski, Akiko Mammoto, Michael Klagsbrun, and Edward Smith
Précis: Urinary levels of an axon guidance molecule implicated in tumor cell invasion may offer a useful noninvasive biomarker to predict disease status, treatment efficacy, or the presence of an invasive phenotype in a common childhood brain tumor.
3727 VEGF Regulates Region-Specific Localization of Perivascular Bone Marrow–Derived Cells in Glioblastoma
Kelly Burrell, Sanjay Singh, Shahrazad Jalali, Richard P. Hill, and Gelareh Zadeh

**Précis:** Targeting perivascular bone marrow–derived cells concurrently with radiation therapy and antiangiogenic therapy provides a critical new therapeutic strategy for glioblastoma, an extremely invasive but nonmetastatic brain tumor.

3740 Autophagy Inhibition by Sustained Overproduction of IL6 Contributes to Arsenic Carcinogenesis
Yuanlin Qi, Mingfang Zhang, Hui Li, Jacqueline A. Frank, Lu Dai, Huijuan Liu, Zhuo Zhang, Chi Wang, and Gang Chen

**Précis:** Procancerous inflammatory states may antagonize autophagic states that help preserve cancer cell survival in hostile microenvironments, suggesting the need to uncouple inflammation and autophagy controls to enable tumor progression.

3753 High Expression of CAI2, a 9p21-Embedded Long Noncoding RNA, Contributes to Advanced-Stage Neuroblastoma
Lisa M. Barnhill, Richard T. Williams, Olga Cohen, Youngjin Kim, Ayse Batova, Jenna A. Mielke, Karen Messer, Minya Pu, Alice L. Yu, and Mitchell B. Diccianni

**Précis:** These findings may explain the paradoxical overexpression of tumor suppressor p16 in pediatric neuroblastomas by defining a novel long noncoding RNA that regulates p16 and may offer a biomarker for the highest-risk disease.

3764 A Regulatory Loop Involving miR-22, Sp1, and c-Myc Modulates CD147 Expression in Breast Cancer Invasion and Metastasis
Ling-Min Kong, Cheng-Gong Liao, Yang Zhang, Jing Xu, Yu Li, Wan Huang, Yi Zhang, Huijie Bian, and Zhi-Nan Chen

**Précis:** This study provides insights into the regulation of a likely driver of invasion and metastasis in breast cancer, with potential implications for prognosis and therapy of advanced forms of this common disease.

3779 hMOB3 Modulates MST1 Apoptotic Signaling and Supports Tumor Growth in Glioblastoma Multiforme
Fengyuan Tang, Lei Zhang, Gondga Xue, Debby Hynx, Yuhua Wang, Peter D. Cron, Christian Hundersucker, Alexander Hergovich, Stephan Frank, Brian A. Hemmings, and Debora Schlutz-Rohmer

**Précis:** These results identify a novel adapter-kinase complex as a candidate therapeutic target to improve the treatment of an aggressive form of brain cancer, which is characterized by inherent drug resistance.

3790 Flotillin-1 Regulates Oncogenic Signaling in Neuroblastoma Cells by Regulating ALK Membrane Association
Arata Tomiyama, Takamasa Uekita, Reiko Kamata, Kazuki Sasaki, Junko Takita, Miki Ohira, Akira Nakagawara, Chifumi Kitanaka, Kentaro Mori, Hideki Yamaguchi, and Ryuichi Sakai

**Précis:** These results define a regulator protein for a receptor tyrosine kinase implicated in neuroblastoma, with implications for understanding emergence of malignant features in this disease.

**PREVENTION AND EPIDEMIOLOGY**

3802 Telomere Shortening Is Associated with Genetic Anticipation in Chinese Von Hippel–Lindau Disease Families
Xiang-hui Ning, Ning Zhang, Teng Li, Peng-jie Wu, Xi Wang, Xue-ying Li, Shuang-he Peng, Jiang-yi Wang, Jin-chao Chen, and Kan Gong

**Précis:** A shortening in telomere length both precedes and anticipates mutation of the tumor suppressor gene VHL in cancer cells, which appears to affect telomere maintenance.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

3810 USP9X Downregulation Renders Breast Cancer Cells Resistant to Tamoxifen
Hendrika M. Oosterkamp, E. Marielle Hijmans, Thijn R. Brummelkamp, Sander Canisius, Lodewyk F.A. Wessels, Wilbert Zwart, and René Bernards

**Précis:** These findings illuminate a mechanism of resistance to a drug widely used to manage ER-positive breast cancers, and they identify a gene signature that predicts responsiveness to this drug in patients with breast cancer.

3821 Neuromedin U: A Candidate Biomarker and Therapeutic Target to Predict and Overcome Resistance to HER-Tyrosine Kinase Inhibitors
Sweta Rani, Claire Corcoran, Liam Shiels, Serena Germano, Susan Breslin, Stephen Madden, Martina S. McDermott, Brigid C. Browne, Norma O’Donovan, John Crown, Martina Gogarty, Annette T. Byrne, and Lorraine O’Driscoll

**Précis:** An extracellular protein that stabilizes the breast cancer oncoprotein HER2 may serve as a candidate biomarker for the action of HER2-targeting drugs, as well as a possible therapeutic target to improve their efficacy.
A Recombinant Reporter System for Monitoring Reactivation of an Endogenously DNA Hypermethylated Gene

Ying Cui, Frederick Hausheer, Robert Beaty, Cynthia Zahnow, Jean Pierre Issa, Frederick Bunz, and Stephen B. Baylin

Précis: These findings offer a new tool and insights for devising optimal clinical experiments to evaluate epigenetic therapies aimed at improving the management and prevention of cancer.

Monoclonal Antibody Targeting of the Cell Surface Molecule TM4SF5 Inhibits the Growth of Hepatocellular Carcinoma

Sanghoon Kwon, Kyung-Chan Choi, Young-Eun Kim, Yang-Wha Ha, Dongbum Kim, Byoung Kwon Park, Guang Wu, Doo-Sik Kim, Younghoo Lee, and Hyung-Joo Kwon

Précis: This work offers a preclinical proof of concept for a cell surface molecule expressed widely in liver cancers as an appealing target for antibody therapeutics.

Mechanisms Promoting Escape from Mitotic Stress–Induced Tumor Cell Death

Rebecca Sinnott, Leah Winters, Brittany Larson, Daniela Mytsa, Patrick Taus, Kathryn M. Cappell, and Angelique W. Whitehurst

Précis: Resistance to mitotic poisons like paclitaxel may be achieved by premature exit from mitosis, such that therapeutic strategies to enhance mitotic arrest in the presence of such poisons may restore their therapeutic benefits.

Loss of Cdk2 and Cyclin A2 Impairs Cell Proliferation and Tumorigenesis

Lakshmi Gopinathan, Shawn Lu Wen Tan, V.C. Padmakumar, Vincenzo Coppola, Lino Tesserollo, and Philipp Kaldis

Précis: These results suggest a rationale to explore cancer cell–targeted combinations of Cdk1 and Cdk2 inhibitors as a general approach for cancer therapy.

CBP-93872 Inhibits NBS1-Mediated ATR Activation, Abrogating Maintenance of the DNA Double-Strand Break–Specific G2 Checkpoint

Takahisa Hirokawa, Bunsoyo Shiotani, Midori Shimada, Kazuhiro Murata, Yoshikazu Johmura, Mayumi Haruta, Hidetoshi Tahara, Hiromitsu Takeyama, and Makoto Nakanishi

Précis: Mechanistic investigations of the drug described in this study may offer a rationale for its use to specifically sensitize p53-mutated cancer cells to chemotherapeutics that act by causing double-strand DNA damage.

Selenium Suppresses Leukemia through the Action of Endogenous Eicosanoids


Précis: These preclinical findings show how supraphysiologic but safe levels of selenium can be administered to selectively target human and murine leukemia stem-like cells, with immediate implications for clinical evaluation.

Monoclonal Antibody Targeting of the Cell Surface Molecule TM4SF5 Inhibits the Growth of Hepatocellular Carcinoma

Sanghoon Kwon, Kyung-Chan Choi, Young-Eun Kim, Yang-Wha Ha, Dongbum Kim, Byoung Kwon Park, Guang Wu, Doo-Sik Kim, Younghoo Lee, and Hyung-Joo Kwon

Précis: This work offers a preclinical proof of concept for a cell surface molecule expressed widely in liver cancers as an appealing target for antibody therapeutics.

Analysis of Chemotherapeutic Response in Ovarian Cancers Using Publicly Available High-Throughput Data

Jesus Gonzalez Bosquet, Douglas C. Marchion, HyeSook Chon, Johnathan M. Lancaster, and Stephen Chanock

Précis: By integrating diverse high-throughput biological data, this study defines a robust molecular signature that could predict the chemoresponse of patients with serous ovarian cancer, nearly a third of whom will not typically respond to chemotherapy, with implications for improving personalized care in this setting.

Say No to DMSO: Dimethylsulfoxide Inactivates Cisplatin, Carboplatin, and Other Platinum Complexes

Matthew D. Hall, Katherine A. Telma, Ki-Eun Chang, Tobie D. Lee, James P. Madigan, John R. Lloyd, Ian S. Goldlust, James D. Hoeschele, and Michael M. Gottesman

Précis: This study calls into question the conclusions of many preclinical studies using platinum drugs dissolved in DMSO, which was discovered to greatly attenuate the cytotoxic properties of these drugs.

Inactivation of p53 Is Insufficient to Allow B Cells and B-Cell Lymphomas to Survive Without Dicer

Clare M. Adams and Christine M. Eischen

Précis: This study of the contributions of microRNA biogenesis to malignant B-cell survival suggest a novel therapeutic opportunity to treat deadly B-cell lymphomas.
NDY1/KDM2B Functions as a Master Regulator of Polycomb Complexes and Controls Self-Renewal of Breast Cancer Stem Cells
Précis: A histone demethylase that influences two epigenetic complexes implicated in cancer may offer a target for future therapeutic modalities.

CDK4/6 and IGF1 Receptor Inhibitors Synergize to Suppress the Growth of p16INK4A-Deficient Pancreatic Cancers
Andreas M. Heilmann, Rushika M. Perera, Veronika Ecker, Brandon N. Nicolay, Nabeel Bardeesy, Cyril H. Benes, and Nicholas J. Dyson
Précis: A combination of targeted therapeutics with synergistic antiproliferative activity in pancreatic cancer cells lacking p16INK4A may have general implications for treating many human cancers characterized by the loss of this tumor suppressor.

Cyclin D1 Integrates Estrogen-Mediated DNA Damage Repair Signaling
Zhiping Li, Ke Chen, Xuanmao Jiao, Chenguang Wang, Nicole E. Willmarth, Mathew C. Casimiro, Weihua Li, Xiaoming Ju, Sung Hoon Kim, Michael P. Lisanti, John A. Katzenellenbogen, and Richard G. Pestell
Précis: A dissociable cytoplasmic function of cyclin D1 that delays the DNA damage response represents yet another nonnuclear feature of this cancer gene contributing to estrogen-mediated breast tumorigenesis.

Mitochondrial Retrograde Signaling Mediated by UCP2 Inhibits Cancer Cell Proliferation and Tumorigenesis
Pauline Esteves, Claire Pecqueur, Céline Ransy, Catherine Esnous, Véronique Lenoir, Frédéric Bouillaud, Anne-Laure Bulteau, Anne Lombris, Carina Prp-Buus, Daniel Ricquier, and Marie-Clotilde Alves-Guerra
Précis: These provocative findings suggest that reorienting the function of mitochondria in cancer cells to favor energy production through oxidative phosphorylation is sufficient to restrict malignant conversion.

Genome-wide Profiling of AP-1–Regulated Transcription Provides Insights into the Invasiveness of Triple-Negative Breast Cancer
Chunyan Zhao, Yichun Qiao, Philip Jonsson, Jian Wang, Li Xu, Pegah Rouhi, Indranil Sinha, Yihai Cao, Cecilia Williams, and Karin Dahlman-Wright
Précis: This study illuminates the pathways through which an aggressive subtype of breast cancer acquires invasive and proliferative properties.

The TGFβ–miR200–MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors
Evgeny Izumchenko, Xiaofei Chang, Christina Michailidi, Luciane Kagohara, Rajani Ravi, Keren Paz, Mariana Brait, Mohammad Hoque, Shizhang Ling, Atul Bedi, and David Sidransky
Précis: These results suggest a molecular metric that may predict the differential response to EGFR inhibitors in patients with tumors that express wild-type EGFR with immediate implications for clinical evaluation.

CORRECTION
Correction: Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

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ABOUT THE COVER

Cancer cells overexpressing uncoupling protein 2 (UCP2), a mitochondrial carrier, shift their metabolism from glycolysis toward oxidative phosphorylation and become less proliferative and poorly tumorigenic. Indeed, immunodeficient mice implanted subcutaneously with melanoma B16F10 cells (top) developed bigger tumors than UCP2 overexpressing B16F10 cells (bottom). Our results further demonstrate that, by controlling mitochondrial substrate routing, UCP2 drives a feed-forward loop from mitochondria to AMPK and HIF, with direct impact on the transformed phenotype of cancer cells. For details, see article by Esteves and colleagues on page 3971.