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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.

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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.

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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.

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These findings suggest that targeting acetate metabolism through ACSS2 inhibitors has the potential to safely and effectively treat a wide range of patients with cancer.
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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 Arafah, 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
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.
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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. Galardy
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
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1347 Functional Determinants of Cell Cycle Plasticity and Sensitivity to CDK4/6 Inhibition
Vishnu Kumarasamy, Paris Vail, Ram Nambar, Agnieszka Z. 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-κB and STAT3 Facilitates Proliferation and Metastasis in Hepatocellular Carcinoma
Qingqing Zhou, Wei Tian, Zhiyuan Jiang, Tingting Huang, Chao Ge, Mengfei Liu, Fangyu Zhao, Tao Yang Chen, Ying Cui, Hong Li, Ming Yao, Jinhun 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.

1375 Enhanced Antitumor Immunity via Endocrine Therapy Prevents Mammary Tumor Relapse and Increases Immune Checkpoint Blockade Sensitivity
Gonzalo R. Sequeira, Ana Sabores, Tomás Dalotto-Moreno, Ramiro M. Perrotta, Gabriela Patacinni, Silvia I. Vanzulli, Maria L. Polo, Derek C. Radisky, Carol A. Sartorius, Virginia Novaro, Caroline A. Lamb, Gabriel A. Rabinovich, Mariana Salatino, and Claudia Lanari
Antiprogestin 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
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 reorient refractory disease.
See related Commentary, p. 1214
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.

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.

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.