


BREAKING INSIGHTS

- 2447** Highlights from Recent Cancer Literature

REVIEWS


- 2449** From MGUS to Multiple Myeloma, a Paradigm for Clonal Evolution of Premalignant Cells
Niels van Nieuwenhuijzen, Ingrid Spaan, Reinier Raymakers, and Victor Peperzak
- 2457** MYD88 L265P Mutation in Lymphoid Malignancies
Xinfang Yu, Wei Li, Qipan Deng, Ling Li, Eric D. Hsi, Ken H. Young, Mingzhi Zhang, and Yong Li

GENOME AND EPIGENOME

- 2463** Bivalent Chromatin Domains in Glioblastoma Reveal a Subtype-Specific Signature of Glioma Stem Cells
Amelia Weber Hall, Anna M. Battenhouse, Haridha Shivram, Adam R. Morris, Matthew C. Cowperthwaite, Max Shpak, and Vishwanath R. Iyer
Significance: Enhancers and bivalent domains in glioblastoma are regulated in a subtype-specific manner that resembles gene regulation in glioma stem cells.
- 2475** PML Recruits TET2 to Regulate DNA Modification and Cell Proliferation in Response to Chemotherapeutic Agent
 Chengli Song, Lina Wang, Xiaoyan Wu, Kai Wang, Dan Xie, Qi Xiao, Songyu Li, Kui Jiang, Lujian Liao, John R. Yates III, Jiing-Dwan Lee, and Qingkai Yang
Significance: Promyelocytic leukemia protein recruits TET2, regulating DNA modification and cell proliferation in response to chemotherapeutic agents.

METABOLISM AND CHEMICAL BIOLOGY

- 2490** Organelle-Derived Acetyl-CoA Promotes Prostate Cancer Cell Survival, Migration, and Metastasis via Activation of Calmodulin Kinase II
Guoyu Yu, Chien-Jui Cheng, Song-Chang Lin, Yu-Chen Lee, Daniel E. Frigo, Li-Yuan Yu-Lee, Gary E. Gallick, Mark A. Titus, Leta K. Nutt, and Sue-Hwa Lin
Significance: This study identifies a cell metabolic pathway that promotes prostate cancer metastasis and suggests prostate cancer may be susceptible to β -oxidation inhibitors.

- 2503** Visualization of Breast Cancer Metabolism Using Multimodal Nonlinear Optical Microscopy of Cellular Lipids and Redox State 

Jue Hou, Joshua Williams, Elliot L. Botvinick, Eric O. Potma, and Bruce J. Tromberg

Significance: These findings provide unique insight into metabolic processes, revealing correlations between cancer metastasis and cellular redox state, lipid metabolism, and extracellular matrix.

- 2513** Extracellular Citrate Affects Critical Elements of Cancer Cell Metabolism and Supports Cancer Development *In Vivo*

Maria E. Mycielska, Katja Dettmer, Petra Rümmele, Katharina Schmidt, Cornelia Prehn, Vladimir M. Milenkovic, Wolfgang Jagla, Gregor M. Madej, Margareta Lantow, Moritz Schladt, Alexander Cecil, Gudrun E. Koehl, Elke Eggenhofer, Christian J. Wachsmuth, Vadivel Ganapathy, Hans J. Schlitt, Karl Kunzelmann, Christine Ziegler, Christian H. Wetzel, Andreas Gaumann, Sven A. Lang, Jerzy Adamski, Peter J. Oefner, and Edward K. Geissler

Significance: Uptake of extracellular citrate through pmCiC can be blocked with gluconate to reduce tumor growth and to alter metabolic characteristics of tumor tissue.

MOLECULAR CELL BIOLOGY

- 2524** Loss of the Nuclear Pool of Ubiquitin Ligase CHIP/STUB1 in Breast Cancer Unleashes the MZF1-Cathepsin Pro-oncogenic Program
Haitao Luan, Bhopal Mohapatra, Timothy A. Bielecki, Insha Mushtaq, Sameer Mirza, Tameka A. Jennings, Robert J. Clubb, Wei An, Dena Ahmed, Rokaya El-Ansari, Matthew D. Storck, Nitish K. Mishra, Chittibabu Guda, Yuri M. Sheinin, Jane L. Meza, Srikumar Raja, Emad A. Rakha, Vimla Band, and Hamid Band
Significance: These findings reveal a novel targetable pathway of breast oncogenesis unleashed by the loss of tumor suppressor ubiquitin ligase CHIP/STUB1.
- 2536** hPCL3s Promotes Hepatocellular Carcinoma Metastasis by Activating β -Catenin Signaling
Zhen Cai, Zhen-Yu Qian, Hao Jiang, Ning Ma, Zhi Li, Li-Yu Liu, Xin-Xin Ren, Yu-Rong Shang, Jing-Jing Wang, Jing-Jing Li, Dong-Ping Liu, Xiu-Ping Zhang, Dan Feng, Qian-Zhi Ni, Yuan-Yuan Feng, Nan Li, Xiao-Yan Zhou, Xiang Wang, Ying Bao, Xue-Li Zhang, Yue-Zhen Deng, and Dong Xie
Significance: hPCL3s has an oncogenic role in hepatocellular carcinoma by activating the β -catenin/IL6 signaling axis to promote metastasis.

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- 2550** ER β -Mediated Alteration of circATP2B1 and miR-204-3p Signaling Promotes Invasion of Clear Cell Renal Cell Carcinoma
Zhenwei Han, Yong Zhang, Yin Sun, Jiaqi Chen, Chawnshang Chang, Xiaolu Wang, and Shuyuan Yeh
Significance: These results identify an ER β /circATP2B1/miR-204-3p/FN1 signaling axis in RCC, suggesting ER β and circular RNA ATP2B1 as prognostic biomarkers for this disease.
- 2564** The NCX1/TRPC6 Complex Mediates TGF β -Driven Migration and Invasion of Human Hepatocellular Carcinoma Cells
Jingyu Xu, Yuan Yang, Rui Xie, Jilong Liu, Xubiao Nie, Jiaying An, Guorong Wen, Xuemei Liu, Hai Jin, and Biguang Tuo
Significance: TGF β induces the formation and activation of a TRPC6/NCX1 molecular complex, which mediates the effects of TGF β on the migration, invasion, and intrahepatic metastasis of HCC.
- 2577** A Novel Mechanism for Activation of GLI1 by Nuclear SMO That Escapes Anti-SMO Inhibitors
Muhammad M. Rahman, Allon Hazan, Joanne L. Selway, Dimalee S. Herath, Catherine A. Harwood, Muhammad S. Pizado, Ravinder Atkar, David P. Kelsell, Kenneth J. Linton, Mike P. Philpott, and Graham W. Neill
Significance: This study describes novel noncanonical Hedgehog signaling, where SMO enters the nucleus to activate GLI1, a mode that is unaffected by SMO inhibitors, thus prompting re-evaluation of current BCC treatment as well as new potential therapies targeting nuclear SMO.
- 2589** Truncated Glioma-Associated Oncogene Homolog 1 (tGLI1) Mediates Mesenchymal Glioblastoma via Transcriptional Activation of CD44
Tadas K. Rimkus, Richard L. Carpenter, Sherona Sirkisoon, Dongqin Zhu, Boris C. Pasche, Michael D. Chan, Glenn J. Lesser, Stephen B. Tatter, Kounosuke Watabe, Waldemar Debinski, and Hui-Wen Lo
Significance: These findings highlight the role of a tumor-specific gain-of-function transcription factor tGLI1 in mesenchymal glioma stem cell maintenance and mesenchymal GBM growth.
- 2601** Targeting the SUMO Pathway Primes All-trans Retinoic Acid-Induced Differentiation of Nonpromyelocytic Acute Myeloid Leukemias
Hayeon Baik, Mathias Boulanger, Mohsen Hosseini, Julie Kowalczyk, Sonia Zaghdoudi, Tamara Salem, Jean-Emmanuel Sarry, Yosr Hicheri, Guillaume Cartron, Marc Piechaczyk, and Guillaume Bossis
Significance: SUMOylation silences key ATRA-responsive genes in nonpromyelocytic acute myeloid leukemias.

TUMOR BIOLOGY AND IMMUNOLOGY


- 2614** RASSF1A Deficiency Enhances RAS-Driven Lung Tumorigenesis
M. Lee Schmidt, Katharine R. Hobbing, Howard Donninger, and Geoffrey J. Clark
Significance: A transgenic mouse model shows that suppression of RASSF1A dramatically enhances Ras-driven tumorigenesis and alters Ras signaling pathway activity.
- 2624** Zeb1 in Stromal Myofibroblasts Promotes Kras-Driven Development of Pancreatic Cancer
Irene Sangrador, Xavier Molero, Fiona Campbell, Sebastià Franch-Expósito, Maria Rovira-Rigau, Esther Samper, Manuel Domínguez-Fraile, Cristina Fillat, Antoni Castells, and Eva C. Vaquero
Significance: Zeb1 expression in stromal myofibroblasts supports PDAC development via collaboration with the epithelial compartment bearing oncogenic Kras mutations.
- 2638** Targeting cyclin D-CDK4/6 Sensitizes Immune-Refractory Cancer by Blocking the SCP3–NANOG Axis
Se Jin Oh, Hanbyoul Cho, Suhyun Kim, Kyung Hee Noh, Kwon-Ho Song, Hyo-Jung Lee, Seon Rang Woo, Suyeon Kim, Chel Hun Choi, Joon-Yong Chung, Stephen M. Hewitt, Jae-Hoon Kim, Seungki Baek, Kyung-Mi Lee, Cassian Yee, Hae-Chul Park, and Tae Woo Kim
Significance: These findings reveal cyclin D1-CDK4/6 inhibition as an effective strategy for controlling SCP3^{high} immune-refractory cancer.
- 2654** Interleukin-30/IL27p28 Shapes Prostate Cancer Stem-like Cell Behavior and Is Critical for Tumor Onset and Metastasis
Carlo Sorrentino, Stefania L. Ciummo, Giuseppe Cipollone, Sara Caputo, Matteo Bellone, and Emma Di Carlo
Significance: IL30 plays an important role in regulating prostate cancer stem-like cell behavior and metastatic potential, therefore targeting this cytokine could hamper prostate cancer progression or recurrence.
- 2669** Loss of Pax5 Exploits Sca1-BCR-ABL^{P190} Susceptibility to Confer the Metabolic Shift Essential for pB-ALL
Alberto Martín-Lorenzo, Franziska Auer, Lai N. Chan, Idoia García-Ramírez, Inés González-Herrero, Guillermo Rodríguez-Hernández, Christoph Bartenhagen, Martin Dugas, Michael Gombert, Sebastian Ginzl, Oscar Blanco, Alberto Orfao, Diego Alonso-López, Javier De Las Rivas, Maria B. García-Cenador, Francisco J. García-Criado, Markus Müschen, Isidro Sánchez-García, Arndt Borkhardt, Carolina Vicente-Dueñas, and Julia Hauer
Significance: Loss of Pax5 drives metabolic reprogramming, which together with Sca1-restricted BCR-ABL expression enables leukemic transformation.

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- 2680** TRPM2 Mediates Neutrophil Killing of Disseminated Tumor Cells
Maya Gershkovitz, Yaki Caspi, Tanya Fainsod-Levi, Ben Katz, Janna Michaeli, Saleh Khawaled, Shaya Lev, Lola Polyansky, Merav E. Shaul, Ronit V. Sionov, Leonor Cohen-Daniel, Rami I. Aqeilan, Yoav D. Shaul, Yasuo Mori, Rotem Karni, Zvi G. Fridlender, Alexander M. Binshtok, and Zvi Granot

Significance: These findings identify the mechanism utilized by neutrophils to kill disseminated tumor cells and to limit metastatic spread.

- 2691** Heterochromatin Protein 1 α Mediates Development and Aggressiveness of Neuroendocrine Prostate Cancer
Xinpei Ci, Jun Hao, Xin Dong, Stephen Y. Choi, Hui Xue, Rebecca Wu, Sifeng Qu, Peter W. Gout, Fang Zhang, Anne M. Haegert, Ladan Fazli, Francesco Crea, Christopher J. Ong, Amina Zoubeidi, Housheng H. He, Martin E. Gleave, Colin C. Collins, Dong Lin, and Yuzhuo Wang

Significance: Heterochromatin proteins play a fundamental role in neuroendocrine prostate cancer, illuminating new therapeutic targets for this aggressive disease.

- 2705** YAP1-Mediated Suppression of USP31 Enhances NF κ B Activity to Promote Sarcomagenesis
Shuai Ye, Matthew A. Lawlor, Adrian Rivera-Reyes, Shaun Egolf, Susan Chor, Koreana Pak, Gabrielle E. Ciotti, Avery C. Lee, Gloria E. Marino, Jennifer Shah, David Niedzwicki, Kristy Weber, Paul M.C. Park, Md. Zahidul Alam, Alison Grazioli, Malay Haldar, Mousheng Xu, Jennifer A. Perry, Jun Qi, and T.S. Karin Eisinger-Mathason

Significance: A new link between Hippo pathway signaling, NF κ B, and epigenetic reprogramming is highlighted and has the potential for therapeutic intervention in soft tissue sarcomas.

TRANSLATIONAL SCIENCE

- 2721** Predictive Gene Signatures Determine Tumor Sensitivity to MDM2 Inhibition
Jo Ishizawa, Kenji Nakamaru, Takahiko Seki, Koichi Tazaki, Kensuke Kojima, Dhruv Chachad, Ran Zhao, Lauren Heese, Wencai Ma, Man Chun John Ma, Courtney DiNardo, Sherry Pierce, Keyur P. Patel, Archie Tse, R. Eric Davis, Arvind Rao, and Michael Andreeff

Significance: This study demonstrates that gene expression profiling combined with TP53 mutational status predicts antitumor effects of MDM2 inhibitors in vitro and in vivo.

- 2732** Mass Spectrometry–Based Proteomics Reveals Potential Roles of NEK9 and MAP2K4 in Resistance to PI3K Inhibition in Triple-Negative Breast Cancers



Filip Mundt, Sandeep Rajput, Shunqiang Li, Kelly V. Ruggles, Arshag D. Mooradian, Philipp Mertins, Michael A. Gillette, Karsten Krug, Zhanfang Guo, Jeremy Hoog, Petra Erdmann-Gilmore, Tina Primeau, Shixia Huang, Dean P. Edwards, Xiaowei Wang, Xuya Wang, Emily Kawaler, D.R. Mani, Karl R. Clauser, Feng Gao, Jingqin Luo, Sherri R. Davies, Gary L. Johnson, Kuan-lin Huang, Christopher J. Yoon, Li Ding, David Fenyo, Matthew J. Ellis, R. Reid Townsend, Jason M. Held, Steven A. Carr, and Cynthia X. Ma

Significance: Integrative phosphoproteogenomic analysis is used to determine intrinsic resistance mechanisms of triple-negative breast tumors to PI3K inhibition.

POPULATION AND PREVENTION SCIENCE

- 2747** Germline Lysine-Specific Demethylase 1 (LSD1/KDM1A) Mutations Confer Susceptibility to Multiple Myeloma
Xiaomu Wei, M. Nieves Calvo-Vidal, Siwei Chen, Gang Wu, Maria V. Revuelta, Jian Sun, Jinghui Zhang, Michael F. Walsh, Kim E. Nichols, Vijai Joseph, Carrie Snyder, Celine M. Vachon, James D. McKay, Shu-Ping Wang, David S. Jayabalan, Lauren M. Jacobs, Dina Becirovic, Rosalie G. Waller, Mykyta Artomov, Agnes Viale, Jayeshkumar Patel, Jude Phillip, Selina Chen-Kiang, Karen Curtin, Mohamed Salama, Djordje Atanackovic, Ruben Niesvizky, Ola Landgren, Susan L. Slager, Lucy A. Godley, Jane Churpek, Judy E. Garber, Kenneth C. Anderson, Mark J. Daly, Robert G. Roeder, Charles Dumontet, Henry T. Lynch, Charles G. Mullighan, Nicola J. Camp, Kenneth Offit, Robert J. Klein, Haiyuan Yu, Leandro Cerchietti, and Steven M. Lipkin


Significance: KDM1A is the first germline autosomal dominant predisposition gene identified in multiple myeloma and provides new insights into multiple myeloma etiology and the mechanistic role of KDM1A as a tumor suppressor during post-germinal center B-cell differentiation.

- 2760** MPO Promoter Polymorphism rs2333227 Enhances Malignant Phenotypes of Colorectal Cancer by Altering the Binding Affinity of AP-2 α
Qingtao Meng, Shenshen Wu, Yajie Wang, Jin Xu, Hao Sun, Runze Lu, Na Gao, Hongbao Yang, Xiaobo Li, Boping Tang, Michael Aschner, and Rui Chen
- Significance:* MPO polymorphisms are a guide for high risk and poor prognosis in patients with colorectal cancer.

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LETTER TO THE EDITOR

- 2770** Bcl-2 Protein Targeting by the p53/p21 Complex—Letter
Liz J. Hernandez Borrero, Rahmat Sikder, Amriti Lulla, Prashanth Gokare, Paulo R. Del Valle, Xiaobing Tian, Shengliang Zhang, Philip H. Abbosh, and Wafik S. El-Deiry

- 2772**  Bcl-2 Protein Targeting by the p53/p21 Complex—Response
Eun Mi Kim, Jongdoo Kim, and Hong-Duck Um

CORRECTION

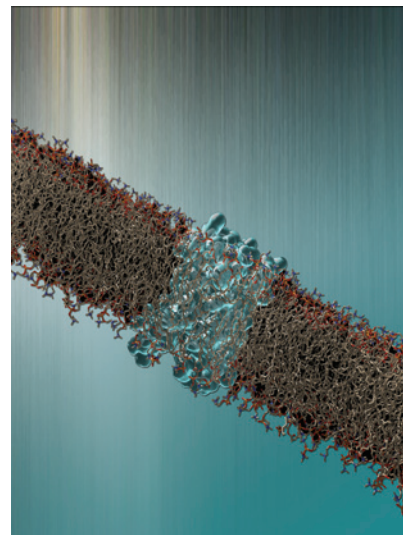
- 2775** Correction: Transglutaminase 2 Is a Direct Target Gene of YAP-TAZ—Response

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ABOUT THE COVER

Plasma membrane citrate transporter (pmCiC), a variant of the mitochondrial SLC25A1 carrier, was found to be expressed in human cancer cells of different origin and responsible for extracellular citrate uptake. Extracellular citrate supports cancer cell metabolism by reducing the need of synthesizing citrate in mitochondria and by promoting fatty acid synthesis. *In vivo* application of gluconate, a specific and irreversible pmCiC inhibitor, was found to reduce subcutaneous human pancreatic tumor growth in mice and to change metabolic characteristics of the tissue. pmCiC is shown as a molecular envelope (light blue) created from a homology model. The membrane is shown as a stick model (beige), with gluconate (green) and citrate (yellow) shown as space-filling models; heteroatoms are color-coded: oxygen, red; nitrogen, blue; phosphorus, orange. The figure was prepared using UCSF Chimera. The figure was prepared by Gregor Madej (University of Regensburg, Regensburg, Bavaria). For details, see article by Mycielska and colleagues on page 2513.



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