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Précis: Loss of a protein that helps organize lipid rafts on the plasma membrane reduces cancerous cell growth, with possible implications for a generalized approach to cancer targeting.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6463  Histone H1.3 Suppresses H19 Noncoding RNA Expression and Cell Growth of Ovarian Cancer Cells
Magdalena Medrzycki, Yunzhe Zhang, Weijia Zhang, Kaixiang Cao, Chenyi Pan, Nathalie Lailler, John F. McDonald, Eric E. Bouhassira, and Yuhong Fan

Précis: These results provide new information about the regulation of a noncoding RNA in ovarian cancer cells, advancing work in a timely new area of RNA physiology and cancer.

6474  Oncogenic Properties of a Spermatogenic Meiotic Variant of Fer Kinase Expressed in Somatic Cells
Etai Yaffe, Elad Hikri, Yoav Elkis, Ortal Cohen, Ariela Segal, Adar Makovski, Alexander Varvak, Sally Shpungin, and Uri Nir

Précis: This provocative study reveals a molecular alteration in the mitochondria of cancer cells that may represent a common pathophysiological root, with possible implications for broad-based treatments.

6486  BRG1/SMARCA4 Inactivation Promotes Non–Small Cell Lung Cancer Aggressiveness by Altering Chromatin Organization
Tess Orvis, Austin Hepperla, Vonn Walter, Shuie Song, Jeremy Simon, Joel Parker, Matthew D. Wilkerson, Nisarg Desai, Michael B. Major, D. Neil Hayes, Ian J. Davis, and Bernard Weissman

Précis: These results offer direct evidence of a tumor suppressor role for a core ATPase found in SWI/SNF chromatin regulatory complexes, the inactivation of which contributes to lung cancer aggressiveness by altering nucleosome positioning and expression at many cancer-associated genes.

6499  Deubiquitination of γ-Tubulin by BAP1 Prevents Chromosome Instability in Breast Cancer Cells
Reihaneh Zarrizi, Julien Albert Menard, Mattias Belting, and Ramin Massoumi

Précis: These findings illuminate a core mechanism preventing genomic instability, with implications for understanding malignant progression.

6509  The Notch Pathway Inhibits TGFβ Signaling in Breast Cancer through HEY1-Mediated Crosstalk
Liangfeng Han, Adam Diehl, Nguyen K. Nguyen, Preethi Korangath, Weiwen Teo, Soonweng Cho, Scott Komirinsky, David L. Huso, Lionel Feigenbaum, Alan Rein, Pedram Argani, Goran Landberg, Manfred Gessler, and Saraswati Sukumar

Précis: These findings identify a particular mechanism of TGFβ signaling as a key element in the development of drug resistance in breast cancer.

6519  STAT1 Drives Tumor Progression in Serous Papillary Endometrial Cancer
Budiman Kharma, Tsukasa Baba, Noriomi Matsumura, Hyun Sook Kang, Junzo Hamanishi, Ryusuke Murakami, Melissa M. McConkey, Samuel Leung, Ken Yamaguchi, Yuko Hosoe, Yumiko Yoshioka, Susan K. Murphy, Masaki Mandai, David G. Huntsman, and Ikuo Konishi

Précis: This study identifies a molecular signature and root oncogenic driver of serous papillary endometrial cancer, a relatively rare and poorly characterized form of uterine cancer that arises in post-menopausal women, with implications for improving its prognosis and treatment.

6531  IGF2 Preserves Osteosarcoma Cell Survival by Creating an Autophagic State of Dormancy That Protects Cells against Chemotherapeutic Stress

Précis: This study provides a mechanistic rationale for blunting IGF/insulin-mediated survival signals in osteosarcoma, a pediatric tumor notorious for its intrinsic therapeutic resistance, as a strategy to improve treatment outcomes.
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**CtBP2 Modulates the Androgen Receptor to Promote Prostate Cancer Progression**  
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**Précis:** A transcriptional co-repressor linked to prostate cancer susceptibility is found here to be an androgen-regulated gene that modulates pro-cancerous downstream signals from the androgen receptor.

### 6554

**Genetic Evidence of a Precisely Tuned Dysregulation in the Hypoxia Signaling Pathway during Oncogenesis**  

**Précis:** These findings offer evidence in humans to validate the "continuum" model of tumor suppression, advancing work beyond the mouse in developing a successor to the classic "two-hit" model in the field.

### 6565

**In Vivo Disruption of an Rb–E2F–Ezh2 Signaling Loop Causes Bladder Cancer**  
Mirentxu Santos, Mónica Martínez-Fernández, Marta Dueñas, Ramón García-Escudero, Begona Alfaya, Felipe Villacampa, Cristina Saiz-Ladera, Clotilde Costa, Marta Oteo, José Duarte, Victor Martínez, Mª José Gómez-Rodríguez, Mª Luisa Martín, Manoli Fernández, Patrick Viator, Miguel A. Morcillo, Julien Sage, Daniel Castellano, Jose L. Rodriguez-Peralto, Federico de la Rosa, and Jesús M Paramio

**Précis:** This study addresses a gap in knowledge concerning the genetic and epigenetic underpinnings of bladder cancer development, which still remain relatively obscure.

### 6578

**Suppression of Deacetylase SIRT1 Mediates Tumor-Suppressive NOTCH Response and Offers a Novel Treatment Option in Metastatic Ewing Sarcoma**  

**Précis:** These findings offer a mechanistic rationale for the use of pharmacological inhibitors of a p53 deacetylase to treat cancers in which NOTCH acts a tumor suppressor.

### PREVENTION AND EPIDEMIOLOGY

### 6589

**High Serum Iron Is Associated with Increased Cancer Risk**  
Chi Pang Wen, June Han Lee, Ya-Ping Tai, Christopher Wen, Shuian Be Wu, Min Kuang Tsai, Dennis P.H. Hsieh, Hung-Che Chiang, Chao Agnes Hsiung, Chung Y. Hsu, and Xi Feng Wu

**Précis:** This large cohort study reveals that high levels of iron in blood serum is a risk marker for a variety of adult cancer, most dramatically in conferring a 3-fold increased risk for liver cancer.

### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

### 6598

**Microenvironment-Derived HGF Overcomes Genetically Determined Sensitivity to Anti-MET Drugs**  
Selma Pennacchietti, Manuela Cazzanti, Andrea Bertotti, William M. Rideout III, May Han, Jeno Gyuris, Timothy Perera, Paolo M. Comoglio, Livio Trusolino, and Paolo Michieli

**Précis:** This study offers preclinical proof of concept for the use of antibodies that neutralize hepatocyte growth factor along with MET-targeting agents as a more effective therapeutic strategy to treat MET-dependent tumors.

### 6610

**Targeting Cancer Stem–like Cells as an Approach to Defeating Cellular Heterogeneity in Ewing Sarcoma**  
Sandrine Cornaz-Buros, Nicolo Riggi, Claudio DeVito, Alexandre Sarre, Igor Letovanec, Paolo Provero, and Ivan Stamenkovic

**Précis:** These results suggest a broadly and immediately applicable approach to improve the treatment of solid tumors that are marked by extensive cellular heterogeneity, likely driven by the plastic nature of cancer stem-like cells, with immediate applications for clinical evaluation.
6623 MPHOSPH1: A Potential Therapeutic Target for Hepatocellular Carcinoma
Xinran Liu, Yafan Zhou, Xinyuan Liu, Anlin Peng, Hao Gong, Lizi Huang, Kaige Ji, Robert B. Petersen, Ling Zheng, and Kun Huang
Précis: These results highlight a critical role for a mitotic kinesin as a critical oncogenic driver and candidate therapeutic target in liver cancer.

6635 Plk1 Inhibition Enhances the Efficacy of Androgen Signaling Blockade in Castration-Resistant Prostate Cancer
Zhe Zhang, Xianzeng Hou, Chen Shao, Junjie Li, Ji-Xin Cheng, Shihuan Kuang, Nihal Ahmad, Timothy Ratliff, and Xiaoqi Liu
Précis: These results offer a mechanistic rationale for evaluating Plk1 inhibitors in clinical development to enhance the efficacy of androgen signaling inhibitors in patients with castration-resistant prostate cancer.

TUMOR AND STEM CELL BIOLOGY

6648 MicroRNA100 Inhibits Self-Renewal of Breast Cancer Stem–like Cells and Breast Tumor Development
Lu Deng, Li Shang, Shoumin Bai, Ji Chen, Xueyan He, Rachel Martin-Trevino, Shanshan Chen, Xiaoyan Li, Xiaojo Meng, Bin Yu, Xiaolin Wang, Yajing Liu, Sean P. McDermott, Alexa E. Ariazi, Christophe Ginestier, Ingrid Ibarra, Jia Ke, Tahra Luther, Shawn G. Clouthier, Lianbo Wang, Ge Shan, Erwei Song, Herui Yao, Gregory J. Hannon, Stephen J. Weiss, Max S. Wicha, and Suling Liu
Précis: These studies provide insight into the mechanisms by which a microRNA gene regulates the self-renewal and tumor-forming potential of cancer stem-like cells, suggesting therapeutic applications for this microRNA in identifying and targeting these cells for cancer treatment.

6661 RABL6A Promotes G1–S Phase Progression and Pancreatic Neuroendocrine Tumor Cell Proliferation in an Rb1-Dependent Manner
Jussara Hagen, Adeline C. Nordman, Linda B. Rosenblatt, Yuhua Xu, Cindy B. Pendergrass, Robert D. Glazer, Ryan W. Askeland, Andrew M. Bellizzi, James R. Howe, Benjamin W. Darbro, and Dawn E. Quelle
Précis: These findings provide insights into Rb1 regulation and cell proliferation in pancreatic neuroendocrine tumors, potentially offering new targets for diagnosis and therapy of this disease.

6668 A Hypusine–eIF5A–PEAK1 Switch Regulates the Pathogenesis of Pancreatic Cancer
Ken Fujimura, Tracy Wright, Jan Strnad, Sharmei Kaushal, Cristina Metildi, Andrew M. Lowy, Michael Bouvet, Jonathan A. Kelber, and Richard L. Klemke
Précis: A selective posttranslational modification important for the development of pancreatic cancers may offer a new therapeutic strategy to treat this disease.

6671 Tumor-Derived Osteopontin Suppresses Antitumor Immunity by Promoting Extramedullary Myelopoiesis
Young-Kyun Kim, Insu Jeon, Hyungseok Seo, Young-Jun Park, Boyeon Song, Kyoo-A Lee, Yongwoong Jeon, Yeonseok Chung, and Chang-Yu Kang
Précis: These findings unveil a novel immunosuppressive role for a factor widely associated with the inflammatory tumor microenvironment, with implications for a general therapeutic strategy in cancer treatment.
GPx2 Suppression of H₂O₂ Stress Links the Formation of Differentiated Tumor Mass to Metastatic Capacity in Colorectal Cancer
Benjamin L. Emmink, Jamila Laoukili, Anna P. Kipp, Jan Koster, Klaas M. Govaert, Szabolcs Fatrai, Andre Verheem, Ernst J.A. Steller, Regina Brigelius-Flohé, Connie R. Jimenez, Inne H.M. Borel Rinkes, and Onno Kranenburg

Précis: Results reveal an unexpected redox-controlled link between formation of a tumor mass and its capacity for metastasis.

RETRACTION
6731 Retraction: Novel HSP90 Inhibitor NVP-HSP990 Targets Cell-Cycle Regulators to Ablate Olig 2-Positive Glioma Tumor-Initiating Cells

ABOUT THE COVER

CD8⁺ T cells are critical for elimination of cancer. A major limitation of therapeutic cancer vaccines is their inability to activate and mobilize CD8⁺ T cells for infiltration into tumor. A vaccine formulation containing SA-4-1BBL and MPL, as a novel adjuvant system shows robust efficacy in activating and recruiting CD8⁺ T cells into the tumor, with subsequent effective tumor destruction in preclinical models. For details, see article by Srivastava and colleagues on page 6441.