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See related article by Kane and colleagues, *Cancer Res* 1997;57:808–11

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- 1174** **Patient-Derived Triple-Negative Breast Cancer Organoids Provide Robust Model Systems That Recapitulate Tumor Intrinsic Characteristics**
Sonam Bhatia, Melissa Kramer, Suzanne Russo, Payal Naik, Gayatri Arun, Kyle Brophy, Peter Andrews, Cheng Fan, Charles M. Perou, Jonathan Preall, Taehoon Ha, Dennis Plenker, David A. Tuveson, Arvind Rishi, John E. Wilkinson, W. Richard McCombie, Karen Kostroff, and David L. Spector
A comprehensive analysis of patient-derived organoids of TNBC provides insights into cellular heterogeneity and mechanisms of tumorigenesis at the single-cell level.

GENOME AND EPIGENOME

- 1193** **Somatic Mutations Enriched in *Cis*-Regulatory Elements Affect Genes Involved in Embryonic Development and Immune System Response in Neuroblastoma**
Vito Alessandro Lasorsa, Annalaura Montella, Sueva Cantalupo, Matilde Tirelli, Carmen de Torres, Sanja Aveic, Gian Paolo Tonini, Achille Iolascon, and Mario Capasso
Assessment of noncoding *cis*-regulatory variants and long-range interaction data highlight the combined effect of somatic mutations in regulatory elements in driving neuroblastoma.

- 1208** **Combined Inhibition of G9a and EZH2 Suppresses Tumor Growth via Synergistic Induction of IL24-Mediated Apoptosis**
Francesco Casciello, Gregory M. Kelly, Priya Ramarao-Milne, Nabilah Kamal, Teneale A. Stewart, Pamela Mukhopadhyay, Stephen H. Kazakoff, Mariska Miranda, Dorim Kim, Felicity M. Davis, Nicholas K. Hayward, Paula M. Vertino, Nicola Waddell, Frank Gannon, and Jason S. Lee
These findings demonstrate a novel role for G9a and EZH2 histone methyltransferases in suppressing apoptosis, which can be targeted with small molecule inhibitors as a potential approach to improve solid cancer treatment.

- 1222** **Association of Genetic Ancestry and Molecular Signatures with Cancer Survival Disparities: A Pan-Cancer Analysis**
Kara Keun Lee, Lavanya Rishishwar, Dongjo Ban, Shashwat Deepali Nagar, Leonardo Mariño-Ramírez, John F. McDonald, and I. King Jordan
This large-cohort, multicancer study identifies four cancer types with cancer survival disparities and seven cancer-related genes that interact with genetic ancestry and contribute to disparities.

METABOLISM AND CHEMICAL BIOLOGY

- 1234** **Disrupting the MYC-TFEB Circuit Impairs Amino Acid Homeostasis and Provokes Metabolic Anergy**
Mario R. Fernandez, Franz X. Schaub, Chunying Yang, Weimin Li, Seongseok Yun, Stephanie K. Schaub, Frank C. Dorsey, Min Liu, Meredith A. Steeves, Andrea Ballabio, Alexandar Tzankov, Zhihua Chen, John M. Koomen, Anders E. Berglund, and John L. Cleveland
MYC suppresses TFEB and autophagy and controls amino acid homeostasis by upregulating amino acid transport and the proteasome, and reactivation of TFEB disables the metabolism of MYC-driven tumors.

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1251 **A Short Isoform of Spermatogenic Enzyme GAPDHS Functions as a Metabolic Switch and Limits Metastasis in Melanoma**

Jennifer G. Gill, Samantha N. Leef, Vijayashree Ramesh, Misty S. Martin-Sandoval, Aparna D. Rao, Lindsey West, Sarah Muh, Wen Gu, Zhiyu Zhao, Gregory A. Hosler, Travis W. Vandergriff, Alison B. Durham, Thomas P. Mathews, and Arin B. Aurora

This study characterizes metabolic changes during cancer metastasis and identifies GAPDHS as a novel regulator of these processes in melanoma cells.

1267 **Lactate Rewires Lipid Metabolism and Sustains a Metabolic-Epigenetic Axis in Prostate Cancer**

Luigi Ippolito, Giuseppina Comito, Matteo Parri, Marta Iozzo, Assia Duatti, Francesca Virgilio, Nicla Lorito, Marina Bacci, Elisa Pardella, Giada Sandrini, Francesca Bianchini, Roberta Damiano, Lavinia Ferrone, Giancarlo la Marca, Sergio Serni, Pietro Spatafora, Carlo V. Catapano, Andrea Morandi, Elisa Giannoni, and Paola Chiarugi

This work shows that stromal-derived lactate induces accumulation of lipid droplets, stimulates epigenetic rewiring, and fosters metastatic potential in prostate cancer.

MOLECULAR CELL BIOLOGY

1283 **Chaperone-Mediated Autophagy Controls Proteomic and Transcriptomic Pathways to Maintain Glioma Stem Cell Activity**

Jaione Auzmendi-Iriarte, Maddalen Otaegi-Ugartemendia, Estefania Carrasco-Garcia, Mikel Azkargorta, Antonio Diaz, Ander Saenz-Antoñanzas, Joaquin Andrés Andermatten, Mikel Garcia-Puga, Idoia Garcia, Alejandro Elua-Pinin, Irune Ruiz, Nicolas Sampron, Felix Elortza, Ana Maria Cuervo, and Ander Matheu

A receptor of chaperone-mediated autophagy regulates glioblastoma stem cells and may serve as a potential biomarker for advanced tumor grade and poor survival in this disease.

1298 **Targeting Squalene Epoxidase Interrupts Homologous Recombination via the ER Stress Response and Promotes Radiotherapy Efficacy**

Zipeng Hong, Tao Liu, Lingfeng Wan, Pengyan Fa, Pankaj Kumar, Yanan Cao, Chandra Bhushan Prasad, Zhaojun Qiu, Joseph Liu, Hongbing Wang, Zaibo Li, Qi-En Wang, Peixuan Guo, Deliang Guo, Ayse S. Yilmaz, Lanchun Lu, Ioanna Papandreou, Naduparambil K. Jacob, Chunhong Yan, Xiaoli Zhang, Qing-Bai She, Zhefu Ma, and Junran Zhang

Squalene epoxidase inhibitors are novel tumor-specific radiosensitizers that promote ER stress and suppress homologous recombination, providing a new potential therapeutic approach to enhance radiotherapy efficacy.

1313 **Alterations of the Mdm2 C-Terminus Differentially Impact Its Function *In Vivo***

Vinod Pant, Neeraj K. Aryal, Shunbin Xiong, Gilda P. Chau, Natalie W. Fowlkes, and Guillermina Lozano

This *in vivo* study highlights that alterations to the C-terminus of Mdm2 perturb its regulation of the tumor suppressor p53.

1321 **Hotspot *ESR1* Mutations Are Multimodal and Contextual Modulators of Breast Cancer Metastasis**

Zheqi Li, Yang Wu, Megan E. Yates, Nilgun Tasdemir, Amir Bahreini, Jian Chen, Kevin M. Levine, Nolan M. Friedigkeit, Azadeh Nasrazadani, Simak Ali, Laki Buluwela, Spencer Arnesen, Jason Gertz, Jennifer K. Richer, Benjamin Troness, Dorraya El-Ashry, Qiang Zhang, Lorenzo Gerratana, Youbin Zhang, Massimo Cristofanilli, Maritza A. Montanez, Prithu Sundd, Callen T. Wallace, Simon C. Watkins, Caterina Fumagalli, Elena Guerini-Rocco, Li Zhu, George C. Tseng, Nikhil Wagle, Jason S. Carroll, Paul Jank, Carsten Denkert, Maria M. Karsten, Jens-Uwe Blohmer, Ben H. Park, Peter C. Lucas, Jennifer M. Atkinson, Adrian V. Lee, and Steffi Oesterreich

Context- and allele-dependent transcriptome and cistrome reprogramming in mutant *ESR1* cell models elicit diverse metastatic phenotypes related to cell adhesion and migration, which can be pharmacologically targeted in metastatic breast cancer.

TUMOR BIOLOGY AND IMMUNOLOGY

1340 **CDK4/6 Inhibition Suppresses p73 Phosphorylation and Activates DR5 to Potentiate Chemotherapy and Immune Checkpoint Blockade**

Jingshan Tong, Xiao Tan, Xiangping Song, Man Gao, Denise Risnik, Suisui Hao, Kaylee Ermine, Peng Wang, Hua Li, Yi Huang, Jian Yu, and Lin Zhang

This work demonstrates how inhibition of CDK4/6 sensitizes cancer cells to chemotherapy and immune checkpoint blockade and may provide a new molecular marker for improving CDK4/6-targeted cancer therapies.

See related commentary, p. 1170

1353 **Tie2 Receptor in Tumor-Infiltrating Macrophages Is Dispensable for Tumor Angiogenesis and Tumor Relapse after Chemotherapy**

Moritz Jakab, Till Rostalski, Ki Hong Lee, Carolin Mogler, and Hellmut G. Augustin

Multiple preclinical tumor models, cell stimulation experiments, and meta-analysis of published tumor single cell RNA sequencing data challenge the reported role of Tie2-positive macrophages for tumor angiogenesis, metastasis, and relapse after chemotherapy.

See related commentary, p. 1172

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1365 **Functional Analysis of *MET* Exon 14 Skipping Alteration in Cancer Invasion and Metastatic Dissemination**

Feng Wang, Yang Liu, Wanglong Qiu, Elaine Shum, Monica Feng, Dejian Zhao, Deyou Zheng, Alain Borczuk, Haiying Cheng, and Balazs Halmos

These findings reveal the mechanistic function of *METΔ14Ex* alteration in driving metastasis and define novel metastasis-related pathways that could be targeted for more effective treatment of lung cancer with *METΔ14Ex* alterations.

1380 **Disruption of Prostaglandin E2 Signaling in Cancer-Associated Fibroblasts Limits Mammary Carcinoma Growth but Promotes Metastasis**

Eiman Elwakeel, Mirko Brüggemann, Jessica Wagih, Olga Lityagina, Mohammed A.F. Elewa, Yingying Han, Timo Frömel, Rüdiger Popp, Adele M. Nicolas, Yannick Schreiber, Elise Gradhand, Dominique Thomas, Rolf Nüsing, Julia Steinmetz-Späh, Rajkumar Savai, Emmanouil Fokas, Ingrid Fleming, Florian R. Greten, Kathi Zarnack, Bernhard Brüne, and Andreas Weigert

The inflammatory lipid prostaglandin E2 suppresses cancer-associated fibroblast expansion and activation to limit primary mammary tumor growth while promoting metastasis.

TRANSLATIONAL SCIENCE

1396 **Neoadjuvant Intratumoral Immunotherapy with TLR9 Activation and Anti-OX40 Antibody Eradicates Metastatic Cancer**

Wan Xing Hong, Idit Sagiv-Barfi, Debra K. Czerwinski, Adrienne Sallets, and Ronald Levy

This work demonstrates the ability of neoadjuvant intratumoral immunotherapy to target local and distant metastatic disease and consequently improve survival.

1409 **A Urinary Drug-Disposing Approach as an Alternative to Intravesical Chemotherapy for Treating Nonmuscle Invasive Bladder Cancer**

Vanessa Bellat, Adam O. Michel, Charlene Thomas, Tracy Stokol, Benjamin B. Choi, and Benedict Law

A noninvasive drug delivery approach that targets the urinary system overcomes the current barriers facing effective treatment of bladder cancer.

1423 **PGC1 α / β Expression Predicts Therapeutic Response to Oxidative Phosphorylation Inhibition in Ovarian Cancer**

Carmen Ghilardi, Catarina Moreira-Barbosa, Laura Brunelli, Paola Ostano, Nicolò Panini, Monica Lupi, Alessia Anastasia, Fabio Fiordaliso, Monica Salio, Laura Formenti, Massimo Russo, Edoardo Arrigoni, Ferdinando Chiaradonna, Giovanna Chiorino, Giulio Draetta, Joseph R. Marszalek, Christopher P. Vellano, Roberta Pastorelli, MariaRosa Bani, Alessandra Decio, and Raffaella Giavazzi

OXPHOS inhibition in ovarian cancer can exploit the metabolic vulnerabilities conferred by high PGC1 α / β expression and offers an effective approach to manage patients on the basis of PGC1 α / β expression.

CORRECTIONS

1435 **Correction: Chromatin Remodeling Factor LSH Drives Cancer Progression by Suppressing the Activity of Fumarate Hydratase**

Xiaozhen He, Bin Yan, Shuang Liu, Jiantao Jia, Weiwei Lai, Xing Xin, Can-e Tang, Dixian Luo, Tan Tan, Yiqun Jiang, Ying Shi, Yating Liu, Desheng Xiao, Ling Chen, Shao Liu, Chao Mao, Gang Yin, Yan Cheng, Jia Fan, Ya Cao, Kathrin Muegge, and Yongguang Tao

1436 **Correction: Hypoxia Drives Dihydropyrimidine Dehydrogenase Expression in Macrophages and Confers Chemoresistance in Colorectal Cancer**

Marie Malier, Khaldoun Gharzeddine, Marie-Hélène Laverrière, Sabrina Marsili, Fabienne Thomas, Magali Court, Thomas Decaens, Gael Roth, and Arnaud Millet

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ABOUT THE COVER

Intravesical chemotherapy for bladder cancer is unreliable and is also limited by incomplete drug delivery and poor compliance. A new urinary drug-disposing approach was developed to improve treatment outcomes by covering the entire urinary system, prolonging exposure of the tumor to drugs, and employing intravenous administration. For details, see the article by Bellat and colleagues on page 1409.

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