Cancer Research

Table of Contents

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BREAKING ADVANCES

399 **Highlights from Recent Cancer Literature**

REVIEWS

401 **Urinary Tobacco Smoke–Constituent Biomarkers for Assessing Risk of Lung Cancer**
Jian-Min Yuan, Lesley M. Butler, Irina Stepanov, and Stephen S. Hecht

412 **ERKs in Cancer: Friends or Foes?**
Xavier Deschênes-Simard, Filippos Kottakis, Sylvain Meloche, and Gerardo Ferbeyre

420 **Bookmarking Target Genes in Mitosis: A Shared Epigenetic Trait of Phenotypic Transcription Factors and Oncogenes?**
Sayyed K. Zaidi, Rodrigo A. Grandy, Cesar Lopez-Camacho, Martin Montecino, Andre J. van Wijnen, Jane B. Lian, Janet L. Stein, and Gary S. Stein

INTEGRATED SYSTEMS AND TECHNOLOGIES

426 **Bridging Population and Tissue Scale Tumor Dynamics: A New Paradigm for Understanding Differences in Tumor Growth and Metastatic Disease**
Jill Gallaher, Aravind Babu, Sylvia Plevritis, and Alexander R.A. Anderson

Précis: *Vascular response is a primary cause of the differences in rates of tumor growth and metastatic disease in two of the most common cancers.*

MICROENVIRONMENT AND IMMUNOLOGY

436 **CCL2/CCR2-Dependent Recruitment of Functional Antigen-Presenting Cells into Tumors upon Chemotherapy**
Yuting Ma, Stephen R. Mattarollo, Sandy Adjemian, Heng Yang, Laetitia Aymeric, Dalil Hannani, João Paulo Portela Catani, Helene Duret, Michele W.L. Teng, Oliver Kepp, Yidan Wang, Antonella Sistigu, Joachim L. Schultze, Gautier Stoll, Lorenzo Galluzzi, Laurence Zitvogel, Mark J. Smyth, and Guido Kroemer

Précis: *These findings illustrate the importance of CCL2/CCR2 signaling pathways for immunogenic chemotherapeutics to elicit their antitumor effects, suggesting risks that CCL2/CCR2 targeting strategies being tested clinically may actually worsen clinical outcomes in cancer patients.*

446 **Immune Chaperone gp96 Drives the Contributions of Macrophages to Inflammatory Colon Tumorigenesis**
Crystal Morales, Saleh Rachidi, Feng Hong, Shaoli Sun, Xinshou Ouyang, Caroline Wallace, Yongliang Zhang, Elizabeth Garret-Mayer, Jennifer Wu, Bei Liu, and Zihai Li

Précis: *By using a macrophage-specific gene knockout mouse, this important study reveals how tumor-associated macrophages not only orchestrate local inflammation but also cell mutagenesis to drive the development of colon cancer.*

460 **MUC1 in Macrophage: Contributions to Cigarette Smoke–Induced Lung Cancer**
Xiuling Xu, Mabel T. Padilla, Bilan Li, Alexandria Wells, Kosuke Kato, Carmen Tellez, Steven A. Belinsky, Kwang Chul Kim, and Yong Lin

Précis: *These results shed light on the mechanisms of inflammation-associated lung carcinogenesis, showing how cigarette smoke promotes contributions from lung macrophages in the tissue microenvironment to promote lung cancer.*

471 **Defective TGF-β Signaling in Bone Marrow–Derived Cells Prevents Hedgehog-Induced Skin Tumors**
Qipeng Fan, Dongsheng Gu, Hailan Liu, Ling Yang, Xiaoli Zhang, Mervin C. Yoder, Mark H. Kaplan, and Jingwu Xie

Précis: *Dysregulation of the Hedgehog pathway in cancer cells drives the formation of a supportive microenvironment, by stimulating a core mechanism of support for the development of myeloid-derived suppressor cells.*

MOLECULAR AND CELLULAR PATHOBIOLOGY

484 **Cyclophilin B Supports Myc and Mutant p53-Dependent Survival of Glioblastoma Multiforme Cells**
Jae Won Choi, Mark A. Schroeder, Jann N. Sarkaria, and Richard J. Bram

Précis: *These results define the protein chaperone cyclophilin B as a promising molecular target for treatment of glioblastoma multiforme, with immediate clinical implications for repositioning the approved drug cyclosporin as a potential therapeutic to treat this aggressive malignancy.*

Table of Contents

497 **IRP2 Regulates Breast Tumor Growth**
Wei Wang, Zhiyong Deng, Heather Hatcher, Lance D. Miller, Xiumin Di, Lia Tesfay, Guangchao Sui, Ralph B. D'Agostino Jr, Frank M. Torti, and Suzy V. Torti

Précis: *These results reveal a new pathway of iron dysregulation in breast cancer and identify IRP2, a master regulator of intracellular iron homeostasis, as an important driver of breast cancer growth.*

508 **Identification of a *Cyclin D1* Network in Prostate Cancer That Antagonizes Epithelial–Mesenchymal Restraint**
Xiaoming Ju, Mathew C. Casimiro, Michael Gormley, Hui Meng, Xuanmao Jiao, Sanjay Katiyar, Marco Crosariol, Ke Chen, Min Wang, Andrew A. Quong, Michael P. Lisanti, Adam Ertel, and Richard G. Pestell

Précis: *This study reveals a novel function for cyclin D1 in mediating the expansion of prostate stem cells that contribute to prostate cancer.*

520 **CUL4A Induces Epithelial–Mesenchymal Transition and Promotes Cancer Metastasis by Regulating ZEB1 Expression**
Yunshan Wang, Mingxin Wen, Yongwon Kwon, Yangyang Xu, Yueyong Liu, Pengju Zhang, Xiuquan He, Qin Wang, Yurong Huang, Kuang-Yu Jen, Mark A. LaBarge, Liang You, Scott C. Kogan, Joe W. Gray, Jian-Hua Mao, and Guangwei Wei

Précis: *These findings suggest a pivotal role for the oncogenic ubiquitin ligase CUL4A in regulating the metastatic behavior of breast cancer cells, with implications for therapeutic targeting of the pathway it regulates.*

532 **p53-Induced miR-15a/16-1 and AP4 Form a Double-Negative Feedback Loop to Regulate Epithelial–Mesenchymal Transition and Metastasis in Colorectal Cancer**
Lei Shi, Rene Jackstadt, Helge Siemens, Huihui Li, Thomas Kirchner, and Heiko Hermeking

Précis: *This mechanistic study sheds new light on opposing circuitries of control for mesenchymal and epithelial states in cancer cells, the balance of which may influence invasive migration and metastasis.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

543 **Circadian Regulation of mTOR by the Ubiquitin Pathway in Renal Cell Carcinoma**
Hiroyuki Okazaki, Naoya Matsunaga, Takashi Fujioka, Fumiyasu Okazaki, Yui Akagawa, Yuuya Tsurudome, Mayumi Ono, Michihiko Kuwano, Satoru Koyanagi, and Shigehiro Ohdo

Précis: *This important study shows how a pivot cell growth regulator is controlled by circadian clock systems, with significant therapeutic implications.*

552 **Blocking eIF5A Modification in Cervical Cancer Cells Alters the Expression of Cancer-Related Genes and Suppresses Cell Proliferation**
Elisabeth Mémin, Mainul Hoque, Mohit R. Jain, Debra S. Heller, Hong Li, Bernadette Cracchiolo, Hartmut M. Hanauske-Abel, Tsafi Pe'ery, and Michael B. Mathews

Précis: *These findings suggest a mechanistic rationale to immediately reposition two approved drugs for cancer treatment, offering a low-risk clinical opportunity to evaluate new therapeutic modalities for cancer treatment.*

563 **Novel Mechanism of MDA-7/IL-24 Cancer-Specific Apoptosis through SARI Induction**
Rupesh Dash, Praveen Bhoopathi, Swadesh K. Das, Siddik Sarkar, Luni Emdad, Santanu Dasgupta, Devanand Sarkar, and Paul B. Fisher

Précis: *These findings define a signaling axis in cancer-specific killing that suggests a strategy to treat both local and metastatic disease.*

575 **Small Molecule Agonists of PPAR-γ Exert Therapeutic Effects in Esophageal Cancer**
Hiroshi Sawayama, Takatsugu Ishimoto, Masayuki Watanabe, Naoya Yoshida, Hidetaka Sugihara, Junji Kurashige, Kotaro Hirashima, Masaaki Iwatsuki, Yoshifumi Baba, Eiji Oki, Masaru Morita, Yoshinobu Shiose, and Hideo Baba

Précis: *A new-generation small molecule agonist of PPAR-γ that is more selective than existing agents may offer a novel route to treat esophageal squamous cancers, with immediate implications for clinical translation.*

586 **Preclinical Therapeutic Efficacy of a Novel Pharmacologic Inducer of Apoptosis in Malignant Peripheral Nerve Sheath Tumors**
Vincent Chau, S. Kyun Lim, Wei Mo, Chiachi Liu, Amish J. Patel, Renée M. McKay, Shuguang Wei, Bruce A. Posner, Jef K. De Brabander, Noelle S. Williams, Luis F. Parada, and Lu Q. Le

Précis: *Using a robust new model of malignant peripheral nerve sheath tumors that recapitulates features of the human malignancy, this study identified a novel proapoptotic small molecule that inhibits tumor cell growth.*

598 ***MDR1* Synonymous Polymorphisms Alter Transporter Specificity and Protein Stability in a Stable Epithelial Monolayer**
King Leung Fung, James Pan, Shinobu Ohnuma, Paul E. Lund, Jessica N. Pixley, Chava Kimchi-Sarfaty, Suresh V. Ambudkar, and Michael M. Gottesman

Précis: *Synonymous "silent" polymorphisms in the multiple drug resistance gene can nonetheless alter the function of the gene product and drive chemotherapeutic resistance.*

Table of Contents

TUMOR AND STEM CELL BIOLOGY

609 **FGFR1–WNT–TGF-β Signaling in Prostate Cancer Mouse Models Recapitulates Human Reactive Stroma**
Julienne L. Carstens, Payam Shahi, Susan Van Tsang, Billie Smith, Chad J. Creighton, Yiqun Zhang, Amber Seamans, Mamatha Seethammagari, Indira Vedula, Jonathan M. Levitt, Michael M. Ittmann, David R. Rowley, and David M. Spencer

Précis: *Targeting the reactive stroma in aggressive prostate adenocarcinoma may generate a two-pronged attack that is more efficacious, by attacking cancer cells as well as the critical stromal tissue driving their outgrowth.*

621 **PPARα Activation Can Help Prevent and Treat Non–Small Cell Lung Cancer**
Nataliya Skrypnyk, Xiwu Chen, Wen Hu, Yan Su, Stacey Mont, Shilin Yang, Mahesha Gangadhariah, Shouzuo Wei, John R. Falck, Jawahar Lal Jat, Roy Zent, Jorge H. Capdevila, and Ambra Pozzi

Précis: *This important study provides a preclinical proof-of-concept for administering clinically approved PPARα agonists to treat lung cancer, with immediate implications to reposition an existing drug treatment that is well tolerated and may be highly efficacious in this setting.*

LETTERS TO THE EDITOR

632 **Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors—Letter**
David C. Binder and Hans Schreiber

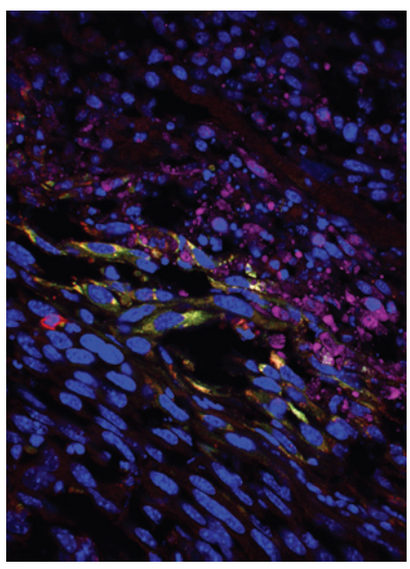
633 **Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors—Response**
Jaikumar Duraiswamy, Gordon J. Freeman, and George Coukos

635 **Editors' Viewpoint—Response**
Mario P. Colombo and George C. Prendergast

CORRECTIONS

636 **Correction: A Single-Nucleotide Substitution Mutator Phenotype Revealed by Exome Sequencing of Human Colon Adenomas**

637 **Correction: Neuropilin-2 Is Upregulated in Lung Cancer Cells during TGF-β1–Induced Epithelial–Mesenchymal Transition**

ABOUT THE COVER

Anthracycline-based chemotherapy promotes the recruitment of CD11c$^+$ (green) CD86$^+$ (red) dendritic cells in close proximity to Caspase 3a$^+$ (magenta) dying tumor cells. This process relies on "eat me" signal ATP and CCL2/CCR2 chemotactic axis. For details, see the article by Ma and colleagues on page 436 of this issue.