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Optical mapping and whole-genome sequencing integration unravels a unique signature of replication stress-induced structural variants that drive genomic evolution and the acquisition of driver events in CCN-HCC.

1482 **Single-Hit Inactivation Drove Tumor Suppressor Genes Out of the X Chromosome during Evolution**

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This work unveils extensive trafficking of TSGs from the X chromosome to autosomes during evolution, thus identifying X-linked TSGs as a genetic Achilles' heel in tumor suppression.

1492 **Colorectal Cancer Is Associated with the Presence of Cancer Driver Mutations in Normal Colon**

Julia Matas, Brendan Kohn, Jeanne Fredrickson, Kelly Carter, Ming Yu, Ting Wang, Xianyong Gui, Thierry Soussi, Victor Moreno, William M. Grady, Miguel A. Peinado, and Rosa Ana Risques

This work suggests prevalent somatic evolution in the normal colon of patients with colorectal cancer, highlighting the potential of employing ultrasensitive gene sequencing to predict disease risk.

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METABOLISM AND CHEMICAL BIOLOGY

- 1503** **Disrupting Circadian Rhythm via the PER1–HK2 Axis Reverses Trastuzumab Resistance in Gastric Cancer**
Jiao Wang, Qiong Huang, Xingbin Hu, Shuyi Zhang, Yu Jiang, Guangyu Yao, Kongzhen Hu, Xin Xu, Bishan Liang, Qijing Wu, Zhenfeng Ma, Yawen Wang, Chunlin Wang, Zhenzhen Wu, Xiaoxiang Rong, Wangjun Liao, and Min Shi
In trastuzumab-resistant HER2-positive gastric cancer, glycolysis fluctuates with a circadian oscillation regulated by the BMAL1–CLOCK–PER1–HK2 axis, which can be disrupted with a metformin-based chronotherapy to overcome trastuzumab resistance.

MOLECULAR CELL BIOLOGY

- 1518** **Autocrine Canonical Wnt Signaling Primes Noncanonical Signaling through ROR1 in Metastatic Castration-Resistant Prostate Cancer**
Fen Ma, Seiji Arai, Keshan Wang, Carla Calagua, Amanda R. Yuan, Larysa Poluben, Zhongkai Gu, Joshua W. Russo, David J. Einstein, Huihui Ye, Meng Xiao He, Yu Liu, Eliezer Van Allen, Adam G. Sowalsky, Manoj K. Bhasin, Xin Yuan, and Steven P. Balk
This work provides fundamental insights into Wnt signaling and prostate cancer cell biology and indicates that a subset of prostate cancer driven by autocrine Wnt signaling is sensitive to Wnt synthesis inhibitors.
- 1534** **Loss of KMT5C Promotes EGFR Inhibitor Resistance in NSCLC via LINC01510-Mediated Upregulation of MET**
Arpita S. Pal, Alejandra Agredo, Nadia A. Lanman, Jihye Son, Ikjot Singh Sohal, Manvir Bains, Chennan Li, Jenna Clingerman, Kayla Gates, and Andrea L. Kasinski
Dysregulation of the epigenetic modifier KMT5C can drive MET-mediated EGFRi resistance, implicating KMT5C loss as a putative biomarker of resistance and H4K20 methylation as a potential target in EGFRi-resistant lung cancer.
- 1548** ***In Vivo* Modeling of Patient Genetic Heterogeneity Identifies New Ways to Target Cholangiocarcinoma**
Nicholas T. Younger, Mollie L. Wilson, Anabel Martinez Lyons, Edward J. Jarman, Alison M. Meynert, Graeme R. Grimes, Konstantinos Gournopoulos, Scott H. Waddell, Peter A. Tennant, David H. Wilson, Rachel V. Guest, Stephen J. Wigmore, Juan Carlos Acosta, Timothy J. Kendall, Martin S. Taylor, Duncan Sproul, Pleasantine Mill, and Luke Boulter
This work shows that, despite significant genetic heterogeneity, intrahepatic cholangiocarcinoma relies on a limited number of signaling pathways to grow, suggesting common therapeutic vulnerabilities across patients.

- 1560** **Extracellular Vesicle–Packaged CDH11 and ITGA5 Induce the Premetastatic Niche for Bone Colonization of Breast Cancer Cells**
Xiao-Qing Li, Rui Zhang, Hong Lu, Xiao-Min Yue, and Yu-Fan Huang
This study provides mechanistic insights into the generation of an osteogenic premetastatic niche by breast cancer-derived EVs and identifies potential EV-derived diagnostic biomarkers and targets for breast cancer bone metastasis.

TUMOR BIOLOGY AND IMMUNOLOGY

- 1575** **Ketogenesis Attenuates KLF5-Dependent Production of CXCL12 to Overcome the Immunosuppressive Tumor Microenvironment in Colorectal Cancer**
Ruozheng Wei, Yuning Zhou, Chang Li, Piotr Rychahou, Shulin Zhang, William B. Titlow, Greg Bauman, Yuanyuan Wu, Jinpeng Liu, Chi Wang, Heidi L. Weiss, B. Mark Evers, and Qingding Wang
This study identifies ketogenesis as a critical regulator of the tumor microenvironment in colorectal cancer and suggests the potential for ketogenic diets as a metabolic strategy to overcome immunosuppression and prolong survival.
See related commentary, p. 1464
- 1589** **Combinatorial Inactivation of Tumor Suppressors Efficiently Initiates Lung Adenocarcinoma with Therapeutic Vulnerabilities**
Maryam Yousefi, Gábor Boross, Carly Weiss, Christopher W. Murray, Jess D. Hebert, Hongchen Cai, Emily L. Ashkin, Saswati Karmakar, Laura Andrejka, Leo Chen, Minwei Wang, Min K. Tsai, Wen-Yang Lin, Chuan Li, Pegah Yakhchalian, Caterina I. Colón, Su-Kit Chew, Pauline Chu, Charles Swanton, Christian A. Kunder, Dmitri A. Petrov, and Monte M. Winslow
To address the large fraction of lung adenocarcinomas lacking mutations in proto-oncogenes for which targeted therapies are unavailable, this work uncovers driver pathways of oncogene-negative lung adenocarcinomas and demonstrates their therapeutic vulnerabilities.

- 1603** **Phosphoinositide-Binding Protein TIPE1 Promotes Alternative Activation of Macrophages and Tumor Progression via PIP3/Akt/TGFβ Axis**
Yang Cheng, Fuxiang Bai, Xiaolei Ren, Renhui Sun, Xiaowei Guo, Wen Liu, Bo Wang, Yongheng Yang, Xiaolu Zhang, Yong Xu, Chunyang Li, Xiaoyun Yang, Lifan Gao, Chunhong Ma, Xueen Li, and Xiaohong Liang
This work provides insight into the fine tuning of macrophage polarization and identifies a potential target for macrophage-based antitumor therapy.

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This study shows that inhibiting the production of ether-phosphatidylserine by targeting phosphatidylserine synthase PTDSS1 limits tumor-associated macrophage expansion and breast tumor growth.

TRANSLATIONAL SCIENCE

1633 **A Novel HER2-Selective Kinase Inhibitor Is Effective in HER2 Mutant and Amplified Non-Small Cell Lung Cancer**

Jieun Son, Jaebong Jang, Tyler S. Beyett, Yoonji Eum, Heidi M. Haikala, Alyssa Verano, Mika Lin, John M. Hatcher, Nicholas P. Kwiatkowski, Pinar Ö. Eser, Michael J. Poitras, Stephen Wang, Man Xu, Prafulla C. Gokhale, Michael D. Cameron, Michael J. Eck, Nathanael S. Gray, and Pasi A. Jänne

This study describes unique mechanisms of action of a new mutant-selective HER2 kinase inhibitor that reduces both kinase activity and protein levels of HER2 in lung cancer.

1646 **Preclinical *In Vivo* Validation of the RAD51 Test for Identification of Homologous Recombination-Deficient Tumors and Patient Stratification**

Benedetta Pellegrino, Andrea Herencia-Roperro, Alba Llop-Guevara, Flaminia Pedretti, Alejandro Moles-Fernández, Cristina Viaplana, Guillermo Villacampa, Marta Guzmán, Olga Rodríguez, Judit Grueso, Jose Jiménez, Enrique J. Arenas, Andrea Degasperi, João M.L. Dias, Josep V. Forment, Mark J. O'Connor, Olivier Déas, Stefano Cairo, Yinghui Zhou, Antonino Musolino, Carlos Caldas, Serena Nik-Zainal, Robert B. Clarke, Paolo Nuciforo, Orland Díez, Xavier Serres-Créixams, Vicente Peg, Martín Espinosa-Bravo, Teresa Macarulla, Ana Oaknin, Joaquín Mateo, Joaquín Arribas, Rodrigo Dienstmann, Meritxell Bellet, Mafalda Oliveira, Cristina Saura, Sara Gutiérrez-Enríquez, Judith Balmaña, and Violeta Serra

This work demonstrates the high accuracy of a histopathology-based test based on the detection of RAD51 nuclear foci in predicting response to PARPi and cisplatin.

CONVERGENCE AND TECHNOLOGIES

1658 **Photoacoustic Tomography Detects Response and Resistance to Bevacizumab in Breast Cancer Mouse Models**

Isabel Quiros-Gonzalez, Michal R. Tomaszewski, Monika A. Golinska, Emma Brown, Laura Ansel-Bollepalli, Lina Hacker, Dominique-Laurent Couturier, Rosa M. Sainz, and Sarah E. Bohndiek

Photoacoustic assessment of tumor oxygenation is a noninvasive early indicator of response to bevacizumab therapy, clearly distinguishing between control, responding, and resistant tumors within just a few weeks of treatment.

EDITOR'S NOTES

1669 **Editor's Note: miR-153 Supports Colorectal Cancer Progression via Pleiotropic Effects That Enhance Invasion and Chemotherapeutic Resistance**

Lei Zhang, Karen Pickard, Veronika Jenei, Marc D. Bullock, Amanda Bruce, Richard Mitter, Gavin Kelly, Christos Paraskeva, John Strefford, John Primrose, Gareth J. Thomas, Graham Packham, and Alex H. Mirnezami

1670 **Editor's Note: Nkx2-8 Downregulation Promotes Angiogenesis and Activates NF- κ B in Esophageal Cancer**

Chuyong Lin, Libing Song, Hui Gong, Aibin Liu, Xi Lin, Jueheng Wu, Mengfeng Li, and Jun Li

1671 **Editor's Note: ITPR1 Protects Renal Cancer Cells against Natural Killer Cells by Inducing Autophagy**

Yosra Messai, Muhammad Zaem Noman, Meriem Hasmim, Bassam Janji, Andrés Tittarelli, Marie Boutet, Véronique Baud, Elodie Viry, Katy Billot, Arash Nanbakhsh, Thouraya Ben Safta, Catherine Richon, Sophie Ferlicot, Emmanuel Donnadieu, Sophie Couve, Betty Gardie, Florence Orlanducci, Laurence Albiges, Jerome Thiery, Daniel Olive, Bernard Escudier, and Salem Chouaib

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ABOUT THE COVER

Intrahepatic cholangiocarcinoma (ICC) arises from the bile ducts within the liver and is characterized by high levels of genetic heterogeneity. Younger and colleagues performed a functional *in vivo* study into the role genetic heterogeneity plays in driving ICC. The cover image depicts lineage traced cells (red) with *Trp53* and *Pten* deletion in the liver bile duct stained for Keratin-19 (cyan), which generate ICC when exposed to inflammation. For details, see the article by Younger and colleagues on page 1548.

doi: 10.1158/0008-5472.CAN-82-8-CVR

