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

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436 CCL2/CCR2-Dependent Recruitment of Functional Antigen-Presenting Cells into Tumors upon Chemotherapy

446 Immune Chaperone gp96 Drives the Contributions of Macrophages to Inflammatory Colon Tumorigenesis
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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

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

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.
Identification of a **Cyclin D1** Network in Prostate Cancer That Antagonizes Epithelial–Mesenchymal Transition and Promotes Cancer Metastasis by Regulating ZEB1 Expression

Xiaoming Ju, Mathew C. Casimiro, Michael Gormley, Hui Meng, Xuanmao Jiao, Sanjay Katiyar, Marco Crusario, 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.

**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, Xiuxuan 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 oncopgenic ubiquitin ligase CUL4A in regulating the metastatic behavior of breast cancer cells, with implications for therapeutic targeting of the pathway it regulates.

**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, Huichi Li, Thomas Kirchner, and Heiko Hermeking

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

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**Therapeutics, Targets, and Chemical Biology**

**Circadian Regulation of mTOR by the Ubiquitin Pathway in Renal Cell Carcinoma**

Hiroyuki Okazaki, Naoya Matsunaga, Takashi Fujioka, Fumiyasu Okazaki, Yui Akagawa, Yuyu 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.

**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 Crucchiolo, Hartmut M. Hanuske-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.

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**Small Molecule Agonists of PPAR-γ Exert Therapeutic Effects in Esophageal Cancer**

Hiroshi Sawayaama, Takatsugu Ishimoto, Masayuki Watanabe, Naoya Yoshida, Hidetaka Sugihara, Junji Kurashige, Kotaro Hirashima, Masaaki Iwatsuki, Yoshifumi Baba, Eiji Oki, Masaru Morita, Yoshinobu Shiobe, 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.

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**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.
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

Anthracine-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.
Cancer Research

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