

November 15, 2019 • Volume 79 • Number 22

BREAKING INSIGHTS

- 5683** Highlights from Recent Cancer Literature

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- 5685** Establishing the Impact of Vascular Damage on Tumor Response to High-Dose Radiation Therapy
Katherine D. Castle and David G. Kirsch
- 5693** Synthetic Lethal Interactions for Kinase Deficiencies to DNA Damage Chemotherapeutics
Lydia Robinson-Garcia, Joana Ferreira da Silva, and Joanna I. Loizou

CANCER RESEARCH HIGHLIGHTS

- 5699** MEK Inhibitors in Lung Cancer—You Can Teach an Old Drug New Tricks
Jonathan J. Havel
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- 5702** Personalized Cancer Therapy: YES1 Is the New Kid on the Block
Kunal Rai
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PRIORITY REPORT

- 5704** Tomoelastography Distinguishes Noninvasively between Benign and Malignant Liver Lesions
Mehrgan Shahryari, Heiko Tzschätzsch, Jing Guo, Stephan R. Marticorena Garcia, Georg Böning, Uli Fehrenbach, Lisa Stencel, Patrick Asbach, Bernd Hamm, Joseph A. Käs, Jürgen Braun, Timm Denecke, and Ingolf Sack
Significance: Solid-fluid tissue properties measured by tomoelastography can distinguish malignant from benign masses with high accuracy and provide quantitative noninvasive imaging biomarkers for liver tumors.

GENOME AND EPIGENOME

- 5711** MUC1-C Activates the NuRD Complex to Drive Dedifferentiation of Triple-Negative Breast Cancer Cells



Tsuyoshi Hata, Hasan Rajabi, Hidekazu Takahashi, Yota Yasumizu, Wei Li, Caining Jin, Mark D. Long, Qiang Hu, Song Liu, Atsushi Fushimi, Nami Yamashita, Ling Kui, Deli Hong, Masaaki Yamamoto, Masaaki Miyoy, Masayuki Hiraki, Takahiro Maeda, Yozo Suzuki, Mehmet K. Samur, and Donald Kufe

Significance: MUC1-C directly interacts with MYC to activate the NuRD complex, mediating regulation of the estrogen receptor in triple-negative breast cancer cells.

METABOLISM AND CHEMICAL BIOLOGY

- 5723** Deoxycytidine Release from Pancreatic Stellate Cells Promotes Gemcitabine Resistance
Simona Dalin, Mark R. Sullivan, Allison N. Lau, Beatrice Grauman-Boss, Helen S. Mueller, Emanuel Kreidl, Silvia Fenoglio, Alba Luengo, Jacqueline A. Lees, Matthew G. Vander Heiden, Douglas A. Lauffenburger, and Michael T. Hemann
Significance: This study provides important new insight into mechanisms that contribute to gemcitabine resistance in PDAC and suggests new avenues for improving gemcitabine efficacy.

MOLECULAR CELL BIOLOGY

- 5734** YES1 Is a Targetable Oncogene in Cancers Harboring YES1 Gene Amplification
Natsuki Hamanaka, Yoshito Nakanishi, Takakazu Mizuno, Kana Horiguchi-Takei, Nukinori Akiyama, Hiromi Tanimura, Masami Hasegawa, Yasuko Satoh, Yukako Tachibana, Toshihiko Fujii, Kiyooki Sakata, Kiyomoto Ogasawara, Hirokato Ebii, Hiroshi Koyano, Haruhiko Sato, Nobuya Ishii, and Toshiyuki Mio
Significance: These findings identify the SRC family kinase YES1 as a targetable oncogene in esophageal cancer and describe a new inhibitor for YES1 that has potential for clinical utility.
See related commentary, p. 5702

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5746 A ceRNA Circuitry Involving the Long Noncoding RNA Khl14-AS, Pax8, and Bcl2 Drives Thyroid Carcinogenesis

Sara C. Credendino, Maria L. Bellone, Nicole Lewin, Elena Amendola, Remo Sanges, Swaraj Basu, Romina Sepe, Myriam Decaussin-Petrucci, Nadia Tinto, Alfredo Fusco, Mario De Felice, and Gabriella De Vita

Significance: This study describes a new ceRNA with potential tumor suppression activity and helps us better understand the regulatory mechanisms during thyroid differentiation and carcinogenesis.

5758 S100A10 Is a Critical Mediator of GAS6/AXL-Induced Angiogenesis in Renal Cell Carcinoma

Yiren Xiao, Hongjuan Zhao, Lei Tian, Rosalie Nolley, Anh N. Diep, Anne Ernst, Katherine C. Fuh, Yu Rebecca Miao, Rie von Eyben, John T. Leppert, James D. Brooks, Donna M. Peehl, Amato J. Giaccia, and Erinn B. Rankin

Significance: These findings show that angiogenesis in renal cell carcinoma (RCC) is regulated through AXL/S100A10 signaling and support the combination of AXL inhibitors with antiangiogenic agents for the treatment of RCC.

5799 Diminished AHR Signaling Drives Human Acute Myeloid Leukemia Stem Cell Maintenance

Michelle Ly, Stefan Rentas, Ana Vujovic, Nicholas Wong, Steven Moreira, Joshua Xu, Nicholas Holzapfel, Sonam Bhatia, Damian Tran, Mark D. Minden, Jonathan S. Draper, and Kristin J. Hope

Significance: The AHR pathway is suppressed in leukemic stem cells (LSC), therefore activating AHR signaling is a potential therapeutic option to target LSCs and to treat acute myeloid leukemia.

5812 MEK Inhibition Modulates Cytokine Response to Mediate Therapeutic Efficacy in Lung Cancer

Mengyu Xie, Hong Zheng, Ranjna Madan-Lala, Wenjie Dai, Nicholas T. Gimbrone, Zhihua Chen, Fumi Kinose, Sarah A. Blackstone, Keiran S.M. Smalley, W. Douglas Cress, Eric B. Haura, Uwe Rix, and Amer A. Beg

Significance: Lung cancer cells are rendered sensitive to MEK inhibitors by TNF α and IFN γ , providing strong mechanistic rationale for combining immunotherapeutics, such as checkpoint blockers, with MEK inhibitor therapy for lung cancer.

See related commentary, p. 5699

TUMOR BIOLOGY AND IMMUNOLOGY

5769 Zebrafish MITF-Low Melanoma Subtype Models Reveal Transcriptional Subclusters and MITF-Independent Residual Disease



Jana Travnickova, Sonia Wojciechowska, Ava Khamseh, Philippe Gautier, Daniel V. Brown, Thomas Lefevre, Alessandro Brombin, Ailith Ewing, Amy Capper, Michaela Spitzer, Ramile Dilshat, Colin A. Semple, Marie E. Mathers, James A. Lister, Eiríkur Steingrímsson, Thierry Voet, Chris P. Ponting, and E. Elizabeth Patton

Significance: This study provides a useful model for MITF-low melanomas and MITF-independent cell populations that can be used to study the mechanisms that drive these tumors as well as identify potential therapeutic options.

5785 N⁶-Methyladenosine Modulates Nonsense-Mediated mRNA Decay in Human Glioblastoma

Fuxi Li, Yang Yi, Yanyan Miao, Wenyong Long, Teng Long, Siyun Chen, Weisheng Cheng, Changye Zou, Yueyuan Zheng, Xingui Wu, Junjun Ding, Kaiyu Zhu, Delin Chen, Qiongcong Xu, Jinkai Wang, Qing Liu, Feng Zhi, Jian Ren, Qi Cao, and Wei Zhao

Significance: These findings establish the oncogenic role of m⁶A writer METTL3 in glioblastoma stem cells.

5826 Tumor-Derived Thymic Stromal Lymphopoietin Expands Bone Marrow B-cell Precursors in Circulation to Support Metastasis

Emeline Ragonnaud, Kanako Moritoh, Monica Bodogai, Fedor Gusev, Soizic Garaud, Chen Chen, Xin Wang, Tuvshintugs Baljinnyam, Kevin G. Becker, Robert W. Maul, Karen Willard-Gallo, Evgeny Rogae, and Arya Biragyn

Significance: Cancer cells induce premature emigration of B-cell precursors from the bone marrow to generate regulatory B cells

TRANSLATIONAL SCIENCE

5839 Absence of HIF1A Leads to Glycogen Accumulation and an Inflammatory Response That Enables Pancreatic Tumor Growth

Marco Maruggi, Fabiana Izidro Layng, Robert Lemos Jr, Guillermina Garcia, Brian P. James, Monica Sevilla, Ferran Soldevilla, Bas J. Baaten, Petrus R. de Jong, Mei Yee Koh, and Garth Powis

Significance: These findings establish a novel mechanism by which tumors support angiogenesis in a HIF1 α -independent manner.

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5849 Oncogenic KRAS Sensitizes Lung Adenocarcinoma to GSK-J4–Induced Metabolic and Oxidative Stress

Beom-Jin Hong, Woo-Yong Park, Hwa-Ryeon Kim, Jin Woo Moon, Ho Yeon Lee, Jun Hyung Park, Seon-Kyu Kim, Youngbin Oh, Jae-Seok Roe, and Mi-Young Kim

Significance: This study not only provides a novel association between KRAS mutation and GSK-J4 sensitivity but also demonstrates the underlying mechanisms, suggesting a potential use of GSK-J4 in cancer patients with KRAS mutations.

5860 HNF4 α -Deficient Fatty Liver Provides a Permissive Environment for Sex-Independent Hepatocellular Carcinoma

Baharan Fekry, Aleix Ribas-Latre, Corrine Baumgartner, Alaa M.T. Mohamed, Mikhail G. Kolonin, Frances M. Sladek, Mamoun Younes, and Kristin L. Eckel-Mahan

Significance: This study provides a mechanism for the growing incidence of hepatocellular carcinoma in both men and women, which is linked to nonalcoholic fatty liver disease.

CONVERGENCE AND TECHNOLOGIES

5874 Investigating the Contribution of Collagen to the Tumor Biomechanical Phenotype with Noninvasive Magnetic Resonance Elastography



Jin Li, Konstantinos Zormpas-Petridis, Jessica K.R. Boulton, Emma L. Reeves, Andreas Heindl, Maria Vinci, Filipa Lopes, Craig Cummings, Caroline J. Springer, Louis Chesler, Chris Jones, Jeffrey C. Bamber, Yinyin Yuan, Ralph Sinkus, Yann Jamin, and Simon P. Robinson

Significance: MR elastography enables noninvasive detection of tumor stiffness and will aid in the development of ECM-targeting therapies

RESOURCE REPORT

5884 A Comprehensive PDX Gastric Cancer Collection Captures Cancer Cell–Intrinsic Transcriptional MSI Traits

Simona Corso, Claudio Isella, Sara E. Bellomo, Maria Apicella, Stefania Durando, Cristina Migliore, Stefano Ughetto, Laura D'Errico, Silvia Menegon, Daniel Moya-Rull, Marilisa Cargnelutti, Tania Capelôa, Daniela Conticelli, Jessica Giordano, Tiziana Venesio, Antonella Balsamo, Caterina Marchiò, Maurizio Degiuli, Rossella Reddavid, Uberto Fumagalli, Stefano De Pascale, Giovanni Sgroi, Emanuele Rausa, Gian Luca Baiocchi, Sarah Molfino, Filippo Pietrantonio, Federica Morano, Salvatore Siena, Andrea Sartore-Bianchi, Maria Bencivenga, Valentina Mengardo, Riccardo Rosati, Daniele Marrelli, Paolo Morgagni, Stefano Rausei, Giovanni Pallabazzer, Michele De Simone, Dario Ribero, Silvia Marsoni, Antonino Sottile, Enzo Medico, Paola Cassoni, Anna Sapino, Eirini Pectasides, Aaron R. Thorner, Anwesha Nag, Samantha D. Drinan, Bruce M. Wollison, Adam J. Bass, and Silvia Giordano

Significance: This study reports a multilevel platform of gastric cancer PDXs and identifies a MSI gastric signature that could contribute to the advancement of precision medicine in gastric cancer.

CORRECTION

5897 Correction: Recent Developments and Therapeutic Strategies against Hepatocellular Carcinoma

Mark Yarchoan, Parul Agarwal, Augusto Villanueva, Shuyun Rao, Laura Dawson, Thomas Karasic, Joseph Llovet, Richard Finn, John Groopman, Hashem El-Serag, Satdarshan Monga, Xin Wei Wang, Michael Karin, Robert Schwartz, Kenneth Tanabe, Lewis Roberts, Preethi Gunaratne, Allan Tsung, Kimberly Brown, Theodore Lawrence, Riad Salem, Amit Singal, Amy Kim, Atoosa Rabiee, Linda Resar, Jeffrey Meyer, Yujin Hoshida, Aiwu Ruth He, Kalpana Ghoshal, Patrick Ryan, Elizabeth Jaffee, Chandan Guha, Lopa Mishra, Norman Coleman, and Mansoor Ahmed



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ABOUT THE COVER

Stereotactic body radiation therapy in which a large radiation dose is delivered with each daily treatment to a tumor target can markedly improve local control, but the mechanism by which high-dose radiation therapy (RT) improves tumor cure has been controversial. Using genetically engineered mouse models of sarcoma and lung cancer, specific cellular compartments (tumor cells vs. endothelial cells) were radiosensitized to characterize the impact on tumor response to high-dose RT. While radiosensitization of tumor endothelial cells increased endothelial cell death and vascular dysfunction, the tumors still recurred following RT. By contrast, radiosensitization of tumor parenchymal cells (depicted in the schematic) directly enhanced radiation-induced growth delay of lung cancers and increased tumor cure of sarcomas. For details, see the article by Castle and Kirsch on page 5685.

