

CANCER RESEARCH

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A C Sai Ma, Bo Zhou, Qian Yang, Yunzhi Pan, Wei Yang, Stephen J. Freedland, Ling-Wen Ding, Michael R. Freeman, Joshua J. Breunig, Neil A. Bhowmick, Jian Pan, H. Phillip Koeffler, and De-Chen Lin
These findings elucidate a transcriptional feedback loop linking epigenomic dysregulation and metabolic alterations in esophageal adenocarcinoma, indicating that blocking this feedback loop could be a potential therapeutic strategy in high-risk individuals.
- 1230** **Tumor Mutational Burden Is Polygenic and Genetically Associated with Complex Traits and Diseases**
A C Xiwei Sun, Angli Xue, Ting Qi, Dan Chen, Dandan Shi, Yang Wu, Zhili Zheng, Jian Zeng, and Jian Yang
This study provides evidence for a polygenic architecture of tumor mutational burden and opens an avenue for the use of whole-genome germline genetic variations to stratify patients with cancer for immunotherapy.

METABOLISM AND CHEMICAL BIOLOGY

- 1240** **Oncogenic N-Ras Mitigates Oxidative Stress-Induced Apoptosis of Hematopoietic Stem Cells**
Gina M. Ney, Kevin B. Yang, Victor Ng, Lu Liu, Meiling Zhao, Wun Kuk, Lila Alaka, Leilani Sampang, Adam Ross, Morgan A. Jones, Xi Jin, Laura M. McKay, Hadie Evarts, and Qing Li
Targeting oncogenic N-Ras-mediated reduction of ROS in hematopoietic stem cells through inhibition of the noncanonical Ras effector PKC may serve as a novel strategy for treatment of leukemia and other Ras-mutated cancers.
- 1252** **Targeting ACS2 with a Transition-State Mimetic Inhibits Triple-Negative Breast Cancer Growth**
Katelyn D. Miller, Katherine Pniewski, Caroline E. Perry, Sara B. Papp, Joshua D. Shaffer, Jesse N. Velasco-Silva, Jessica C. Casciano, Tomas M. Aramburu, Yellamelli V.V. Srikanth, Joel Cassel, Emmanuel Skordalakes, Andrew V. Kossenkov, Joseph M. Salvino, and Zachary T. Schug
These findings suggest that targeting acetate metabolism through ACS2 inhibitors has the potential to safely and effectively treat a wide range of patients with cancer.

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MOLECULAR CELL BIOLOGY

1265 **Hypoxia-Induced Suppression of Alternative Splicing of MBD2 Promotes Breast Cancer Metastasis via Activation of FZD1**

Zhaoji Liu, Linchong Sun, Yongping Cai, Shengqi Shen, Tong Zhang, Nana Wang, Gongwei Wu, Wenhao Ma, Shi-Ting Li, Caixia Suo, Yijie Hao, Wei-Dong Jia, Gregg L. Semenza, Ping Gao, and Huafeng Zhang

This study defines the opposing roles and clinical relevance of MBD2a and MBD2c, two MBD2 alternative splicing products, in hypoxia-driven breast cancer metastasis.

1279 **MEK Inhibition Reverses Aberrant Signaling in Melanoma Cells through Reorganization of NRas and BRAF in Self Nanoclusters**

Oren Yakovian, Julia Sajman, Rand Arafeh, Yair Neve-Oz, Michal Alon, Yardena Samuels, and Eilon Sherman

Nanoscale dynamic organization of WT and mutant NRas relative to BRAF serves as a regulatory mechanism for NRas signaling and may be a viable therapeutic target for its sensitivity to MEKi.

1293 **PLK1 Induces Chromosomal Instability and Overrides Cell-Cycle Checkpoints to Drive Tumorigenesis**

Lilia Gheghiani, Lei Wang, Youwei Zhang, Xavier T.R. Moore, Jinglei Zhang, Steven C. Smith, Yijun Tian, Liang Wang, Kristi Turner, Colleen K. Jackson-Cook, Nitai D. Mukhopadhyay, and Zheng Fu

These findings establish roles for PLK1 as a potent proto-oncogene and a CIN gene and provide insights for the development of effective treatment regimens across PLK1-overexpressing and CIN-positive cancers.

1308 **Systematic Analysis of Intronic miRNAs Reveals Cooperativity within the Multicomponent *FTX* Locus to Promote Colon Cancer Development**

Zhi Hao Kwok, Bin Zhang, Xiao Hong Chew, Jia Jia Chan, Velda Teh, Henry Yang, Dennis Kappei, and Yvonne Tay

Our study illustrates the functional relationships between individual components of multigenic loci in regulating cancer progression.

See related commentary, p. 1212

1321 ***USP24* Is a Cancer-Associated Ubiquitin Hydrolase, Novel Tumor Suppressor, and Chromosome Instability Gene Deleted in Neuroblastoma**

Tibor Bedekovics, Sajjad Hussain, Ying Zhang, Asma Ali, Young J. Jeon, and Paul J. Galaray

This study identifies the chromosome instability gene *USP24* as frequently deleted in neuroblastoma and provides important insight into the pathogenesis of this aggressive childhood cancer.

1332

Differential Regulation of Cancer Progression by CDK4/6 Plays a Central Role in DNA Replication and Repair Pathways

Meiou Dai, Julien Boudreault, Ni Wang, Sophie Poulet, Girija Daliah, Gang Yan, Alaa Moamer, Sergio A. Burgos, Siham Sabri, Suhad Ali, and Jean-Jacques Lebrun

In-depth transcriptomic analysis identifies cyclin-dependent kinases CDK4 and CDK6 as regulators of metastasis through distinct signaling pathways and reveals the DNA replication/repair pathway as central in promoting these effects.

1347

Functional Determinants of Cell Cycle Plasticity and Sensitivity to CDK4/6 Inhibition

Vishnu Kumarasamy, Paris Vail, Ram Nambiar, Agnieszka K. Witkiewicz, and Erik S. Knudsen

This work provides a mechanistic insight toward understanding the functional roles of multiple cell cycle regulators that drive plasticity and sensitivity to CDK4/6 inhibition.

1361

A Positive Feedback Loop of AKR1C3-Mediated Activation of NF- κ B and STAT3 Facilitates Proliferation and Metastasis in Hepatocellular Carcinoma

Qingqing Zhou, Wei Tian, Zhiyuan Jiang, Tingting Huang, Chao Ge, Tengfei Liu, Fangyu Zhao, Taoyang Chen, Ying Cui, Hong Li, Ming Yao, Jinjun Li, and Hua Tian

These findings elucidate a novel AKR1C3-driven signaling loop that regulates proliferation and metastasis in HCC, providing potential prognostic and therapeutic targets in this disease.

TUMOR BIOLOGY AND IMMUNOLOGY

1375

Enhanced Antitumor Immunity via Endocrine Therapy Prevents Mammary Tumor Relapse and Increases Immune Checkpoint Blockade Sensitivity

Gonzalo R. Sequeira, Ana Sahores, Tomás Dalotto-Moreno, Ramiro M. Perrotta, Gabriela Pataccini, Silvia I. Vanzulli, María L. Polo, Derek C. Radisky, Carol A. Sartorius, Virginia Novaro, Caroline A. Lamb, Gabriel A. Rabinovich, Mariana Salatino, and Claudia Lanari

Antiprogesterin therapy induces immunogenic tumor cell death in PRA-overexpressing tumors, eliciting an adaptive immune memory response that protects mice from future tumor recurrence and increases sensitivity to PD-L1 blockade.

1388

Replication Gaps Underlie BRCA Deficiency and Therapy Response

A C

Nicholas J. Panzarino, John J. Kraiss, Ke Cong, Min Peng, Michelle Mosqueda, Sumeet U. Nayak, Samuel M. Bond, Jennifer A. Calvo, Mihir B. Doshi, Matt Bere, Jianhong Ou, Bin Deng, Lihua J. Zhu, Neil Johnson, and Sharon B. Cantor

This study suggests that ssDNA replication gaps are fundamental to the toxicity of genotoxic agents and underlie the BRCA-cancer phenotype "BRCAness," yielding promising biomarkers, targets, and opportunities to resensitize refractory disease.

See related Commentary, p. 1214

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1398 **Dual Inhibition of MEK and AXL Targets Tumor Cell Heterogeneity and Prevents Resistant Outgrowth Mediated by the Epithelial-to-Mesenchymal Transition in NSCLC**

Jessica M. Konen, B. Leticia Rodriguez, Aparna Padhye, Joshua K. Ochieng, Laura Gibson, Lixia Diao, Natalie W. Fowlkes, Jared J. Fradette, David H. Peng, Robert J. Cardnell, Jeffrey J. Kovacs, Jing Wang, Lauren A. Byers, and Don L. Gibbons

This study shows that a novel combination of MEK and AXL inhibitors effectively bypasses EMT-mediated drug resistance in KRAS/p53-mutant non-small cell lung cancer by targeting EMT subpopulations, thereby preventing tumor cell survival.

TRANSLATIONAL SCIENCE

1413 **Targeting the IRAK1-S100A9 Axis Overcomes Resistance to Paclitaxel in Nasopharyngeal Carcinoma**

Lizhen Liu, Sailan Liu, Peng Deng, Yujing Liang, Rong Xiao, Lin-Quan Tang, Jinghong Chen, Qiu-Yan Chen, Peiyong Guan, Shu-Mei Yan, Xiangliang Huang, Jing Han Hong, Jianfeng Chen, Yichen Sun, Bin Tean Teh, Qiang Yu, Hai-Qiang Mai, and Jing Tan

Deregulation of the IRAK1-S100A9 axis correlates with poor prognosis, contributes to chemoresistance in nasopharyngeal carcinoma, and can be targeted by pacritinib to overcome chemoresistance in nasopharyngeal carcinoma.

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ABOUT THE COVER

Cancer is a heterogeneous disease with extensive genetic complexity. The circles in the middle represent a normal cell with germline variations. In cancer, germline variants can affect the tumor mutational burden, both of which contribute to the emergence of different types of cancer cells. For details, see article by Sun and colleagues on page 1230.

