


BREAKING INSIGHTS

- 1261** Highlights from Recent Cancer Literature

REVIEWS

- 1263**  **An Interactive Resource to Probe Genetic Diversity and Estimated Ancestry in Cancer Cell Lines**
 Julie Dutil, Zhihua Chen, Alvaro N. Monteiro, Jamie K. Teer, and Steven A. Eschrich
- 1274** **Citrullination in Cancer**
 Arseniy E. Yuzhalin
- 1285** **The Critical Role of RNA m⁶A Methylation in Cancer**
 Qing Lan, Pei Y. Liu, Jacob Haase, Jessica L. Bell, Stefan Hüttelmaier, and Tao Liu

CANCER RESEARCH HIGHLIGHTS

- 1293** **Exosomal miRNA Cargo as Mediator of Immune Escape Mechanisms in Neuroblastoma**
 Thomas D. Schmittgen
See related article by Neviani and colleagues; Cancer Res 79(6):1151–64
- 1295** **Homeostatic Roles of STING in Cell Proliferation and Chromosomal Instability**
 David Gius and Yueming Zhu
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- 1297** **Remodeling Collapsed DNA Replication Forks for Cancer Development**
 Sotirios K. Sotiriou and Thanos D. Halazonetis
See related article, p. 1612
- 1299** **Going Beyond the Sequences: TCR Binding Patterns at the Service of Cancer Detection**
 Vincent Zoete and George Coukos
See related article, p. 1671
- 1302** **Several Faces of Glutaminase Regulation in Cells**
 Ana C.P. Mafra and Sandra M.G. Dias
See related article, p. 1398

GENOME AND EPIGENOME

- 1305** **Genome-Wide Screening and Functional Analysis Identifies Tumor Suppressor Long Noncoding RNAs Epigenetically Silenced in Hepatocellular Carcinoma**
 Feiyue Xu, Chi Han Li, Chi Hin Wong, George G. Chen, Paul Bo San Lai, Shengwen Shao, Stephen L. Chan, and Yangchao Chen
Significance: EZH2-mediated loss of lncRNAs TCAM1P-004 and RP11-598D14.1 hinders the formation of tumor suppressor lncRNA–protein complexes and subsequently promotes HCC growth.
- 1318** **Landscape of Germline and Somatic Mitochondrial DNA Mutations in Pediatric Malignancies**
 Petr Triska, Kristiyana Kaneva, Daria Merkurjev, Noor Sohail, Marni J. Falk, Timothy J. Triche Jr, Jaclyn A. Biegel, and Xiaowu Gai
Significance: This pan-cancer mtDNA study establishes the landscape of germline and tumor mtDNA mutations and identifies hotspots of tumor mtDNA mutations to pinpoint key mitochondrial functions in pediatric malignancies.

METABOLISM AND CHEMICAL BIOLOGY



- 1331** **p300 Mediates Muscle Wasting in Lewis Lung Carcinoma**

 Thomas K. Sin, James Z. Zhu, Guohua Zhang, and Yi-Ping Li
Significance: These findings demonstrate that tumor-induced muscle wasting in mice is abrogated by knockout, mutation of Lys39 or Asp1399, and pharmacological inhibition of p300.
- 1343** **Tumor pH and Protein Concentration Contribute to the Signal of Amide Proton Transfer Magnetic Resonance Imaging**

 Kevin J. Ray, Manon A. Simard, James R. Larkin, James Coates, Paul Kinchesh, Sean C. Smart, Geoff S. Higgins, Michael A. Chappell, and Nicola R. Sibson
Significance: These findings advance our understanding of amide proton transfer magnetic resonance imaging (APT MRI) of tumors and may improve the interpretation of APT MRI in clinical settings.

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1353 Cytochrome *c* Deficiency Confers Apoptosome and Mitochondrial Dysfunction in African-American Men with Prostate Cancer

Rahul Kumar, Tariq A. Bhat, Elise M. Walsh, Ajay K. Chaudhary, Jordan O'Malley, John S. Rhim, Jianmin Wang, Carl D. Morrison, Kristopher Attwood, Wiam Bshara, James L. Mohler, Neelu Yadav, and Dhyana Chandra

Significance: Mechanistic insights on prostate cancer health disparity among American men provide novel approaches to restore mitochondrial function, which can address therapeutic resistance and aggressiveness in African-American men with prostate cancer.

1369 Interplay between TRAP1 and Sirtuin-3 Modulates Mitochondrial Respiration and Oxidative Stress to Maintain Stemness of Glioma Stem Cells

Hye-Kyung Park, Jun-Hee Hong, Young Taek Oh, Sung Soo Kim, Jinlong Yin, An-Jung Lee, Young Chan Chae, Jong Heon Kim, Sung-Hye Park, Chul-Kee Park, Myung-Jin Park, Jong Bae Park, and Byoung Heon Kang

Significance: Discovery and functional analysis of a TRAP1-SIRT3 complex in glioma stem cells identify potential target proteins for glioblastoma treatment.

1383 PAK4 Phosphorylates Fumarase and Blocks TGF β -Induced Cell Growth Arrest in Lung Cancer Cells



Tao Chen, Ting Wang, Wenhua Liang, Qin Zhao, Qiuqing Yu, Chun-Min Ma, Lingang Zhuo, Dong Guo, Ke Zheng, Chengzhi Zhou, Shupeei Wei, Wenhua Huang, Juhong Jiang, Jing Liu, Shiyue Li, Jianxing He, Yuhui Jiang, and Nanshan Zhong

Significance: Fumarase counteracts CSL via its metabolic activity to facilitate TGF β -induced cell growth arrest, an effect largely blocked by PAK4-mediated phosphorylation of fumarase.

MOLECULAR CELL BIOLOGY

1398 Nutrient Stress–Dysregulated Antisense lncRNA GLS-AS Impairs GLS-Mediated Metabolism and Represses Pancreatic Cancer Progression



Shi-Jiang Deng, Heng-Yu Chen, Zhu Zeng, Shichang Deng, Shuai Zhu, Zeng Ye, Chi He, Ming-Liang Liu, Kang Huang, Jian-Xin Zhong, Feng-Yu Xu, Qiang Li, Yang Liu, Chunyou Wang, and Gang Zhao

Significance: These findings show that lncRNA GLS-AS mediates a feedback loop of Myc and GLS, providing a potential therapeutic target for metabolic reprogramming in pancreatic cancer.

See related commentary, p. 1302

1413 Loss of FOXP3 and TSC1 Accelerates Prostate Cancer Progression through Synergistic Transcriptional and Posttranslational Regulation of c-MYC



Lianpin Wu, Baozhu Yi, Shi Wei, Dapeng Rao, Youhua He, Gurudatta Naik, Sejong Bae, Xiaoguang M. Liu, Wei-Hsiung Yang, Guru Sonpavde, Runhua Liu, and Lizhong Wang

Significance: These results establish the principle of a synergistic action of TSC1 and FOXP3 during prostate cancer progression and provide new therapeutic targets for patients who have prostate cancer with two signaling defects.

1426 Disruption of Endolysosomal RAB5/7 Efficiently Eliminates Colorectal Cancer Stem Cells



Mitsunobu Takeda, Jun Koseki, Hidekazu Takahashi, Norikatsu Miyoshi, Naohiro Nishida, Junichi Nishimura, Taishi Hata, Chu Matsuda, Tsunekazu Mizushima, Hirofumi Yamamoto, Hideshi Ishii, Yuichiro Doki, Masaki Mori, and Naotsugu Haraguchi

Significance: These findings show that endosomal/lysosomal RAB5 and RAB7, which regulate mitophagy, are essential for the survival of colon cancer stem cells.

1438 4E-BP1 Is a Tumor Suppressor Protein Reactivated by mTOR Inhibition in Head and Neck Cancer



Zhiyong Wang, Xiaodong Feng, Alfredo A. Molinolo, Daniel Martin, Lynn Vitale-Cross, Nijiro Nohata, Mizuo Ando, Amy Wahba, Panomwat Amornphimoltham, Xingyu Wu, Mara Gilardi, Michael Allevalo, Victoria Wu, Dana J. Steffen, Philip Tofilon, Nahum Sonenberg, Joseph Califano, Qianming Chen, Scott M. Lippman, and J. Silvio Gutkind

Significance: These findings suggest that EIF4E-BP1 acts as a tumor suppressor in HNSCC and that 4E-BP1 dephosphorylation mediates the therapeutic response to mTORi, providing a mechanistic biomarker for future precision oncology trials.

1451 YY1 Complex Promotes Quaking Expression via Super-Enhancer Binding during EMT of Hepatocellular Carcinoma



Jingxia Han, Jing Meng, Shuang Chen, Xiaorui Wang, Shan Yin, Qiang Zhang, Huijuan Liu, Rong Qin, Zhongwei Li, Weilong Zhong, Chao Zhang, Heng Zhang, Yuanhao Tang, Tingting Lin, Wanfeng Gao, Xiaoyun Zhang, Lan Yang, Yanrong Liu, Hong-gang Zhou, Tao Sun, and Cheng Yang

Significance: These findings identify the YY1/p65/p300 complex as a regulator of QKI expression, identifying several potential therapeutic targets for the treatment of HCC.

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1465 STING Promotes Homeostasis via Regulation of Cell Proliferation and Chromosomal Stability

Diana Rose E. Ranoa, Ryan C. Widau, Stephen Mallon, Akash D. Parekh, Claudia M. Nicolae, Xiaona Huang, Michael J. Bolt, Ainhoa Arina, Renate Parry, Stephen J. Kron, George-Lucian Moldovan, Nikolai N. Khodarev, and Ralph R. Weichselbaum

Significance: These findings provide clear mechanistic understanding of role of STING in cell-cycle regulation, which may be exploited in cancer therapy because most normal cells express STING, while many tumor cells do not.

See related commentary, p. 1295

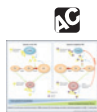
1520 Tumor Suppressor miRNA-204-5p Regulates Growth, Metastasis, and Immune Microenvironment Remodeling in Breast Cancer

Bok Sil Hong, Han Suk Ryu, Namshin Kim, Jisun Kim, Eunshin Lee, Hyunhye Moon, Kyoung Hyoun Kim, Min-Sun Jin, Nam Hoon Kwon, Sunghoon Kim, Donghyun Kim, Doo Hyun Chung, Kyeonghun Jeong, Kwangsoo Kim, Ki Yoon Kim, Han-Byoel Lee, Wonshik Han, Jihui Yun, Jong-Il Kim, Dong-Young Noh, and Hyeong-Gon Moon

Significance: This study demonstrates that regulation of PI3K/Akt signaling by miR-204-5p suppresses tumor metastasis and immune cell reprogramming in breast cancer.

TUMOR BIOLOGY AND IMMUNOLOGY

1480 An Orally Active Galectin-3 Antagonist Inhibits Lung Adenocarcinoma Growth and Augments Response to PD-L1 Blockade



Lynda Vuong, Eleni Kouverianou, Claire M. Rooney, Brian J. McHugh, Sarah E.M. Howie, Christopher D. Gregory, Stuart J. Forbes, Neil C. Henderson, Fredrik R. Zetterberg, Ulf J. Nilsson, Hakon Leffler, Paul Ford, Anders Pedersen, Lise Gravelle, Susan Tantawi, Hans Schambye, Tariq Sethi, and Alison C. MacKinnon

Significance: A novel and orally active galectin-3 antagonist inhibits lung adenocarcinoma growth and metastasis and augments response to PD-L1 blockade.

1493 Anti-PD-L1 Treatment Results in Functional Remodeling of the Macrophage Compartment



Huizhong Xiong, Stephanie Mittman, Ryan Rodriguez, Marina Moskalenko, Patricia Pacheco-Sanchez, Yagai Yang, Dorothee Nickles, and Rafael Cubas

Significance: This work demonstrates that increased IFN γ signaling following anti-PD-L1 treatment can remodel the macrophage compartment to enhance T-cell responses.

1507 Cognate Nonlytic Interactions between CD8⁺ T Cells and Breast Cancer Cells Induce Cancer Stem Cell-like Properties

Roland G. Stein, Stefan Ebert, Laura Schlahsa, Claus J. Scholz, Matthias Braun, Petra Hauck, Evi Horn, Camelia-Maria Monoranu, Vincent J. Thiemann, Michael P. Wustrow, Sebastian F. Häusler, Itsaso Montalbán del Barrio, Tanja N. Stüber, Matthias Wöfl, Johannes Diel, Andreas Rosenwald, Joachim E. Diessner, Achim Wöckel, and Jörg Wischhusen

Significance: This study shows that ineffective immune responses not only fail to clear a malignancy, but can also activate pathways in cancer cells, which promote stemness and tumor-seeding capacity.

1535 Pomalidomide Alters Pancreatic Macrophage Populations to Generate an Immune-Responsive Environment at Precancerous and Cancerous Lesions



Ligia I. Bastea, Geou-Yarh Liou, Veethika Pandey, Alicia K. Fleming, Christina A. von Roemeling, Heike Doeppler, Zhimin Li, Yushi Qiu, Brandy Edenfield, John A. Copland, Han W. Tun, and Peter Storz

Significance: These findings reveal new insights into how macrophage populations within the pancreatic cancer microenvironment can be modulated, providing the means to turn the microenvironment from immunosuppressive to immune-responsive.

1549 Whole Genome-Derived Tiled Peptide Arrays Detect Prediagnostic Autoantibody Signatures in Non-Small-Cell Lung Cancer



Yuanqing Yan, Nan Sun, Hong Wang, Makoto Kobayashi, Jon J. Ladd, James P. Long, Ken C. Lo, Jigar Patel, Eric Sullivan, Thomas Albert, Gary E. Goodman, Kim-Anh Do, and Samir M. Hanash

Significance: This study provides a modality for early diagnosis of NSCLC for precision oncology that can be applied to other cancer types.

1558 CCL27/CCL28-CCR10 Chemokine Signaling Mediates Migration of Lymphatic Endothelial Cells

Tara Karnezis, Rae H. Farnsworth, Nicole C. Harris, Steven P. Williams, Carol Caesar, David J. Byrne, Prad Herle, Maria L. Macheda, Ramin Shayan, You-Fang Zhang, Sezer Yazar, Simon J. Takouridis, Craig Gerard, Stephen B. Fox, Marc G. Achen, and Steven A. Stacker

Significance: This study shows that the remodeling of lymphatic vessels in cancer is influenced by CCL27 and CCL28 chemokines, which may serve as future targets to modulate metastatic spread.

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1573 Cervical Cancer–Instructed Stromal Fibroblasts Enhance IL23 Expression in Dendritic Cells to Support Expansion of Th17 Cells

Barbara Walch-Rückheim, Russalina Ströder, Laura Theobald, Jennifer Pahne-Zeppenfeld, Subramanya Hegde, Yoo-Jin Kim, Rainer Maria Bohle, Ingolf Juhasz-Böss, Erich-Franz Solomayer, and Sigrun Smola

Significance: Cervical cancer cells differentially regulate IL23 and IL12 in DC fibroblast cocultures in an IL6/C/EBP β /IL1 β -dependent manner, thereby supporting the expansion of Th17 cells during cancer progression.

1587 RIPK3-Induced Inflammation by I-MDSCs Promotes Intestinal Tumors

Asha Jayakumar and Alfred L.M. Bothwell

Significance: The specific role of Ripk3 in intestinal tumors and MDSC function sheds light on a key inflammatory mechanism driving tumorigenesis and allows for possible therapeutic intervention.

1600 Nod1 Imprints Inflammatory and Carcinogenic Responses toward the Gastric Pathogen *Helicobacter pylori*

Giovanni Suarez, Judith Romero-Gallo, Maria B. Piazuolo, Johanna C. Sierra, Alberto G. Delgado, M. Kay Washington, Shailja C. Shah, Keith T. Wilson, and Richard M. Peek Jr

Significance: These findings suggest that manipulation of NOD1 may represent a novel strategy to prevent or treat pathologic outcomes induced by *H. pylori* infection.

1612 Smarcal1 and Zranb3 Protect Replication Forks from Myc-Induced DNA Replication Stress

Matthew V. Puccetti, Clare M. Adams, Saul Kushinsky, and Christine M. Eischen

Significance: Smarcal1 and Zranb3 are essential, but nonredundant, for responding to DNA replication stress and stabilizing replication forks following Myc overexpression.

See related commentary, p. 1297

1624 Local Delivery of *Ox40l*, *Cd80*, and *Cd86* mRNA Kindles Global Anticancer Immunity

Ole Audun Werner Haabeth, Timothy R. Blake, Colin J. McKinlay, Anders A. Tveita, Adrienne Sallets, Robert M. Waymouth, Paul A. Wender, and Ronald Levy

Significance: The mRNA–CART system is a highly effective delivery platform for delivering immunostimulatory genes into the tumor microenvironment for potential therapeutic development.

1635 Eomes⁺T-bet^{low} CD8⁺ T Cells Are Functionally Impaired and Are Associated with Poor Clinical Outcome in Patients with Acute Myeloid Leukemia

Bei Jia, Chenchen Zhao, Kevin L. Rakszawski, David F. Claxton, W. Christopher Ehmann, Witold B. Rybka, Shin Mineishi, Ming Wang, Hiroko Shike, Michael G. Bayerl, Jeffrey M. Sivik, Todd D. Schell, Joseph J. Drabick, Raymond J. Hohl, and Hong Zheng

Significance: These findings reveal that a high frequency of Eomes⁺T-bet^{low} CD8⁺ T cells predicts poor clinical outcome in AML and that targeting Eomes may provide a therapeutic benefit against AML.

TRANSLATIONAL SCIENCE

1646 MNK1/NODAL Signaling Promotes Invasive Progression of Breast Ductal Carcinoma *In Situ*



Qianyu Guo, Vivian Z. Li, Jessica N. Nichol, Fan Huang, William Yang, Samuel E.J. Preston, Zahra Talat, Hanne Lefrère, Henry Yu, Guihua Zhang, Mark Basik, Christophe Gonçalves, Yao Zhan, Dany Plourde, Jie Su, Jose Torres, Maud Marques, Sara Al Habyan, Krikor Bijian, Frédéric Amant, Michael Witcher, Fariba Behbod, Luke McCaffrey, Moulay Alaoui-Jamali, Nadia V. Giannakopoulos, Muriel Brackstone, Lynne-Marie Postovit, Sonia V. del Rincón, and Wilson H. Miller Jr


Significance: These findings provide new mechanistic insight into progression of ductal carcinoma and support clinical application of MNK1 inhibitors to delay progression of indolent ductal carcinoma in situ to invasive ductal carcinoma.

1658 Epithelial-to-Mesenchymal Transition Is a Mechanism of ALK Inhibitor Resistance in Lung Cancer Independent of ALK Mutation Status

Koji Fukuda, Shinji Takeuchi, Sachiko Arai, Ryohei Katayama, Shigeki Nanjo, Azusa Tanimoto, Akihiro Nishiyama, Takayuki Nakagawa, Hirokazu Taniguchi, Takeshi Suzuki, Tadaaki Yamada, Hiroshi Nishihara, Hironori Ninomiya, Yuichi Ishikawa, Satoko Baba, Kengo Takeuchi, Atsushi Horiike, Noriko Yanagitani, Makoto Nishio, and Seiji Yano

Significance: These findings show that dual inhibition of HDAC and ALK receptor tyrosine kinase activities provides a means to circumvent crizotinib resistance in lung cancer.

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- 1671** **Biophysicochemical Motifs in T-cell Receptor Sequences Distinguish Repertoires from Tumor-Infiltrating Lymphocyte and Adjacent Healthy Tissue**
 Jared Ostmeier, Scott Christley, Inimary T. Toby, and Lindsay G. Cowell
Significance: This study presents a novel computational approach to identify T-cell repertoire differences between normal and tumor tissue.
See related commentary, p. 1299

- 1681** **Metastatic Tumor-in-a-Dish, a Novel Multicellular Organoid to Study Lung Colonization and Predict Therapeutic Response**
Prabhu Ramamoorthy, Sufi Mary Thomas, Gaurav Kaushik, Dharmalingam Subramaniam, Katherine M. Chastain, Animesh Dhar, Ossama Tawfik, Anup Kasi, Weijing Sun, Satish Ramalingam, Sumedha Gunewardena, Shahid Umar, Joshua M. Mammen, Subhash B. Padhye, Scott J. Weir, Roy A. Jensen, G. Sitta Sittampalam, and Shrikant Anant
Significance: A lung organoid that exhibits characteristics of a normal human lung was developed to study the biology of metastatic disease and therapeutic intervention.

CONVERGENCE AND TECHNOLOGIES

- 1696** **Transcriptomics Associates Molecular Features with ¹⁸F-Fluorocholine PET/CT Imaging Phenotype and Its Potential Relationship to Survival in Hepatocellular Carcinoma**
Sandi A. Kwee, Maarit Tiirikainen, Miles M. Sato, Jared D. Acoba, Runmin Wei, Wei Jia, Loic Le Marchand, and Linda L. Wong
Significance: A pathobiological framework for HCC brings together multiple prognostically relevant gene signatures via convergence with ¹⁸F-fluorocholine PET/CT imaging phenotype.

POPULATION AND PREVENTION SCIENCE

- 1705** **A miRNA Expression Signature in Breast Tumor Tissue Is Associated with Risk of Distant Metastasis**
Thomas E. Rohan, Tao Wang, Sheila Weinmann, Yihong Wang, Juan Lin, Mindy Ginsberg, and Olivier Loudig
Significance: A novel predictive scoring system for patients with breast cancer includes clinical variables and the expression levels of 13 miRNAs, and may help to identify those at increased risk of distant metastasis.

CORRECTIONS

- 1714** **Correction: Reduced CD160 Expression Contributes to Impaired NK-cell Function and Poor Clinical Outcomes in Patients with HCC**
Haoyu Sun, Jing Xu, Qiang Huang, Mei Huang, Kun Li, Kun Qu, Hao Wen, Renyong Lin, Meijuan Zheng, Haiming Wei, Weihua Xiao, Rui Sun, Zhigang Tian, and Cheng Sun
- 1715** **Correction: SIX1 Promotes Tumor Lymphangiogenesis by Coordinating TGF β Signals That Increase Expression of VEGF-C**
Dan Liu, Li Li, Xiao-Xue Zhang, Dong-Yi Wan, Bi-Xin Xi, Zheng Hu, Wen-Cheng Ding, Da Zhu, Xiao-Li Wang, Wei Wang, Zuo-Hua Feng, Hui Wang, Ding Ma, and Qing-Lei Gao

EDITOR'S NOTE

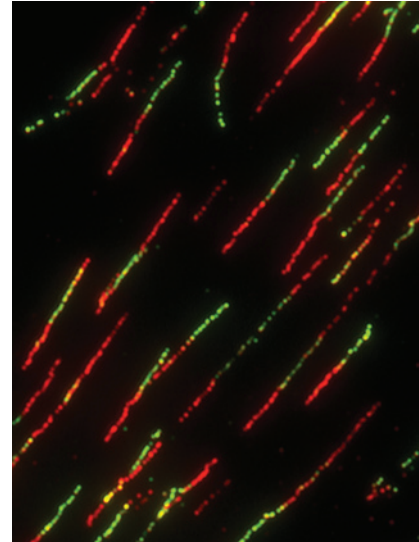
- 1716** **Editor's Note: From the Cyclooxygenase-2 Inhibitor Celecoxib to a Novel Class of 3-Phosphoinositide-Dependent Protein Kinase-1 Inhibitors**
Jiuxiang Zhu, Jui-Wen Huang, Ping-Hui Tseng, Ya-Ting Yang, Joseph Fowble, Chung-Wai Shiau, Yeng-Jeng Shaw, Samuel K. Kulp, and Ching-Shih Chen

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ABOUT THE COVER

The image is a photograph of strands of DNA from primary mouse B cells isolated from *Zranb3*- or *Smarca1*-deficient $E\mu$ -*myc* transgenic mice pulse-labeled with IdU (red) and CldU (green) detected by immunofluorescence and microscopy. The technique is called DNA fiber labeling. For details, see article by Puccetti and colleagues on page 1612.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

79 (7)

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