

BREAKING INSIGHTS

- 1 Highlights from Recent Cancer Literature

CANCER RESEARCH HIGHLIGHTS

- 3 Type I Protein Arginine Methyltransferases Overexpression Promotes Transformation and Potentiates Her2/Neu-Driven Tumorigenesis

Zachary L. Watson and Benjamin G. Bitler

See related article, p. 21

- 5 Time for a "Plan B" in Peritoneal Metastatic Disease

Claudio Tripodo

See related article, p. 159

GENOME AND EPIGENOME

- 7 Multiregion Sequencing Reveals the Genetic Heterogeneity and Evolutionary History of Osteosarcoma and Matched Pulmonary Metastases



Di Wang, Xiaohui Niu, Zhijie Wang, Cheng-Li Song, Zhen Huang, Ke-Neng Chen, Jianchun Duan, Hua Bai, Jiachen Xu, Jun Zhao, Yu Wang, Minglei Zhuo, X. Sunney Xie, Xiaozheng Kang, Yanhua Tian, Liangliang Cai, Jie-Fei Han, Tongtong An, Yu Sun, Shugeng Gao, Jun Zhao, Jianming Ying, Luhua Wang, Jie He, and Jie Wang

Significance: High-throughput sequencing of primary and metastatic osteosarcoma provides new insights into the diagnosis of and potential clinical therapeutic strategies for pulmonary metastasis.

- 21 Mouse Models of Overexpression Reveal Distinct Oncogenic Roles for Different Type I Protein Arginine Methyltransferases

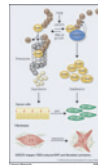
Jianqiang Bao, Alessandra Di Lorenzo, Kevin Lin, Yue Lu, Yi Zhong, Manu M. Sebastian, William J. Muller, Yanzhong Yang, and Mark T. Bedford

Significance: These findings establish Cre-activated mouse models of three different arginine methyltransferases, PRMT1, CARM1, and PRMT6, which are overexpressed in human cancers, providing a valuable tool for the study of PRMT function in tumorigenesis.

See related commentary, p. 3

MOLECULAR CELL BIOLOGY

- 33 TGF β -Activated USP27X Deubiquitinase Regulates Cell Migration and Chemoresistance via Stabilization of Snail1



Guillem Lambies, Martina Miceli, Catalina Martínez-Guillamon, Rubén Olivera-Salguero, Raúl Peña, Carolina-Paola Frías, Irene Calderón, Boyko S. Atanassov, Sharon Y. R. Dent, Joaquín Arribas, Antonio García de Herreros, and Víctor M. Díaz

Significance: These findings show that inhibition of USP27X destabilizes Snail1 to impair EMT and renders tumor cells sensitive to chemotherapy, thus opening new strategies for the inhibition of Snail1 expression and its protumoral actions.

- 47 CXADR-Mediated Formation of an AKT Inhibitory Signalosome at Tight Junctions Controls Epithelial–Mesenchymal Plasticity in Breast Cancer



Azadeh Nilchian, Joel Johansson, Aram Ghalali, Sandra T. Asanin, Ana Santiago, Oskar Rosencrantz, Kerstin Sollerbrant, C. Theresa Vincent, Malin Sund, Ulla Stenius, and Jonas Fuxe

Significance: The tight junction protein CXADR controls epithelial-mesenchymal plasticity in breast cancer by stabilizing the AKT regulators PTEN and PHLPP2.

- 61 Mammary Precancerous Stem and Non-Stem Cells Evolve into Cancers of Distinct Subtypes

Wen Bu, Zhenyu Liu, Weiyu Jiang, Chandandeep Nagi, Shixia Huang, Dean P. Edwards, Eunji Jo, Qianxing Mo, Chad J. Creighton, Susan G. Hilsenbeck, Andrew D. Leavitt, Michael T. Lewis, Stephen T. C. Wong, and Yi Li

Significance: This work uses a novel mouse mammary gland cancer model to show that tumors initiated from different precancerous mammary epithelial cells are distinct.

- 72 Aberrant Activation of β -Catenin Signaling Drives Glioma Tumorigenesis via USP1-Mediated Stabilization of EZH2

Li Ma, Kangyu Lin, Guoqiang Chang, Yiwen Chen, Chen Yue, Qing Guo, Sicong Zhang, Zhiliang Jia, Tony T. Huang, Aidong Zhou, and Suyun Huang

Significance: These findings identify the β -catenin-USP1-EZH2 signaling axis as a critical mechanism for glioma tumorigenesis that may serve as a new therapeutic target in glioblastoma.

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- 86** **Histone Demethylase KDM4B Promotes DNA Damage by Activating Long Interspersed Nuclear Element-1**
Ying Xiang, Kai Yan, Qian Zheng, Haiqiang Ke, Jie Cheng, Wenjun Xiong, Xin Shi, Lei Wei, Min Zhao, Fei Yang, Ping Wang, Xing Lu, Li Fu, Xuemei Lu, and Feng Li
Significance: The histone demethylase KDM4B promotes tumorigenesis by inducing retrotransposition and DNA damage.

- 99** **Temozolomide Induces Senescence and Repression of DNA Repair Pathways in Glioblastoma Cells via Activation of ATR–CHK1, p21, and NF-κB**
Dorthe Aasland, Laura Götzinger, Laura Hauck, Nancy Berte, Jessica Meyer, Melanie Effenberger, Simon Schneider, Emelie E. Reuber, Wynand P. Roos, Maja T. Tomicic, Bernd Kaina, and Markus Christmann
Significance: These findings reveal a mechanism by which the anticancer drug temozolomide induces senescence and downregulation of DNA repair pathways in glioma cells.

- 114** **Loss of the BCR-FGFR1 GEF Domain Suppresses RHOA Activation and Enhances B-Lymphomagenesis in Mice**
Tianxiang Hu, Yating Chong, Sumin Lu, Haiyan Qin, Mingqiang Ren, Natasha M. Savage, Chang-Sheng Chang, and John K. Cowell
Significance: RHOA activation is a critical event in the progression of BCR–FGFR1–driven leukemogenesis in stem cell leukemia and lymphoma syndrome and is regulated by the BCR GEF domain.

- 125** **Inhibition of Thioredoxin/Thioredoxin Reductase Induces Synthetic Lethality in Lung Cancers with Compromised Glutathione Homeostasis**
Xiang Yan, Xiaoshan Zhang, Li Wang, Ran Zhang, Xingxiang Pu, Shuhong Wu, Lei Li, Pan Tong, Jing Wang, Qing H. Meng, Vanessa B. Jensen, Luc Girard, John D. Minna, Jack A. Roth, Stephen G. Swisher, John V. Heymach, and Bingliang Fang
Significance: These findings demonstrate that lung cancers with compromised expression of enzymes required for glutathione homeostasis, including reduced GSR gene expression, may be targeted by thioredoxin/thioredoxin reductase inhibitors.

- 133** **PIN1 Maintains Redox Balance via the c-Myc/NRF2 Axis to Counteract Kras-Induced Mitochondrial Respiratory Injury in Pancreatic Cancer Cells**
Chen Liang, Si Shi, Mingyang Liu, Yi Qin, Qingcai Meng, Jie Hua, Shunrong Ji, Yuqing Zhang, Jingxuan Yang, Jin Xu, Quanxing Ni, Min Li, and Xianjun Yu
Significance: This study suggests that antioxidation protects Kras-mutant pancreatic cancer cells from oxidative injury, which may contribute to development of a targeted therapeutic strategy for Kras-driven PDAC by impairing redox homeostasis.

TUMOR BIOLOGY AND IMMUNOLOGY

- 146** **M2 Macrophage-Derived Exosomes Promote Cell Migration and Invasion in Colon Cancer**
Jingqin Lan, Li Sun, Feng Xu, Lu Liu, Fuqing Hu, Da Song, Zhenlin Hou, Wei Wu, Xuelai Luo, Jing Wang, Xianglin Yuan, Junbo Hu, and Guihua Wang
Significance: These findings report a functional role for miRNA-containing exosomes derived from M2 macrophages in regulating migration and invasion of colorectal cancer cells.

- 159** **Activation of B-1 Cells Promotes Tumor Cell Killing in the Peritoneal Cavity**
Marcela A. Haro, Allison M. Dyevoich, James P. Phipps, and Karen M. Haas
Significance: This work identifies a critical antitumor role for innate-like B cells localized within the peritoneal cavity and demonstrates a novel strategy to activate their tumor-killing potential.
See related commentary, p. 5


- 171** **Treatment-Induced Tumor Cell Apoptosis and Secondary Necrosis Drive Tumor Progression in the Residual Tumor Microenvironment through MerTK and IDO1**
Thomas A. Werfel, David L. Elion, Bushra Rahman, Donna J. Hicks, Violeta Sanchez, Paula I. Gonzales-Ericsson, Mellissa J. Nixon, Jamaal L. James, Justin M. Balko, Peggy A. Scherle, Holly K. Koblisch, and Rebecca S. Cook
Significance: These findings show in a model of Her2⁺ breast cancer that necrosis secondary to impaired efferocytosis activates IDO1 to drive immunosuppression and tumor progression.

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- 183** **miR-146a Controls Immune Response in the Melanoma Microenvironment**
Justin Mastroianni, Natalie Stickel, Hana Androva, Kathrin Hanke, Wolfgang Melchinger, Sandra Duquesne, Dominik Schmidt, Martina Falk, Geoffroy Andrieux, Dietmar Pfeifer, Heide Dierbach, Annette Schmitt-Graeff, Frank Meiss, Melanie Boeries, and Robert Zeiser
Significance: These findings identify a microRNA-based mechanism by which melanoma cells escape the immune system, providing a new therapeutic strategy to improve the current management of patients with melanoma.

- 196** **Adipokines Deregulate Cellular Communication via Epigenetic Repression of Gap Junction Loci in Obese Endometrial Cancer**
Srikanth R. Polusani, Yi-Wen Huang, Guangcun Huang, Chun-Wei Chen, Chiou-Miin Wang, Li-Ling Lin, Pawel Osmulski, Nicholas D. Lucio, Lu Liu, Ya-Ting Hsu, Yufan Zhou, Chun-Lin Lin, Irene Aguilera-Barrantes, Philip T. Valente, Edward R. Kost, Chun-Liang Chen, Eun Yong Shim, Sang Eun Lee, Jianhua Ruan, Maria E. Gaczynska, Pearly Yan, Paul J. Goodfellow, David G. Mutch, Victor X. Jin, Bruce J. Nicholson, Tim H.-M. Huang, and Nameer B. Kirma
Significance: Studies reveal that adipose-derived stem cells in endometrial cancer pathogenesis influence epigenetic repression of gap junction loci, which suggests targeting of gap junction activity as a preventive strategy for obesity-associated endometrial cancer.

TRANSLATIONAL SCIENCE

- 209** **Activation of PP2A and Inhibition of mTOR Synergistically Reduce MYC Signaling and Decrease Tumor Growth in Pancreatic Ductal Adenocarcinoma**

Brittany L. Allen-Petersen, Tyler Risom, Zipei Feng, Zhiping Wang, Zina P. Jenny, Mary C. Thoma, Katherine R. Pelz, Jennifer P. Morton, Owen J. Sansom, Charles D. Lopez, Brett Sheppard, Dale J. Christensen, Michael Ohlmeyer, Goutham Narla, and Rosalie C. Sears
Significance: These findings present a combinatorial strategy targeting serine/threonine protein phosphatase PP2A and mTOR in PDA, a cancer for which there are currently no targeted therapeutic options.
- 220** **Measurement of Plasma Cell-Free Mitochondrial Tumor DNA Improves Detection of Glioblastoma in Patient-Derived Orthotopic Xenograft Models**
Richard Mair, Florent Mouliere, Christopher G. Smith, Dineika Chandrananda, Davina Gale, Francesco Marass, Dana W.Y. Tsui, Charles E. Massie, Alan J. Wright, Colin Watts, Nitzan Rosenfeld, and Kevin M. Brindle
Significance: These findings show that detection of tumor mitochondrial DNA is more sensitive than circulating tumor DNA analysis to detect and monitor tumor burden in patient-derived orthotopic xenografts of glioblastoma.

- 231** **Genetic Variants of VEGFA and FLT4 Are Determinants of Survival in Renal Cell Carcinoma Patients Treated with Sorafenib**
Daniel J. Crona, Andrew D. Skol, Veli-Matti Leppänen, Dylan M. Glubb, Amy S. Etheridge, Eleanor Hilliard, Carol E. Peña, Yuri K. Peterson, Nancy Klauber-DeMore, Kari K. Alitalo, and Federico Innocenti
Significance: Clinical and mechanistic data identify germline genetic variants in VEGFA and FLT4 as markers of survival in patients with metastatic renal cell carcinoma.

- 242** **Hyperpolarized MRI Visualizes Warburg Effects and Predicts Treatment Response to mTOR Inhibitors in Patient-Derived ccRCC Xenograft Models**
Yiyu Dong, Roozbeh Eskandari, Chelsea Ray, Kristin L. Granlund, Lidia Dos Santos-Cunha, Vesselin Z. Miloushev, Sui Seng Tee, Sangmoo Jeong, Omer Aras, Ying-Bei Chen, Emily H. Cheng, James J. Hsieh, and Kayvan R. Keshari
Significance: These findings demonstrate hyperpolarized [¹⁻¹³C]pyruvate MRI as a tool for accurately assessing the clinical success of mTOR inhibition in patients with ccRCC.

- 251** **MDM2-Recruiting PROTAC Offers Superior, Synergistic Antiproliferative Activity via Simultaneous Degradation of BRD4 and Stabilization of p53**
John Hines, Schan Lartigue, Hanqing Dong, Yimin Qian, and Craig M. Crews
Significance: These findings present the first BRD4-targeting MDM2-based PROTAC that possesses potent, distinct, and synergistic biological activities associated with both ends of this heterobifunctional molecule.

CONVERGENCE AND TECHNOLOGIES


- 263** **A Gene Expression Classifier from Whole Blood Distinguishes Benign from Malignant Lung Nodules Detected by Low-Dose CT**

Andrew V. Kossenkov, Rehman Qureshi, Noor B. Dawany, Jayamanna Wickramasinghe, Qin Liu, R. Sonali Majumdar, Celia Chang, Sandy Widura, Trisha Kumar, Wen-Hwai Horng, Eric Konnisto, Gerard Criner, Jun-Chieh J. Tsay, Harvey Pass, Sai Yendamuri, Anil Vachani, Thomas Bauer, Brian Nam, William N. Rom, Michael K. Showe, and Louise C. Showe
Significance: These findings describe a minimally invasive and clinically practical pulmonary nodule classifier that has good diagnostic ability at distinguishing benign from malignant pulmonary nodules.

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POPULATION AND PREVENTION SCIENCE

274 A Collaborative Analysis of Individual Participant Data from 19 Prospective Studies Assesses Circulating Vitamin D and Prostate Cancer Risk

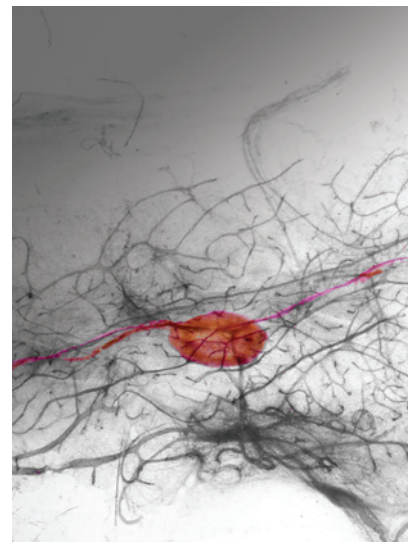


Ruth C. Travis, Aurora Perez-Cornago, Paul N. Appleby, Demetrius Albanes, Corinne E. Joshi, Pamela L. Lutsey, Alison M. Mondul, Elizabeth A. Platz, Stephanie J. Weinstein, Tracy M. Layne, Kathy J. Helzlsouer, Kala Visvanathan, Domenico Palli, Petra H. Peeters, Bas Bueno-de-Mesquita, Antonia Trichopoulou, Marc J. Gunter, Konstantinos K. Tsilidis, Maria-Jose Sánchez, Anja Olsen, Hermann Brenner, Ben Schöttker, Laura Perna, Bernd Holleczeck, Paul Knekt, Harri Rissanen, Bu B. Yeap, Leon Flicker, Osvaldo P. Almeida, Yuen Yee Elizabeth Wong, June M. Chan, Edward L. Giovannucci, Meir J. Stampfer, Giske Ursin, Randi E. Gislefoss, Tone Bjørge, Haakon E. Meyer, Rune Blomhoff, Shoichiro Tsugane, Norie Sawada, Dallas R. English, Darryl W. Eyles, Alicia K. Heath, Elizabeth J. Williamson, Jonas Manjer, Johan Malm, Martin Almquist, Loic Le Marchand, Christopher A. Haiman, Lynne R. Wilkens, Jeannette M. Schenk, Cathy M. Tangen, Amanda Black, Michael B. Cook, Wen-Yi Huang, Regina G. Ziegler, Richard M. Martin, Freddie C. Hamdy, Jenny L. Donovan, David E. Neal, Mathilde Touvier, Serge Hercberg, Pilar Galan, Mélanie Deschasaux, Timothy J. Key, and Naomi E. Allen

Significance: This international collaboration comprises the largest prospective study on blood vitamin D and prostate cancer risk and shows no association with aggressive disease but some evidence of a higher risk of nonaggressive disease.

ABOUT THE COVER

Whole mount images of a mouse mammary glands stained with Carmine alum after being isolated from nulliparous PRMT6^{T^B} at 7 months of age. Note the hyperbranching of the mammary ducts in the K5-PRMT6^{T^B} mammary gland. For details, see article by Bao and colleagues on page 21.



CORRECTIONS

286 Correction: Silencing of HSP90 Cochaperone AHA1 Expression Decreases Client Protein Activation and Increases Cellular Sensitivity to the HSP90 Inhibitor 17-Allylamino-17-Demethoxygeldanamycin
Joanna L. Holmes, Swee Y. Sharp, Steve Hobbs, and Paul Workman

287 Correction: *In vitro* Biological Characterization of a Novel, Synthetic Diaryl Pyrazole Resorcinol Class of Heat Shock Protein 90 Inhibitors
Swee Y. Sharp, Kathy Boxall, Martin Rowlands, Chrisostomos Prodromou, S. Mark Roe, Alison Maloney, Marissa Powers, Paul A. Clarke, Gary Box, Sharon Sanderson, Lisa Patterson, Thomas P. Matthews, Kwai-Ming J. Cheung, Karen Ball, Angela Hayes, Florence Raynaud, Richard Marais, Laurence Pearl, Sue Eccles, Wynne Aherne, Edward McDonald, and Paul Workman

288 Acknowledgment to Reviewers



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Cancer Res 2019;79:1-298.

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