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ATM Loss Confers Greater Sensitivity to ATR Inhibition Than PARP Inhibition in Prostate Cancer
ATM loss occurs in a subset of prostate tumors. This study shows that deleting ATM in prostate cancer models does not significantly increase sensitivity to PARP inhibition but does sensitize to ATR inhibition.
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2101 Loss of Apc Rapidly Impairs DNA Methylation Programs and Cell Fate Decisions in Lgr5+ Intestinal Stem Cells
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2114 Hispanic/Latino Patients with Gastric Adenocarcinoma Have Distinct Molecular Profiles Including a High Rate of Germline CDH1 Variants
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2125 Peptidylarginine Deiminase IV Regulates Breast Cancer Stem Cells via a Novel Tumor Cell–Autonomous Suppressor Role
Nelle Moshkovitch, Humberto J. Ochoa, Binwu Tang, Howard H. Yang, Yuan Yang, Jing Huang, Maxwell P. Lee, and Lalage M. Wakefield
These findings demonstrate a novel activity of the citrullinating enzyme PADI4 in suppressing breast cancer stem cells through epigenetic repression of stemness master transcription factors NANOG and OCT4.

2138 CircFOKK2 Promotes Growth and Metastasis of Pancreatic Ductal Adenocarcinoma by Complexing with RNA-Binding Proteins and Sponging MiR-942
Chi Hin Wong, Ut Kei Lou, Youjia Li, Stephen L. Chan, Joanna HM Tong, Ka-Fai To, and Yangchao Chen
This study reveals a prominent role for the circRNA circFOKK2 in PDAC progression, suggesting that circFOKK2 might be a novel diagnostic marker for PDAC.

METABOLISM AND CHEMICAL BIOLOGY

2150 GPD1 Enhances the Anticancer Effects of Metformin by Synergistically Increasing Total Cellular Glycerol-3-Phosphate
Jianjiang Xie, Jianheng Ye, Zhiduan Cai, Yong Luo, Nelles Moshkovitch, Humberto J. Ochoa, Binwu Tang, Howard H. Yang, Yuan Yang, Jing Huang, Maxwell P. Lee, and Lalage M. Wakefield
These findings demonstrate a novel activity of the citrullinating enzyme PADI4 in suppressing breast cancer stem cells through epigenetic repression of stemness master transcription factors NANOG and OCT4.

2158 USP10 Promotes Proliferation of Hepatocellular Carcinoma by Deubiquitinating and Stabilizing YAP/TAZ
Hong Zhu, Fangjie Yan, Tao Yuan, Meijia Qian, Tianyi Zhou, Xiaoyang Dai, Ji Cao, Meidan Ying, Xiaowu Dong, Qiaojun He, and Bo Yang
These findings identify USP10 as a DUB of YAP/TAZ and its role in hepatocellular carcinoma progression, which may serve as a potential therapeutic target for hepatocellular carcinoma treatment.

2163 Golgi-Localized PAQR4 Mediates Antiapoptotic Ceramidase Activity in Breast Cancer
Line Pedersen, Pouda Panahandeh, Muntequa I. Siraji, Stian Knappskog, Per Eystein Lønning, Ruth Gordillo, Philipp E. Scherer, Anders Molven, Knut Teigen, and Nils Halberg
Induction of and cellular dependency on de novo sphingolipid synthesis via PAQR4 highlights a central vulnerability in breast cancer that may serve as a viable therapeutic target.

MOLECULAR CELL BIOLOGY

2175 Hypomethylation-Linked Activation of PLCE1 Impedes Autophagy and Promotes Tumorigenesis through MDM2-Mediated Ubiquitination and Destabilization of p53
Yunzhao Chen, Huahua Xin, Hao Peng, Qi Shi, Menglu Li, Jie Yu, Yanxia Tian, Xueping Han, Xi Chen, Yi Zheng, Jun Li, Zhihao Yang, Lan Yang, Jianming Hu, Xiaobin Cui, and Feng Li
These findings identify hypomethylation-mediated activation of PLCE1 as a potential oncogene that blocks cellular autophagy of esophageal carcinoma by facilitating the MDM2-dependent ubiquitination of p53 and subsequent degradation.

2190 Rapalogs-Mediated Repression of Tribbles Pseudokinase 3 Regulates Pre-mRNA Splicing
Bojana Stefanovska, Cecile Edith Vicier, Thibault Dayris, Vasily Ogryzko, Veronique Scott, Ibrahim Bouakka, Suzette Delaloge, Anna Rocca, Olivia Le Saux, Olivier Trédan, Thomas Bachelot, Fabrice André, and Olivia Fromigué
Independent of mTOR signaling, rapalogs induce cytotoxicity by dysregulating spliceosome function via repression of TRIB3, the loss of which may, in the long term, contribute to therapeutic resistance.

2204 PSF Promotes ER-Positive Breast Cancer Progression via Posttranscriptional Regulation of ESR1 and SCFD2
Yuichi Mitobe, Kaori Iino, Ken-ichi Takayama, Kazuhiro Ikeda, Takashi Suzuki, Kenjiro Aogi, Hidekata Kawabata, Yutaka Suzuki, Kuniko Horie-Inoue, and Satoshi Inoue
This study defines oncogenic roles of RNA-binding protein PSF, which exhibits posttranscriptional regulation in ER-positive breast cancer.

2230 H2A Monoubiquitination Links Glucose Availability to Epigenetic Regulation of the Endoplasmic Reticulum Stress Response and Cancer Cell Death
Yilei Zhang, Jiejun Shi, Xiaoguang Liu, Zhennia Xiao, Guang Lei, Hyemin Lee, Pranavi Koppula, Weijie Cheng, Chao Mao, Li Zhuang, Li Ma, Wei Li, and Boyi Gan
These findings link glucose deprivation and H2A ubiquitination to regulation of the ER stress response in tumor growth and demonstrate pharmacologic susceptibility to inhibition of polycomb and glucose transporters.
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TUMOR BIOLOGY AND IMMUNOLOGY

2257  The Interplay between Slow-Cycling, Chemoresistant Cancer Cells and Fibroblasts Creates a Proinflammatory Niche for Tumor Progression

2273  Long Noncoding RNA MRPL23-AS1 Promotes Adenoid Cystic Carcinoma Lung Metastasis
Chu-Wen Chen, Min Fu, Zhi-Hao Du, Fei Zhao, Wen-Wen Yang, Li-Hua Xu, Sheng-Lin Li, and Xi-Yuan Ge
This study identifies a novel metastasis-promoting IncRNA MRPL23-AS1, which mediates the transcriptional silencing of E-cadherin through forming a RNA–protein complex with EZH2.

2286  Systematic Establishment of Robustness and Standards in Patient-Derived Xenograft Experiments and Analysis

2298  Targeting Glycosylated PD-1 Induces Potent Antitumor Immunity
Linlin Sun, Chia-Wei Li, Ezra M. Chung, Riyao Yang, Yong-Soo Kim, Andrew H. Park, Yun-Ju Lai, Yi Yang, Yu-Han Wang, Jielyn Liu, Yufan Qiu, Kay-Hooi Kohoo, Jun Yao, Jennifer L. Hsu, Jong-Ho Cha, Li-Chuan Chan, Jung-Mao Hsu, Heng-Huan Lee, Stephen S. Yoo, and Mien-Chie Hung
These findings demonstrate that glycosylation of PD-1 is functionally significant and targeting glycosylated PD-1 may serve as a means to improve immunotherapy response.

2311  Infiltrating Mast Cell–Mediated Stimulation of Estrogen Receptor Activity in Breast Cancer Cells Promotes the Luminal Phenotype
Maria Teresa Majorini, Valeria Cancila, Alice Rigoni, Laura Botti, Matteo Dugo, Tiziana Triulzi, Loriis De Cecco, Enrico Fontanella, Elena Jachetti, Elida Taglialuce, Claudia Chiiodoni, Claudio Tripodo, Mario P. Colombo, and Daniele Lecis
Mast cells impact breast cancer outcome by directly affecting the phenotype of tumor cells through stimulation of the estrogen receptor pathway.

2325  RUNX1 Is a Driver of Renal Cell Carcinoma Correlating with Clinical Outcome
These data reveal a novel unexplored oncogenic role for RUNX genes in kidney cancer and indicate that targeting the effects of RUNX transcriptional activity could be relevant for clinical intervention in ccRCC.

TRANSLATIONAL SCIENCE

2340  FGF Trapping Inhibits Multiple Myeloma Growth through c-Myc Depuration–Induced Mitochondrial Oxidative Stress
Roberto Ronca, Gaia C. Ghedini, Federica Maccarini, Antonio Sacco, Silvia L. Locatelli, Eleonora Foglio, Sara Taranto, Elisabetta Grillo, Sara Matarazzo, Riccardo Castelli, Giuseppe Paganini, Vanessa Desantis, Nadia Cattane, Annamaria Cattaneo, Marco Mor, Carmelo Carlo-Stella, Angelo Belotti, Aldo M. Roccaro, Marco Presta, and Arianna Giacomini
This study provides new insights into the mechanisms by which FGF antagonists promote multiple myeloma cell death.

2355  Targeted Inhibition of the E3 Ligase SCFSkp2/Cks1 Has Antitumor Activity in RB1-Deficient Human and Mouse Small-Cell Lung Cancer
Hongling Zhao, Niloj J. Iqbal, Vinethuk Sukrithan, Cari Nicholas, Yingjiao Xue, Cindy Yu, Joseph Locker, Jentao Zou, Edward L. Schwartz, and Liang Zhu
There are no effective therapies for SCLC. The identification of an actionable target downstream of RB1, inactivated in SCLC and other advanced tumors, could have a broad impact on its treatment.

2368  IRE1α Disruption in Triple-Negative Breast Cancer Cooperates with Antiangiogenic Therapy by Reversing ER Stress Adaptation and Remodeling the Tumor Microenvironment
Jonathan M. Harnoss, Adrien Le Thomas, Mike Reichelt, Ofer Guttman, Thomas D. Wu, Scot A. Marsters, Anna Shemorry, David A. Lawrence, David Kan, Ehsud Segal, Mark Merchant, Klara Totpal, Lisa M. Crocker, Kathryn Mesh, Monika Dohse, Margaret Solon, Zora Modrusan, Joachim Rudolph, Hartmut Koeppen, Peter Walter, and Avi Ashkenazi
Pharmacologic IRE1α kinase inhibition reverses ultrastructural distension of the ER, normalizes the tumor vasculature, and remodels the cellular TME attenuating TNBC growth in mice.
BRD4 Levels Determine the Response of Human Lung Cancer Cells to BET Degraders That Potently Induce Apoptosis through Suppression of Mcl-1

Dan Zong, Jiajia Gu, Giovanna C. Cavalcante, Weilong Yao, Guoqing Zhang, Shaomeng Wang, Taofeek K. Owonikoko, Xia He, and Shi-Yong Sun

The current study demonstrates the potential of novel BET degraders in the treatment of lung cancer and warrants clinical validation of BET degraders in lung cancer with high levels of BRD4.

CONVERGENCE AND TECHNOLOGIES

Model-Based Inference and Classification of Immunologic Control Mechanisms from TKI Cessation and Dose Reduction in Patients with CML

Tom Hähnel, Christoph Baldow, Joëlle Guilhot, François Guilhot, Susanne Saussele, Satu Mustjoki, Stefanie Jilg, Philipp J. Jost, Stephanie Dulucq, François-Xavier Mahon, Ingo Roeder, Artur C. Fassoni, and Ingmar Glauche

This mathematical modeling approach provides strong evidence that different immunological configurations in patients with CML determine their response to therapy cessation and that dose reductions can help to prospectively infer different risk groups.

See related commentary, p. 2083

Hybrid Epithelial–Mesenchymal Phenotypes Are Controlled by Microenvironmental Factors

Gianluca Selvaggio, Sara Canato, Archana Pawar, Pedro T. Monteiro, Patrícia S. Guerreiro, M. Manuela Brás, Florence Janody, and Claudine Chaouiya

A multidisciplinary study sheds light on microenvironmental signals controlling cancer cell plasticity along EMT and suggests that hybrid and mesenchymal phenotypes arise through independent molecular paths.

Correction: Hypoxia-Induced WSB1 Promotes the Metastatic Potential of Osteosarcoma Cells

Ji Cao, Yijie Wang, Rong Dong, Guanyu Lin, Ning Zhang, Jing Wang, Nengming Lin, Yongchuan Gu, Ling Ding, Meidan Ying, Qiaojun He, and Bo Yang

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ABOUT THE COVER

The FGF system plays a pivotal role in multiple myeloma growth and dissemination. FGF antagonists promote mitochondrial oxidative stress and apoptosis in myeloma cells by inducing proteasomal degradation of the c-Myc oncoprotein. Inhibition of the FGF system prevents the homing of grafted human myeloma cells to the bone marrow-like caudal niche of zebrafish embryos. This study provides new insights into the mechanisms by which FGF antagonists promote multiple myeloma cell death. For details, see article by Ronca and colleagues on page 2340.
# Cancer Research

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