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**AACR**  
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## BREAKING ADVANCES

- 639 Highlights from Recent Cancer Literature

## REVIEWS

- 641 **The Structural Basis of PI3K Cancer Mutations: From Mechanism to Therapy**  
Shujuan Liu, Stefan Knapp, and Ahmed Ashour Ahmed
- 647 **The Four Faces of Autophagy: Implications for Cancer Therapy**  
David A. Gewirtz
- 652 **Role of CHD5 in Human Cancers: 10 Years Later**  
Venkatadri Kolla, Tiangang Zhuang, Mayumi Higashi, Koumudi Naraparaju, and Garrett M. Brodeur

## PERSPECTIVE

- 659 **Beyond the Cancer Cell: Progression-Level Determinants Highlight the Multiscale Nature of Carcinogenesis Risk**  
Lynn Hlatky and Philip Hahnfeldt
- Précis:* The prevalent cancer-cell oriented view of carcinogenesis risk neglects the important contribution of population-level interactions during tumor progression as vital modulators of that risk.

## PRIORITY REPORT

- 665 **A Mechanism of Hypoxia-Mediated Escape from Adaptive Immunity in Cancer Cells**  
Ivraym B. Barsoum, Chelsea A. Smallwood, D. Robert Siemens, and Charles H. Graham
- Précis:* These findings are important because they establish a causal link between hypoxia and tumor escape from T cell-mediated immunity, and they open new avenues of investigation into the use of agonists of nitric oxide signaling with potential uses in cancer immunotherapy.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 675 **Sequential Application of a Cytotoxic Nanoparticle and a PI3K Inhibitor Enhances Antitumor Efficacy**  
Ambarish Pandey, Ashish Kulkarni, Bhaskar Roy, Aaron Goldman, Sasmit Sarangi, Poulomi Sengupta, Colin Phipps, Jawahar Kopparam, Michael Oh, Sudipta Basu, Mohammad Kohandel, and Shiladitya Sengupta
- Précis:* This study illustrates the importance of determining the proper sequencing of a nanomedicine and a targeted therapeutic to provide the highest efficacy.
- 686 **Monitoring Chemotherapeutic Response by Hyperpolarized <sup>13</sup>C-Fumarate MRS and Diffusion MRI**  
Lionel Mignon, Prasanta Dutta, Gary V. Martinez, Parastou Foroutan, Robert J. Gillies, and Bénédicte F. Jordan
- Précis:* These important results offer preclinical validation of a generalizable, noninvasive imaging strategy to monitor responses to cancer therapy at the earliest times after delivery, addressing an urgent need in dynamic clinical trial designs and personalized therapy where quick transitions between different agents are needed to define the most efficacious modalities in individual patients.

## MICROENVIRONMENT AND IMMUNOLOGY

- 695 **Metastatic Growth Progression Caused by PSGL-1-Mediated Recruitment of Monocytes to Metastatic Sites**  
Alexandra Hoos, Darya Protsyuk, and Lubor Borsig
- Précis:* Endogenous selectin ligands, primarily PSGL-1, that can recruit a class of prometastatic monocytes into the lung may offer new targets to block or attenuate pulmonary metastasis, a common site of progression for a variety of types of human cancer.

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- 705 **Dendritic Cells in Tumor-Associated Tertiary Lymphoid Structures Signal a Th1 Cytotoxic Immune Contexture and License the Positive Prognostic Value of Infiltrating CD8<sup>+</sup> T Cells**



Jérémy Goc, Claire Germain, Thi Kim Duy Vo-Bourgais, Audrey Lupo, Christophe Klein, Samantha Knockaert, Luc de Chaisemartin, Hanane Ouakrim, Etienne Becht, Marco Alifano, Pierre Validire, Romain Remark, Scott A. Hammond, Isabelle Cremer, Diane Damotte, Wolf-Herman Fridman, Catherine Sautès-Fridman, and Marie-Caroline Dieu-Nosjean

**Précis:** Lymph node-like structures called tertiary lymphoid structures (TLS) that can form in tumors act to shape the immune character of the tumor microenvironment, tilting T-cell responses toward an effective cytotoxic response against malignant cells.

- 716 **Tumor-Derived GM-CSF Promotes Inflammatory Colon Carcinogenesis via Stimulating Epithelial Release of VEGF**

Yi Wang, Gencheng Han, Ke Wang, Guijun Liu, Renxi Wang, He Xiao, Xinying Li, Chunmei Hou, Beifen Shen, Renfeng Guo, Yan Li, and Guojiang Chen

**Précis:** These findings reveal insights into the inflammatory processes underlying the development of colitis-associated colon cancer, with immediate therapeutic implications for clinical consideration.

- 727 **SIRT1 Limits the Function and Fate of Myeloid-Derived Suppressor Cells in Tumors by Orchestrating HIF-1 $\alpha$ -Dependent Glycolysis**

Guangwei Liu, Yujing Bi, Bo Shen, Hui Yang, Yan Zhang, Xiao Wang, Huanrong Liu, Yun Lu, Jiongbo Liao, Xi Chen, and Yiwei Chu

**Précis:** The SIRT1-mTOR-HIF1 $\alpha$ -dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of MDSCs in the tumor environment.

- 738 **Extracellular Vesicles Modulate the Glioblastoma Microenvironment via a Tumor Suppression Signaling Network Directed by miR-1**

Agnieszka Bronisz, Yan Wang, Michal O. Nowicki, Pierpaolo Peruzzi, Khairul I. Ansari, Daisuke Ogawa, Leonora Balaj, Gianluca De Rienzo, Marco Mineo, Ichiro Nakano, Michael C. Ostrowski, Fred Hochberg, Ralph Weissleder, Sean E. Lawler, E. Antonio Chiocca, and Jakub Godlewski

**Précis:** This seminal report offers penetrating molecular insights into how the cargo of extracellular vesicles secreted by cancer cells is organized to influence the tumor microenvironment.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 751 **miRNA-491-5p and GIT1 Serve as Modulators and Biomarkers for Oral Squamous Cell Carcinoma Invasion and Metastasis**



Wei-Chieh Huang, Shih-Hsuan Chan, Te-Hsuan Jang, Jer-Wei Chang, Ying-Chin Ko, Tzu-Chen Yen, Shang-Lun Chiang, Wei-Fan Chiang, Tien-Yu Shieh, Chun-Ta Liao, Jyh-Lyh Juang, Hsueh-Chun Wang, Ann-Joy Cheng, Ya-Ching Lu, and Lu-Hai Wang

**Précis:** This study defines a regulatory axis for invasion and metastasis in oral squamous cell carcinomas that are on the rise, with potential implications for its use in clinical prognosis.

- 765 **Histone Chaperone CHAF1A Inhibits Differentiation and Promotes Aggressive Neuroblastoma**

Eveline Barbieri, Kathleen De Preter, Mario Capasso, Zaowen Chen, Danielle M. Hsu, Gian Paolo Tonini, Steve Lefever, John Hicks, Rogier Versteeg, Andrea Pession, Frank Speleman, Eugene S. Kim, and Jason M. Shoheit

**Précis:** These findings identify a general modifier of chromatin modification and metabolism that is elevated in neuroblastoma cells, where it inhibits differentiation and promotes aggressive growth.

- 775 **hSETD1A Regulates Wnt Target Genes and Controls Tumor Growth of Colorectal Cancer Cells**

Tal Salz, Guangyao Li, Frederic Kaye, Lei Zhou, Yi Qiu, and Suming Huang

**Précis:** These findings define a targetable enzyme activity that sustains colorectal cancer by collaborating with a core oncogenic transcriptional program.

- 787 **Cysteine Catabolism: A Novel Metabolic Pathway Contributing to Glioblastoma Growth**

Antony Prabhu, Bhaswati Sarcar, Soumen Kahali, Zhigang Yuan, Joseph J. Johnson, Klaus-Peter Adam, Elizabeth Kensicki, and Prakash Chinnaiyan

**Précis:** An enzyme that determines the balance between cysteine catabolism and glutathione synthesis may offer a readily tractable target for therapy of aggressive brain cancers.



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**797**    **Compensatory Functions and Interdependency of the DNA-Binding Domain of BRCA2 with the BRCA1–PALB2–BRCA2 Complex**

Muthana Al Abo, Donniphat Dejsuphong, Kouji Hirota, Yasukazu Yonetani, Mitsuyoshi Yamazoe, Hitoshi Kurumizaka, and Shunichi Takeda

*Précis:* These findings suggest a means to more accurately predict the efficacy of antimalignant therapies by analyzing mutations in the BRCA2 gene of tumor biopsies.

**808**    **Cancer-Derived Mutations in KEAP1 Impair NRF2 Degradation but not Ubiquitination**

Bridgid E. Hast, Erica W. Cloer, Dennis Goldfarb, Heng Li, Priscila F. Siesser, Feng Yan, Vonn Walter, Ning Zheng, D. Neil Hayes, and Michael B. Major

*Précis:* Functional analysis of somatic mutations in a regulator of the oncogenic transcription factor NRF2 reveals insights into a pivotal stress modifier pathway that preserves the viability of cancer cells subjected to radiotherapy or chemotherapy.

**818**    **Glioblastoma Cell Enrichment Is Critical for Analysis of Phosphorylated Drug Targets and Proteomic–Genomic Correlations**

Claudius Mueller, Ana C. deCarvalho, Tom Mikkelsen, Norman L. Lehman, Valerie Calvert, Virginia Espina, Lance A. Liotta, and Emanuel F. Petricoin III

*Précis:* These findings drive home the necessity for careful cancer cell enrichment in biospecimens used to form the basis for targeted therapy selection.

**829**    **Cell Fate Factor DACHI Represses YB-1–Mediated Oncogenic Transcription and Translation**



Kongming Wu, Ke Chen, Chenguang Wang, Xuanmao Jiao, Liping Wang, Jie Zhou, Jing Wang, Zhiping Li, Sankar Addya, Poul H. Sorensen, Michael P. Lisanti, Andrew Quong, Adam Ertel, and Richard G. Pestell

*Précis:* Basal-like breast cancers, a relatively aggressive disease subtype, may be governed in part by a cell fate pathway that directs epithelial–mesenchymal transition and metastasis.

**840**    **Adenosine-to-Inosine RNA Editing Mediated by ADARs in Esophageal Squamous Cell Carcinoma**



Yan-Ru Qin, Jun-Jing Qiao, Tim Hon Man Chan, Ying-Hui Zhu, Fang-Fang Li, Haibo Liu, Jing Fei, Yan Li, Xin-Yuan Guan, and Leilei Chen


*Précis:* While little investigated in cancer, RNA editing may offer important insights with implications for the diagnosis, prognosis, and treatment of human cancers, as illustrated in this study of the most common form of esophageal cancer.

## PREVENTION AND EPIDEMIOLOGY

**852**    **Risk of Ovarian Cancer and the NF- $\kappa$ B Pathway: Genetic Association with *IL1A* and *TNFSF10***

Bridget Charbonneau, Matthew S. Block, William R. Bamlet, Robert A. Vierkant, Kimberly R. Kalli, Zachary Fogarty, David N. Rider, Thomas A. Sellers, Shelley S. Tworoger, Elizabeth Poole, Harvey A. Risch, Helga B. Salvesen, Lambertus A. Kiemeny, Laura Baglietto, Graham G. Giles, Gianluca Severi, Britton Trabert, Nicolas Wentzensen, Georgia Chenevix-Trench, for AOCS/ACS group, Alice S. Whittemore, Weiva Sieh, Jenny Chang-Claude, Elisa V. Bandera, Irene Orlow, Kathryn Terry, Marc T. Goodman, Pamela J. Thompson, Linda S. Cook, Mary Anne Rossing, Roberta B. Ness, Steven A. Narod, Jolanta Kupryjanczyk, Karen Lu, Ralf Butzow, Thilo Dörk, Tanja Pejovic, Ian Campbell, Nhu D. Le, Clareann H. Bunker, Natalia Bogdanova, Ingo B. Runnebaum, Diana Eccles, James Paul, Anna H. Wu, Simon A. Gayther, Estrid Hogdall, Florian Heitz, Stanley B. Kaye, Beth Y. Karlan, Hoda Anton Culver, Jacek Gronwald, Claus K. Hogdall, Diether Lambrechts, Peter A. Fasching, Usha Menon, Joellen Schildkraut, Celeste Leigh Pearce, Douglas A. Levine, Susanne Kruger Kjaer, Daniel Cramer, James M. Flanagan, Catherine M. Phelan, Robert Brown, Leon F.A.G. Massuger, Honglin Song, Jennifer A. Doherty, Camilla Krakstad, Dong Liang, Kunle Odunsi, Andrew Berchuck, Allan Jensen, Jan Lubiński, Heli Nevanlinna, Yukie T. Bean, Galina Lurie, Argyrios Ziogas, Christine Walsh, Evelyn Despierre, Louise Brinton, Alexander Hein, Anja Rudolph, Agnieszka Dansonka-Mieszkowska, Sara H. Olson, Philipp Harter, Jonathan Tyrer, Allison F. Vitonis, Angela Brooks-Wilson, Katja K. Aben, Malcolm C. Pike, Susan J. Ramus, Elisabeth Wik, Cezary Cybulski, Jie Lin, Lara Sucheston, Robert Edwards, Valerie McGuire, Jenny Lester, Andreas du Bois, Lene Lundvall, Shan Wang-Gohrke, Lukasz M. Szafron, Sandrina Lambrechts, Hannah Yang, Matthias W. Beckmann, Liisa M. Pelttari, Anne M. Van Altena, David van den Berg, Mari K. Halle, Aleksandra Gentry-Maharaj, Ira Schwaab, Urmila Chandran, Janusz Menkiszak, Arif B. Ekici, Lynne R. Wilkens, Arto Leminen, Francesmary Modugno, Grace Friel, Joseph H. Rothstein, Ignace Vergote, Montserrat Garcia-Closas, Michelle A.T. Hildebrandt, Piotr Sobiczewski, Linda E. Kelemen, Paul D.P. Pharoah, Kirsten Moysich, Keith L. Knutson,

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- Julie M. Cunningham, Brooke L. Fridley, and Ellen L. Goode  
*Précis:* Results from this huge clinical study confirm and extend the evidence of a close correlation between two genetic markers and risks of ovarian cancer.
- 862** **HIC1 Silencing in Triple-Negative Breast Cancer Drives Progression through Misregulation of LCN2**  
 Guangcun Cheng, Xueqing Sun, Jinglong Wang, Gang Xiao, Xiumin Wang, Xuemei Fan, Lidong Zu, Mingang Hao, Qing Qu, Yan Mao, Yunjing Xue, and Jianhua Wang  
*Précis:* These findings offer a preclinical proof-of-concept to block a targetable molecule in the tumor microenvironment as a strategy to treat triple-negative breast cancers, an aggressive subtype with no existing targeted therapy.
- THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**
- 873** **The CXCL7/CXCR1/2 Axis Is a Key Driver in the Growth of Clear Cell Renal Cell Carcinoma**  
Renaud Grépin, Mélanie Guyot, Sandy Giuliano, Marina Boncompagni, Damien Ambrosetti, Emmanuel Chamorey, Jean-Yves Scoazec, Sylvie Negrier, Hélène Simonnet, and Gilles Pagès  
*Précis:* Clinical and preclinical results provide a rationale for CXCL7 detection in tumor samples as a basis for the application of CXCL7 antibodies or inhibitors of the CXCL7 receptors to improve the survival of patients with metastatic clear cell renal cell carcinoma.
- 884** **Dramatic Antitumor Effects of the Dual MET/ RON Small-Molecule Inhibitor LY2801653 in Non-Small Cell Lung Cancer**  
Ichiro Kawada, Rifat Hasina, Qudsia Arif, Jeffrey Mueller, Erin Smithberger, Aliya N. Husain, Everett E. Vokes, and Ravi Salgia  
*Précis:* These findings offer a robust preclinical proof-of-concept for dual targeting of the MET/ RON tyrosine receptor kinases as a promising small molecule modality to treat lung cancer, with potential implications for broader applications in additional cancers where these kinases may be key oncogenic drivers.
- 896** **Prognostic and Therapeutic Impact of Argininosuccinate Synthetase 1 Control in Bladder Cancer as Monitored Longitudinally by PET Imaging**  
 Michael D. Allen, Phuong Luong, Chantelle Hudson, Julius Leyton, Barbara Delage, Essam Ghazaly, Rosalind Cutts, Ming Yuan, Nelofer Syed, Cristiana Lo Nigro, Laura Lattanzio, Malgorzata Chmielewska-Kassassir, Ian Tomlinson, Rebecca Roylance, Hayley C. Whitaker, Anne Y. Warren, David Neal, Christian Frezza, Luis Beltran, Louise J. Jones, Claude Chelala, Bor-Wen Wu, John S. Bomalaski, Robert C. Jackson, Yong-Jie Lu, Tim Crook, Nicholas R. Lemoine, Stephen Mather, Julie Foster, Jane Sosabowski, Norbert Avril, Chien-Feng Li, and Peter W. Szlosarek  
*Précis:* This important study offers a preclinical proof-of-concept for a targeted strategy to treat bladder cancers, in which targeted therapies have yet to show any significant impact on patient survival.
- 908** **Blocking Lactate Export by Inhibiting the Myc Target MCT1 Disables Glycolysis and Glutathione Synthesis**  
Joanne R. Doherty, Chunying Yang, Kristen E.N. Scott, Michael D. Cameron, Mohammad Fallahi, Weimin Li, Mark A. Hall, Antonio L. Amelio, Jitendra K. Mishra, Fangzheng Li, Mariola Tortosa, Heide Marika Genau, Robert J. Rounbehler, Yunqi Lu, Chi V. Dang, K. Ganesh Kumar, Andrew A. Butler, Thomas D. Bannister, Andrea T. Hooper, Keziban Unsal-Kacmaz, William R. Roush, and John L. Cleveland  
*Précis:* These findings suggest an antimetabolic strategy to attack cancers where Myc is deregulated, a long-standing challenge in the field, by blocking the lactate transporter in combination with metformin treatment.
- 921** **Nutlin-3a Efficacy in Sarcoma Predicted by Transcriptomic and Epigenetic Profiling**  
Kathleen I. Pishas, Susan J. Neuhaus, Mark T. Clayer, Andreas W. Schreiber, David M. Lawrence, Michelle Perugini, Robert J. Whitfield, Gelareh Farshid, Jim Manavis, Steve Chryssidis, Bronwen J. Mayo, Rebecca C. Haycox, Kristen Ho, Michael P. Brown, Richard J. D'Andrea, Andreas Evdokiou, David M. Thomas, Jayesh Desai, David F. Callen, and Paul M. Nielsen  
*Précis:* These results address the reason for a lack of predictive markers for cancer cell sensitivity to a class of p53 agonists being examined clinically, offering an alternate rationale for defining inclusion criteria for patient recruitment to trials.



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**932** **FANCD1 Localization by Mismatch Repair Is Vital to Maintain Genomic Integrity after UV Irradiation**



Shawna Guillemette, Amy Branagan, Min Peng, Aashana Dhruva, Orlando D. Schärer, and Sharon B. Cantor

**Précis:** A tumor suppressor that is mutated in hereditary forms of breast and ovarian cancer is found to suppress mutations induced by UV light through its role in supporting checkpoint responses.

## TUMOR AND STEM CELL BIOLOGY

**945** **A Transgenic Mouse Model for Early Prostate Metastasis to Lymph Nodes**

Hyun-Kyung Ko, Shin Akakura, Jennifer Peresie, David W. Goodrich, Barbara A. Foster, and Irwin H. Gelman

**Précis:** Combined genetic loss of *SSeCKS/Akap12* and *Rb* in the mouse causes prostatic intraepithelial neoplasia (PIN) associated with rapid lymph node metastasis, addressing a gap in preclinical models to address early progression of prostate cancer.

**954** **Metastasis Suppressor KISS1 Seems to Reverse the Warburg Effect by Enhancing Mitochondrial Biogenesis**

Wen Liu, Benjamin H. Beck, Kedar S. Vaidya, Kevin T. Nash, Kyle P. Feeley, Scott W. Ballinger, Keke M. Pounds, Warren L. Denning, Anne R. Diers, Aimee Landar, Animesh Dhar, Tomoo Iwakuma, and Danny R. Welch

**Précis:** These findings suggest unexpected links between a central metastasis suppression function, mitochondrial biogenesis, and *PGC1 $\alpha$* -regulated energy metabolism.

**964** **Targeting Akt3 Signaling in Triple-Negative Breast Cancer**

Y. Rebecca Chin, Taku Yoshida, Andriy Marusyk, Andrew H. Beck, Kornelia Polyak, and Alex Tokor

**Précis:** By defining a function for a less-studied Akt isoform in the growth of triple-negative breast cancer, this study suggests possible therapeutic benefits to targeting Akt3-specific signaling.

## RETRACTION

**974** **Retraction: Mechanistic Analysis of the Role of BLCA-4 in Bladder Cancer Pathobiology**

## CORRECTIONS

**975** **Correction: Aerosol Delivery of Glucosylated Polyethylenimine/Phosphatase and Tensin Homologue Deleted on Chromosome 10 Complex Suppresses Akt Downstream Pathways in the Lung of *K-ras* Null Mice**

**976** **Correction: Membrane versus Soluble Isoforms of TNF- $\alpha$  Exert Opposing Effects on Tumor Growth and Survival of Tumor-Associated Myeloid Cells**

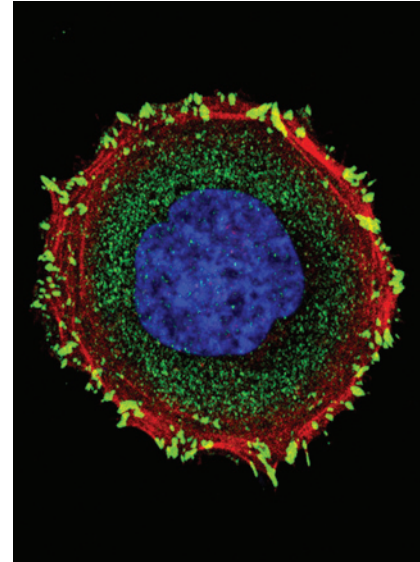
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## ABOUT THE COVER

Focal adhesion signaling activates several pathways related to cancer cell migration and invasion. As seen under confocal microscope, immunofluorescence-decorated proteins of a cancer cell, the mature focal adhesion complexes in green form punctates on cell peripheral, whereas actin cables in red form the boundary of the cell peripheral. The miR-491-5p inhibited focal adhesion formation and thus cancer cell migration via targeting GIT1, a scaffold protein that interacts with paxillin and is important for the formation of mature focal adhesion complexes. Re-expression of GIT1 reversed miR-491-5p-mediated inhibition of focal adhesion formation. For details, see article by Wei-Chieh Huang and colleagues on page 751.



# Cancer Research

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