

BREAKING INSIGHTS

- 421** Highlights from Recent Cancer Literature

REVIEW

- 423** A Blazing Landscape: Neuroinflammation Shapes Brain Metastasis
Hila Doron, Tobias Pukrop, and Neta Erez

CANCER RESEARCH HIGHLIGHTS

- 437** Epigenetic Drift in Colorectal Cancer—It's Probably Later Than You Think
Carmen Sapienza
See related article, p. 495
- 439** A Dynamic Cis-Regulation Pattern Underlying Epithelial Ovarian Cancer Susceptibility
Jiyeon Choi and Kevin M. Brown
See related article, p. 467

CONTROVERSY AND CONSENSUS

- 441** Is Adjuvant Chemotherapy Efficient in Colon Cancer with High Microsatellite Instability? A Look Towards the Future
Guido V. Schiappacasse Cocio and Enrico D. Schiappacasse

PRIORITY REPORTS

- 445** Activation of Peroxisome Proliferator-Activated Receptors α and δ Synergizes with Inflammatory Signals to Enhance Adoptive Cell Therapy
Samuel D. Saibil, Michael St. Paul, Robert C. Laister, Carlos R. Garcia-Batres, Kavita Israni-Winger, Alisha R. Elford, Natasha Grimshaw, Céline Robert-Tissot, Dominic G. Roy, Russell G. Jones, Linh T. Nguyen, and Pamela S. Ohashi
Significance: Dual activation of peroxisome proliferator-activated receptors α and δ improves the efficacy of adoptive cell therapy by reprogramming T-cell metabolism and cytokine expression.

- 452** Radiosensitivity Is an Acquired Vulnerability of PARPi-Resistant BRCA1-Deficient Tumors

Marco Barazas, Alessia Gasparini, Yike Huang, Asli Küçükosmanoğlu, Stefano Annunziato, Peter Bouwman, Wendy Sol, Ariena Kersbergen, Natalie Proost, Renske de Korte-Grimmerink, Marieke van de Ven, Jos Jonkers, Gerben R. Borst, and Sven Rottenberg

Significance: These findings uncover radiosensitivity as a novel, therapeutically viable vulnerability of BRCA1-deficient mouse mammary cells that have acquired drug resistance due to the loss of the 53BP1 pathway.

- 461** Mosaic Y Loss Is Moderately Associated with Solid Tumor Risk

Erikka Loftfield, Weiyan Zhou, Meredith Yeager, Stephen J. Chanock, Neal D. Freedman, and Mitchell J. Machiela

Significance: Evidence from the UK Biobank indicates mosaic chromosome Y loss in leukocytes is moderately associated with increased incidence of select solid tumors.

GENOME AND EPIGENOME

- 467** Functional Analysis and Fine Mapping of the 9p22.2 Ovarian Cancer Susceptibility Locus

Melissa A. Buckley, Nicholas T. Woods, Jonathan P. Tyrer, Gustavo Mendoza-Fandiño, Kate Lawrenson, Dennis J. Hazelett, Hamed S. Najafabadi, Anxhela Gjyshi, Renato S. Carvalho, Paulo C. Lyra Jr, Simon G. Coetzee, Howard C. Shen, Ally W. Yang, Madalene A. Earp, Sean J. Yoder, Harvey Risch, Georgia Chenevix-Trench, Susan J. Ramus, Catherine M. Phelan, Gerhard A. Coetzee, Houtan Noushmehr, Timothy R. Hughes, Thomas A. Sellers, Ellen L. Goode, Paul D. Pharoah, Simon A. Gayther, and Alvaro N.A. Monteiro, on behalf of the Ovarian Cancer Association Consortium

Significance: Mapping the 9p22.2 ovarian cancer risk locus identifies BNC2 as an ovarian cancer risk gene.

See related commentary, p. 439

- 482** TET2-Dependent Hydroxymethylome Plasticity Reduces Melanoma Initiation and Progression

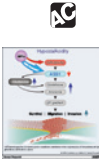
Elise Bonvin, Enrico Radaelli, Martin Bizet, Flavie Luciani, Emilie Calonne, Pascale Putmans, David Nittner, Nitesh Kumar Singh, Sara Francesca Santagostino, Valérie Petit, Lionel Larue, Jean Christophe Marine, and François Fuks

Significance: This work emphasizes the importance of epigenome plasticity in cancer development and highlights the involvement of druggable epigenetic factors in cancer.



Table of Contents

- 495** **Implications of Epigenetic Drift in Colorectal Neoplasia**
Georg E. Luebeck, William D. Hazelton, Kit Curtius, Sean K. Maden, Ming Yu, Kelly T. Carter, Wynn Burke, Paul D. Lampe, Christopher I. Li, Cornelia M. Ulrich, Polly A. Newcomb, Maria Westerhoff, Andrew M. Kaz, Yanxin Luo, John M. Inadomi, and William M. Grady
Significance: These findings present age-related methylomic drift in colorectal neoplasia as evidence that premalignant cells can persist for decades before becoming cancerous.
See related commentary, p. 437
- 505** **Genetic Data from Nearly 63,000 Women of European Descent Predicts DNA Methylation Biomarkers and Epithelial Ovarian Cancer Risk**
Yaohua Yang, Lang Wu, Xiang Shu, Yingchang Lu, Xiao-Ou Shu, Qiuyin Cai, Alicia Beeghly-Fadiel, Bingshan Li, Fei Ye, Andrew Berchuck, Hoda Anton-Culver, Susana Banerjee, Javier Benitez, Line Bjørge, James D. Brenton, Ralf Butzow, Ian G. Campbell, Jenny Chang-Claude, Kexin Chen, Linda S. Cook, Daniel W. Cramer, Anna deFazio, Joe Dennis, Jennifer A. Doherty, Thilo Dörk, Diana M. Eccles, Digna Velez Edwards, Peter A. Fasching, Renée T. Fortner, Simon A. Gayther, Graham G. Giles, Rosalind M. Glasspool, Ellen L. Goode, Marc T. Goodman, Jacek Gronwald, Holly R. Harris, Florian Heitz, Michelle A. Hildebrandt, Estrid Høgdall, Claus K. Høgdall, David G. Huntsman, Siddhartha P. Kar, Beth Y. Karlan, Linda E. Kelemen, Lambertus A. Kiemeny, Susanne K. Kjaer, Anita Koushik, Diether Lambrechts, Nhu D. Le, Douglas A. Levine, Leon F. Massuger, Keitaro Matsuo, Taymaa May, Iain A. McNeish, Usha Menon, Francesmary Modugno, Alvaro N. Monteiro, Patricia G. Moorman, Kirsten B. Moysich, Roberta B. Ness, Heli Nevanlinna, Håkan Olsson, N. Charlotte Onland-Moret, Sue K. Park, James Paul, Celeste L. Pearce, Tanja Pejovic, Catherine M. Phelan, Malcolm C. Pike, Susan J. Ramus, Elio Riboli, Cristina Rodriguez-Antona, Isabelle Romieu, Dale P. Sandler, Joellen M. Schildkraut, Veronica W. Setiawan, Kang Shan, Nadeem Siddiqui, Weiva Sieh, Meir J. Stampfer, Rebecca Sutphen, Anthony J. Swerdlow, Lukasz M. Szafron, Soo Hwang Teo, Shelley S. Tworoger, Jonathan P. Tyrer, Penelope M. Webb, Nicolas Wentzensen, Emily White, Walter C. Willett, Alicja Wolk, Yin Ling Woo, Anna H. Wu, Li Yan, Drakoulis Yannoukakos, Georgia Chenevix-Trench, Thomas A. Sellers, Paul D.P. Pharoah, Wei Zheng, and Jirong Long
Significance: Identification of novel DNA methylation markers associated with EOC risk suggests that methylation at multiple CpG may affect EOC risk through regulation of gene expression.

METABOLISM AND CHEMICAL BIOLOGY

- 518** **Acid-Induced Downregulation of ASS1 Contributes to the Maintenance of Intracellular pH in Cancer**

Alon Silberman, Omer Goldman, Odeya Boukobza Assayag, Adi Jacob, Shiran Rabinovich, Lital Adler, Joo Sang Lee, Rom Keshet, Alona Sarver, Julia Frug, Noa Stettner, Sivan Galai, Erez Persi, Keren Bahar Halpern, Yehudit Zaltsman-Amir, Ben Pode-Shakked, Raya Eilam, Yair Anikster, Sandesh C.S. Nagamani, Igor Ulitsky, Eytan Ruppim, and Ayelet Erez
Significance: Cancer cells in an acidic or hypoxic environment downregulate the expression of the urea cycle enzyme ASS1, which provides them with a redox and pH advantage, resulting in better survival.

MOLECULAR CELL BIOLOGY

- 534** **A GYS2/p53 Negative Feedback Loop Restricts Tumor Growth in HBV-Related Hepatocellular Carcinoma**

Shi-Lu Chen, Chris Zhiyi Zhang, Li-Li Liu, Shi-Xun Lu, Ying-Hua Pan, Chun-Hua Wang, Yang-Fan He, Cen-Shan Lin, Xia Yang, Dan Xie, and Jing-Ping Yun
Significance: We elucidated the clinical significance, biological function, and regulation of the HBx/GYS2/p53 axis, which supplement the understanding of tumor glycogen metabolism and provide potential prognostic and therapeutic targets for HCC treatment.
- 546** **Differential Subcellular Localization Regulates Oncogenic Signaling by ROS1 Kinase Fusion Proteins**

Dana S. Neel, David V. Allegakoen, Victor Olivas, Manasi K. Mayekar, Golzar Hemmati, Nilanjana Chatterjee, Collin M. Blakely, Caroline E. McCoach, Julia K. Rotow, Anh Le, Niki Karachaliou, Rafael Rosell, Jonathan W. Riess, Robert Nichols, Robert C. Doebele, and Trever G. Bivona
Significance: ROS1 fusion oncoproteins exhibit differential activation of MAPK signaling according to subcellular localization, with ROS1 fusions localized to endosomes the strongest activators of MAPK signaling.
- 557** **Cis-Acting circ-CTNNB1 Promotes β -Catenin Signaling and Cancer Progression via DDX3-Mediated Transactivation of YY1**
Feng Yang, Erhu Fang, Hong Mei, Yajun Chen, Huanhuan Li, Dan Li, Huajie Song, Jianqun Wang, Mei Hong, Wenjing Xiao, Xiaojing Wang, Kai Huang, Liduan Zheng, and Qiangsong Tong
Significance: These findings reveal the oncogenic functions of a cis-acting circular RNA in β -catenin activation and cancer progression, with potential value as a therapeutic target for human cancers.

TUMOR BIOLOGY AND IMMUNOLOGY

572 Super-Enhancer–Associated Long Noncoding RNA HCCL5 is Activated by ZEB1 and Promotes the Malignancy of Hepatocellular Carcinoma

Li Peng, Binyuan Jiang, Xiaoqing Yuan, Yuntan Qiu, Jiangyun Peng, Yongsheng Huang, Chaoyang Zhang, Yin Zhang, Zhaoyu Lin, Jinsong Li, Weicheng Yao, Weixi Deng, Yaqin Zhang, Meng Meng, Xi Pan, Chunquan Li, Dong Yin, Xinyu Bi, Guancheng Li, and De-Chen Lin

Significance: These findings identify the lncRNA HCCL5 as a super-enhancer–driven oncogenic factor that promotes the malignancy of hepatocellular carcinoma.

585 Precise Spatiotemporal Interruption of Regulatory T-cell–Mediated CD8⁺ T-cell Suppression Leads to Tumor Immunity

Xiaoyu Zhou, Shushu Zhao, Yue He, Shuang Geng, Yan Shi, and Bin Wang

Significance: These findings reveal a strong tumor suppressive effect invoked by minimal blockade of tumor draining lymph node regulatory T cells during early versus late tumorigenesis.

598 Hepatic Endothelial Notch Activation Protects against Liver Metastasis by Regulating Endothelial-Tumor Cell Adhesion Independent of Angiocrine Signaling



Sebastian A. Wohlfeil, Verena Häfele, Bianca Dietsch, Kai Schledzewski, Manuel Winkler, Johanna Zierow, Thomas Leibing, Mona Malek Mohammadi, Joerg Heineke, Carsten Sticht, Victor Olsavszky, Philipp-Sebastian Koch, Cyrill Géraud, and Sergij Goerd

Significance: Manipulation of Notch signaling in the endothelium has opposing, organ-specific effects on metastasis to the lung and the liver, demonstrating that this pathway should be targeted in a cell- and context-specific fashion.

611 Macrophage-Derived IL1 β and TNF α Regulate Arginine Metabolism in Neuroblastoma



Livingstone Fultang, Laura D. Gamble, Luciana Gneo, Andrea M. Berry, Sharon A. Egan, Fenna De Bie, Orli Yogev, Georgina L. Eden, Sarah Booth, Samantha Brownhill, Ashley Vardon, Carmel M. McConville, Paul N. Cheng, Murray D. Norris, Heather C. Etchevers, Jayne Murray, David S. Ziegler, Louis Chesler, Ronny Schmidt, Susan A. Burchill, Michelle Haber, Carmela De Santo, and Francis Mussai

Significance: These findings illustrate that cross-talk between myeloid cells and tumor cells creates a metabolic regulatory loop that promotes neuroblastoma progression.

TRANSLATIONAL SCIENCE

625 Inhibitor of Differentiation-1 Sustains Mutant KRAS-Driven Progression, Maintenance, and Metastasis of Lung Adenocarcinoma via Regulation of a FOSL1 Network

Marta Román, Inés López, Elisabeth Guruceaga, Iosune Baraibar, Margarita Ecay, María Collantes, Ernest Nadal, Adrián Vallejo, Silvia Cadenas, Marta Echavarri-de Miguel, Jae Hwi Jang, Patxi San Martín-Uriz, Laura Castro-Labrador, Amaia Vilas-Zornoza, David Lara-Astiaso, Mariano Ponz-Sarvisé, Christian Rolfo, Edgardo S. Santos, Luis E. Raez, Simona Taverna, Carmen Behrens, Walter Weder, Ignacio I. Wistuba, Silvestre Vicent, and Ignacio Gil-Bazo

Significance: These findings highlight the prognostic significance of the transcriptional regulator Id1 in KRAS-mutant lung adenocarcinoma and provide mechanistic insight into how it controls tumor growth and metastasis.

639 Inhibition of Notch Signaling Enhances Chemosensitivity in B-cell Precursor Acute Lymphoblastic Leukemia

Paul Takam Kanga, Giada Dal Collo, Martina Midolo, Annalisa Adamo, Pietro Delfino, Angela Mercuri, Simone Cesaro, Elda Mimiola, Massimiliano Bonifacio, Angelo Andreini, Marco Chilosi, and Mauro Krampira

Significance: Inhibition of Notch signaling enhances the chemosensitivity of B-ALL cells, suggesting Notch inhibition as a potential therapeutic strategy to improve the outcome of patients with B-ALL.

650 DNA Methylation Controls Metastasis-Suppressive 14q32-Encoded miRNAs



Go Oshima, Elizabeth C. Poli, Michael J. Bolt, Alexandre Chlenski, Martin Forde, Jessica M.S. Jutzy, Neha Biyani, Mitchell C. Posner, Sean P. Pitroda, Ralph R. Weichselbaum, and Nikolai N. Khodarev

Significance: This study investigates epigenetic regulation of metastasis-suppressive miRNAs and the effect on metastasis.

663 CML Hematopoietic Stem Cells Expressing IL1RAP Can Be Targeted by Chimeric Antigen Receptor–Engineered T Cells



Walid Warda, Fabrice Larosa, Mathieu Neto Da Rocha, Rim Trad, Eric Deconinck, Ziad Fajloun, Cyril Faure, Denis Caillot, Marius Moldovan, Severine Valmary-Degano, Sabeha Biichle, Etienne Daguindau, Francine Garnache-Ottou, Sebastien Tabruyn, Olivier Adotevi, Marina Deschamps, and Christophe Ferrand

Significance: These findings present the first characterization and proof of concept of a chimeric antigen receptor directed against IL1RAP expressed by leukemic stem cells in the context of CML.


Table of Contents

POPULATION AND PREVENTION SCIENCE

- 676** **Smoking and Urinary Cotinine Levels Are Predictors of Increased Risk for Gastric Intestinal Metaplasia**
Kyungeun Kim, Yoosoo Chang, Jiin Ahn, Hyo-Joon Yang, Ju Young Jung, Seokkyun Kim, Chong Il Sohn, and Seungho Ryu
Significance: A large-scale cohort study of nearly 200,000 adults associates smoking with increased risk for gastric intestinal metaplasia, a precursor lesion of stomach cancer.

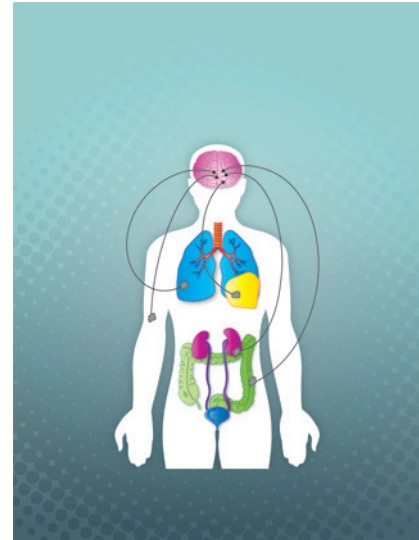
CORRECTION

- 685** **Correction: Celestrol Suppresses Angiogenesis-Mediated Tumor Growth through Inhibition of AKT/Mammalian Target of Rapamycin Pathway**
Xiufeng Pang, Zhengfang Yi, Jing Zhang, Binbin Lu, Bokyung Sung, Weijing Qu, Bharat B. Aggarwal, and Mingyao Liu

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ABOUT THE COVER

The incidence of brain metastasis is on the rise and despite advances in treatment strategies, prognosis remains poor. Integrated data from multiple resources show the epidemiology and survival of patients with brain metastasis from several cancer types. The brain microenvironment is crucial in facilitating metastatic growth, and neuroinflammation plays a central role in shaping the brain metastatic niche. For details on recent advances in our understanding of the brain metastatic microenvironment and neuroinflammation, see review by Doron and colleagues on page 423.



Cancer Research

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