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### MOLECULAR AND CELLULAR PATHOBIOLOGY

**6142**

**Distinct Patterns of Dysregulated Expression of Enzymes Involved in Androgen Synthesis and Metabolism in Metastatic Prostate Cancer Tumors**

Nicholas Mitsiades, Clifford C. Sung, Nikolaus Schultz, Daniel C. Danila, Bin He, Vijay Kumar Eedunuri, Martin Fleisher, Chris Sander, Charles L. Sawyer, and Howard I. Scher

*Précis:* Metastatic prostate carcinomas exhibit heterogeneous and distinct patterns of dysregulated expression of enzymes involved in androgen metabolism, which can contribute to the maintenance of intratumoral androgens and AR transcriptional activity despite castrate serum levels of testosterone.

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**6153**

**Geminin Functions Downstream of p53 in K-ras–Induced Gene Amplification of Dihydrofolate Reductase**

Ling Shen, Takashi Nishioka, Jinjin Guo, and Changyan Chen

*Précis:* Findings provide insight into the mechanistic relationship between ras mutations and gene amplification, which occur in more than 30% of all human malignancies.

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### PREVENTION AND EPIDEMIOLOGY

**6163**

**An Insertion/Deletion Polymorphism within RERT-lncRNA Modulates Hepatocellular Carcinoma Risk**

Zhansheng Zhu, Xueren Gao, Yan He, Hua Zhao, Qiang Yu, Deke Jiang, Pingzhao Zhang, Xiaopin Ma, Huixing Huang, Dong Dong, Jiao Wan, Zhenyong Gu, Xinghong Jiang, Long Yu, and Yuzhen Gao

*Précis:* An insertion/deletion polymorphism in a novel long non-coding RNA influences liver cancer risk and affects expression of a prolyl hydroxylase for the hypoxia regulatory factor HIF-1α.

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**6173**

**Genetic Variants in miRNAs Predict Bladder Cancer Risk and Recurrence**

Melin Wang, Haiyan Chu, Pu Li, Lin Yuan, Guangbo Fu, Lan Ma, Danni Shi, Dongyan Zhong, Na Tong, Chao Qin, Changjun Yin, and Zhengdong Zhang

*Précis:* MicroRNA variations in human populations may represent important sources of cancer risk and recurrence, but they are only beginning to be probed as potential theranostic markers.

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### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**6183**

**Contributions of Recent and Past Sexual Partnerships on Incident Human Papillomavirus Detection: Acquisition and Reactivation in Older Women**

Anne F. Rositch, Anne E. Burke, Raphael P. Viscidi, Michelle L. Silver, Kathryn Chang, and Patti E. Gravitt

*Précis:* Most incident HPV infection appears to be attributable to past sexual behavior at older ages, supporting a natural history model of viral latency and reactivation, which must be considered in developing recommendations for cervical cancer screening, as more highly exposed women transition through menopause in coming decades.

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**6191**

**Ultrasound-Targeted Microbubble Destruction to Deliver siRNA Cancer Therapy**

Andrew R. Carson, Charles F. McTiernan, Linda Laverty, Michelle Grata, Xiaoping Leng, Jianjun Wang, Xucai Chen, and Flordeliza S. Villanueva

*Précis:* This study addresses the need for pharmacological strategies to effectively target therapeutic siRNA to tumors for cancer therapy.

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**6200**

**Targeting the Transposase Domain of the DNA Repair Component Metnase to Enhance Chemotherapy**

Elizabeth A. Williamson, Leah Damiani, Andrei Leitao, Chelin Hu, Helen Hathaway, Tudor Oprea, Larry Sklar, Montaser Shaheen, Julie Bauman, Wei Wang, Jac A. Nickoloff, Suk-Hee Lee, and Robert Hromas

*Précis:* Findings suggest that an approved antibiotic drug might be immediately repositioned to enhance the effectiveness of DNA-damaging chemotherapies used widely as first-line treatment of metastatic cancer.

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**6209**

**Augmentation of Therapeutic Responses in Melanoma by Inhibition of IRAK-1,-4**

Ratika Srivastava, Degui Geng, Yingjia Liu, Lixin Zheng, Zhaoqiang Li, Mary Ann Joseph, Colleen McKenna, Navneeta Bansal, Augusto Ochoa, and Eduardo Davila

*Précis:* Toll-like receptors are thought to operate as proinflammatory receptors in immune cells, but this study lends credence to the idea that their frequent overexpression on cancer cells also has functional import, with potential prognostic and therapeutic implications.
Raf Kinase Inhibitor RKIP Inhibits MDA-9/Syntenin-Mediated Metastasis in Melanoma


Précis: This study provides mechanistic insights into an important pathway of metastasis in melanoma, one of the most aggressive cancers, possibly stimulating new therapeutic strategies to block or reverse this process in patients.

Oxidative Stress-Regulated Lentiviral TK/GCV Gene Therapy for Lung Cancer Treatment


Précis: This study provides proof-of-concept for use of a modified lentiviral-mediated gene therapy to destroy lung tumors, where expression of the therapeutic gene is controlled by a powerful antioxidant response element that is strongly upregulated in the cancer cells.

A Novel Evolutionarily Conserved Element Is a General Transcriptional Repressor of p21WAF1/CIP1

Weiguo Xu, Qi Zhu, Zhenghua Wu, Hao Guo, Fengjuan Wu, Dhahiiri S. Masahausi, Chengjie Zheng, and Dawei Li

Précis: The study revealed that a low level expression of the tumor suppressor p21 is maintained by an evolutionarily-conserved repression element that can be turned "off" by selected chemotherapeutic drugs to slow cancer growth.

Halofuginone Inhibits the Establishment and Progression of Melanoma Bone Metastases

Patricia Juarez, Khalid S. Mohammad, Juan Juan Yin, Pierrick G. J. Fournier, Ryan C. McKenna, Holly W. Davis, Xiang H. Peng, Maria Niewolna, Delphine Javelaud, John M. Chirgwin, Alain Mauviel, and Theresa A. Guise

Précis: A natural product that activates the integrated stress response and modulates TpL7 immunity is shown here to block TGF-β induced signals that drive bone and brain metastasis in melanoma, suggesting therapeutic applications of this compound for therapy of advanced forms of this disease.

Carbon Source and Myc Expression Influence the Antiproliferative Actions of Metformin

Shiva Javeshghani, Mahvash Zakikhani, Shane Austin, Miguel Bazile, Marie-José Blouin, Ivan Topisirovic, Julie St-Pierre, and Michael N. Pollak

Précis: Our studies provide new insight into factors that define the subset of cancers whose growth may be inhibited by the antidiabetic drug meformin.

Epithelial-to-Mesenchymal Transition Induced by TGF-β1 Is Mediated by Blimp-1–Dependent Repression of BMP-5

Mathilde Romagnoli, Karine Belguise, Ziyang Yu, Xiaobo Wang, Esther Landesman-Bollag, David C. Seldin, Dany Chaibos, Sophie Barillé-Nion, Pascal Jérémie, Margaret L. Seldin, and Gail E. Sonenshein

Précis: An important B cell regulatory factor identified as a key Ras effector is found to connect Ras and TGF-β signaling pathways, which coordinate EMT in cancer cells, a hallmark of invasion and metastatic behavior.

A Single-Nucleotide Substitution Mutator Phenotype Revealed by Exome Sequencing of Human Colon Adenomas


Précis: This important study suggests that precancerous lesions have already evolved a mutator phenotype that can drive malignant progression and also reveals mechanistic insights into how point mutations accumulate.

Acknowledgment to Reviewers
ABOUT THE COVER

A mutator phenotype revealed in colon adenomas. Point mutations identified by exome sequencing are indicated as green dots in vertical columns. Loss of heterozygosity targeting chromosome 5 in one of these adenomas is shown by the blue circles forming horizontal lines. This matrix of data formed the basis for determining mutation rates in normal colon tissue and in precancerous adenoma lesions, revealing the presence of a mutator phenotype in the latter. For details, please see the article by Nikolaev and colleagues on page 6279.
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