2375 Highlights from Recent Cancer Literature

Cancer Cell Lines for Drug Discovery and Development
Jennifer L. Wilding and Walter F. Bodmer

COX-2 Drives Metastatic Breast Cells from Brain Lesions into the Cerebrospinal Fluid and Systemic Circulation
Joshua E. Allen, Akshal S. Patel, Varun V. Prabhu, David T. Dicker, Jonas M. Sheehan, Michael J. Glantz, and Wafik S. El-Deiry

Précis: These important findings suggest that COX-2 inhibitors should be investigated in breast cancer patients with brain metastases as a simple immediate strategy to prevent systemic recurrence.

An Integrated Computational Model of the Bone Microenvironment in Bone-Metastatic Prostate Cancer
Arturo Araujo, Leah M. Cook, Conor C. Lynch, and David Basanta

Précis: This work establishes a computational model that can be tailored for rapid assessment of experimental therapies and delivery of precision medicine to prostate cancer patients with bone metastases.

Endothelial-Specific Notch Blockade Inhibits Vascular Function and Tumor Growth through an eNOS-Dependent Mechanism
Alexandre Patenaude, Megan Fuller, Linda Chang, Fred Wong, Grigoris Palouras, Rebecca Shaw, Alastair H. Kyle, Patricia Umlandt, Jennifer H.E. Baker, Erika Diaz, Jade Tong, Andrew I. Minchinton, and Aly Karsan

Précis: This study uncovers a novel mechanism of nitric oxide production in endothelial cells in tumors, with implications for understanding the peculiar character of tumor blood vessels.

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SWI/SNF Factors Required for Cellular Resistance to DNA Damage Include ARID1A and ARID1B and Show Interdependent Protein Stability
Reiko Watanabe, Ayako Ui, Shin-ichiro Kanno, Hideaki Ogiwara, Takahiro Nagase, Takashi Kohno, and Akira Yasui

Preceding: Cancer cells lacking in the expression of SWI/SNF transcription factors are deficient in DNA repair and potentially vulnerable to DNA damage, with implications for predicting cytotoxic drug responses and addressing resistance.

PREVENTION AND EPIDEMIOLOGY

Telomere Length in Peripheral Blood Leukocytes and Lung Cancer Risk: A Large Case–Control Study in Caucasians
Beatriz Sanchez-Espiridion, Meng Chen, Joe Y. Chang, Charles Lu, David W. Chang, Jack A. Roth, Xifeng Wu, and Jian Gu

Preceding: This large epidemiologic study addresses a controversy concerning an association between telomere length in peripheral blood leukocytes and lung cancer susceptibility, revealing that risk is associated differentially with different histologic subtypes.

Curcumin Promotes Autophagic Survival of a Subset of Colon Cancer Stem Cells, Which Are Ablated by DCLK1-siRNA
Carla Kantara, Malaney O'Connell, Shubhashish Sarkar, Stephanie Moya, Robert Ulrich, and Pomila Singh

Preceding: These interesting findings suggest a use for the spice curcumin, which has chemopreventive properties for colon cancer, by combining it with therapies that target colon cancer stem-like cells to promote more durable remissions in this setting.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Activation of the Glutamate Receptor GRM1 Enhances Angiogenic Signaling to Drive Melanoma Progression
Yu Wen, Jiadong Li, Jasmine Koo, Seung-Shick Shin, Yong Lin, Byeong-Seon Jeong, Janice M. Mehnert, Suzie Chen, Karine A. Cohen-Sola, and James S. Goydos

Preceding: These findings offer a mechanistic rationale for combinatorial therapy of melanoma with GRM1 inhibitors, with immediate implications on trial designs for the clinical development of this class of antimetabolic agents.
Curative Properties of Noninternalizing Antibody–Drug Conjugates Based on Maytansinoids

Elena Perrino, Martina Steiner, Nikolaus Krall, Gonçalo J.L. Bernarde, Francesca Pretto, Giulio Casi, and Dario Neri

Précis: This study offers the first preclinical demonstration that antibody-drug conjugates targeting the microenvironment can be fully curative and that cancer cell internalization is not necessary for the efficacy of this emerging class of cancer therapeutics.

STAT3-Mediated Autophagy Dependence Identifies Subtypes of Breast Cancer Where Autophagy Inhibition Can Be Efficacious

Paola Maycotte, Christy M. Gearheart, Rebecca Barnard, Suraj Aryal, Jean M. Mulcahy Levy, Susan P. Fosmire, Ryan J. Hansen, Michael J. Morgan, Christopher C. Porter, Daniel L. Gustafson, and Andrew Thorburn

Précis: This study shows how STAT3 makes triple-negative breast cancer cells dependent on autophagy for survival, even in nutrient-rich conditions, implicating this factor as a marker for autophagy addiction and efficacious responses to autophagy inhibitors.

Survival in Patients with High-Risk Prostate Cancer Is Predicted by miR-221, Which Regulates Proliferation, Apoptosis, and Invasion of Prostate Cancer Cells by Inhibiting IRF2 and SOCS3

Burkhard Kneitz, Markus Krebs, Charis Kalogirou, Maria Schubert, Steven Joniau, Hein van Poppel, Evelyne Lerut, Susanne Kneitz, Claus Jürgen Scholz, Christian Thiele, Manfred Gessler, Hubertus Riedmiller, and Martin Spahn

Précis: These results identify a microRNA with significant potential as a prognostic biomarker and therapeutic target for improving clinical management of patients with aggressive prostate cancer.

GRHL1 Acts as Tumor Suppressor in Neuroblastoma and Is Negatively Regulated by MYCN and HDAC3

Johannes Fabian, Marco Lodrini, Ina Oehme, Marie C. Schier, Theresa M. Thole, Thomas Hiescher, Annette Kopp-Schneider, Lennart Opitz, David Capper, Andreas von Deimling, Inga Wießand, Till Milde, Ulrich Mahlknecht, Frank Westermann, Odilia Popanda, Frederik Roels, Barbara Hero, Frank Berthold, Matthias Fischer, Andreas E. Kulozik, Olaf Witt, and Hedwig E. Deubzer

Précis: These findings suggest a new avenue of therapeutic intervention in neuroblastoma based on the application of small molecule inhibitors of histone deacetylases.

Mechanistic Elucidation of the Antitumor Properties of Withaferin A in Breast Cancer

Arumugam Nagalingam, Panjamurthy Kuppusamy, Shivendra V. Singh, Dipali Sharma, and Neeraj K. Saxena

Précis: These findings reveal the key nodes of Withaferin A action in breast cancer to establish surrogate biomarkers for its efficacy and help in clinical development of this bioactive molecule.

CD44v8-10 Is a Cancer-Specific Marker for Gastric Cancer Stem Cells

Wen Min Lau, Eileen Teng, Hui Shan Chong, Kirsten Anne Pagaduan Lopez, Amy Yuh Ling Tay, Manuel Salto-Tellez, Asim Shabbir, Jimmy Bok Yan So, and Shing Leng Chan

Précis: This study defines a variant form of the common stem cell marker CD44 with properties that may make it superior for practical clinical use in targeting cancer stem-like cells, with important therapeutic implications.

Genetic Suppression of Inflammation Blocks the Tumor-Promoting Effects of TGF-β in Gastric Tissue

Mitsuhiko Ota, Masahito Horiguchi, Victoria Fang, Kotaro Shibahara, Kyuichi Kadoya, Cynthia Loomis, Michael Cammer, and Daniel B. Rifkin

Précis: Genetic ablation of adaptive immunity eliminates the development of tumors in a mouse model of gastric cancer driven by TGF-β hypomorphism, highlighting the critical contribution of inflammation to TGF-β-mediated tumorigenesis.

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ABOUT THE COVER

Aberrant expression of the T-box transcription factor brachyury in human carcinomas drives the phenomenon of epithelial-mesenchymal transition (EMT), a phenotypic modulation that facilitates tumor dissemination and resistance to conventional anti-neoplastic therapies. Hamilton and colleagues show that acquisition of a mesenchymal-like phenotype could also significantly reduce the susceptibility of cancer cells to lysis by both antigen-specific T cells and natural killer cells. This defect was observed even in the presence of a stable engagement between the immune effector cells and the tumor cells, as demonstrated by the effective polar actin polymerization observed at the interacting surface area. The phenomenon of immune resistance of mesenchymal-like cells was correlated to their decreased levels of cell cycle kinase CDK1, a defect that could be countered by treatment with a specific inhibitor of WEE1. For details, see article by Hamilton and colleagues on page 2510.
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