

August 15, 2019 • Volume 79 • Number 16

BREAKING INSIGHTS

- 3993** Highlights from Recent Cancer Literature

REVIEWS

- 3995** Chromosomal Instability in Tumor Initiation and Development
Duc-Hiep Bach, Wei Zhang, and Anil K. Sood
- 4003** Microenvironmental Metabolism Regulates Antitumor Immunity
Verra M. Ngwa, Deanna N. Edwards, Mary Philip, and Jin Chen

CANCER RESEARCH HIGHLIGHTS

- 4009** Precision Therapy for Aggressive Endometrial Cancer by Reactivation of Protein Phosphatase 2A
Kaitlin Haines and Gloria S. Huang
See related article, p. 4242

CONTROVERSY AND CONSENSUS

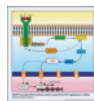
- 4011** Connecting Students with Patients and Survivors to Enhance Cancer Research Training
Robert N. Riter and Robert S. Weiss

MOLECULAR CELL BIOLOGY

- 4015** MYC Regulates the HIF2 α Stemness Pathway via Nanog and Sox2 to Maintain Self-Renewal in Cancer Stem Cells versus Non-Stem Cancer Cells
Bikul Das, Bidisha Pal, Rashmi Bhuyan, Hong Li, Anupam Sarma, Sukanya Gayan, Joyeeta Talukdar, Sorra Sandhya, Seema Bhuyan, Gayatri Gogoi, Arvin M. Gouw, Debabrat Baishya, Jason R. Gotlib, Amal C. Katak, and Dean W. Felsher
Significance: These findings show that the HIF2 α stemness pathway maintains leukemic stem cells downstream of MYC in human and mouse T-cell leukemias.

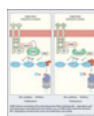


- 4026** Identification of Novel RAS Signaling Therapeutic Vulnerabilities in Diffuse Intrinsic Pontine Gliomas



Robert F. Koncar, Brittany R. Dey, Ann-Catherine J. Stanton, Nishant Agrawal, Michelle L. Wassell, Lauren H. McCarl, Abigail L. Locke, Lauren Sanders, Olena Morozova-Vaske, Max I. Myers, Ronald L. Hamilton, Angel M. Carcaboso, Gary Kohanbash, Baoli Hu, Nduka M. Amankulor, James Felker, Madhuri Kambhampati, Javad Nazarian, Oren J. Becher, C. David James, Rintaro Hashizume, Alberto Broniscer, Ian F. Pollack, and Sameer Agnihotri
Significance: These findings identify the H3K27M mutation as an enhancer of RAS activation in DIPG and ERK5 as a novel, immediately actionable molecular target.

- 4042** The Pro-Oncogenic Adaptor CIN85 Acts as an Inhibitory Binding Partner of Hypoxia-Inducible Factor Prolyl Hydroxylase 2



Nina Kozlova, Daniela Mennerich, Anatoly Samoylenko, Elitsa Y. Dimova, Peppi Koivunen, Ekaterina Biterova, Kati Richter, Antti Hassinen, Sakari Kellokumpu, Aki Manninen, Ilkka Miinalainen, Virpi Glumoff, Lloyd Ruddock, Lyudmyla Borysivna Drobot, and Thomas Kietzmann

Significance: This study provides unprecedented evidence for an oxygen-independent mechanism of PHD2 regulation that has important implications in cancer cell survival.

- 4057** ID1 Is Critical for Tumorigenesis and Regulates Chemoresistance in Glioblastoma

Rohit Sachdeva, Megan Wu, Sandra Smiljanic, Oleksandra Kaskun, Kimia Ghannad-Zadeh, Angela Celebre, Keren Isaev, A. Sorana Morissy, Jennifer Guan, Jiefei Tong, Jeffrey Chan, Taylor M. Wilson, Sayf Al-Omaishi, David G. Munoz, Peter B. Dirks, Michael F. Moran, Michael D. Taylor, Jüri Reimand, and Sunit Das

Significance: These findings show that the transcriptional regulator ID1 is critical for glioblastoma initiation and chemoresistance and that inhibition of ID1 enhances the effect of temozolomide, delays tumor recurrence, and prolongs survival.

- 4072** Isoflavone ME-344 Disrupts Redox Homeostasis and Mitochondrial Function by Targeting Heme Oxygenase 1

Leilei Zhang, Jie Zhang, Zhiwei Ye, Yefim Manevich, Lauren E. Ball, Jennifer R. Bethard, Yu-Lin Jiang, Ann-Marie Broome, Annamaria C. Dalton, Gavin Y. Wang, Danyelle M. Townsend, and Kenneth D. Tew

Significance: A novel cytotoxic isoflavone is shown to inhibit heme oxygenase, a desirable yet elusive target that disrupts redox homeostasis, causing cell death.

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4086 TRIM67 Activates p53 to Suppress Colorectal Cancer Initiation and Progression

Shiyan Wang, Yanquan Zhang, Junzhe Huang, Chi Chun Wong, Jianning Zhai, Chuangen Li, Guifeng Wei, Liuyang Zhao, Guoping Wang, Hong Wei, Zengren Zhao, and Jun Yu

Significance: The TRIM67/p53 axis represents a novel therapeutic target that could be harnessed to improve chemotherapy efficacy in colorectal cancer expressing wild-type p53 but with repressed p53 signaling.

4099 Recycling Endosomes in Mature Epithelia Restrain Tumorigenic Signaling

Luca D'Agostino, Yingchao Nie, Sayantani Goswami, Kevin Tong, Shiyan Yu, Sheila Bandyopadhyay, Juan Flores, Xiao Zhang, Iyshwarya Balasubramanian, Ivor Joseph, Ryotaro Sakamori, Victoria Farrell, Qi Li, Chung S. Yang, Bin Gao, Ronaldo P. Ferraris, Ghassan Yehia, Edward M. Bonder, James R. Goldenring, Michael P. Verzi, Lanjing Zhang, Y. Tony Ip, and Nan Gao

Significance: Recycling endosome traffic in mature epithelia constitutes a novel tumor suppressing mechanism.

4113 Inactivation of Bap1 Cooperates with Losses of Nf2 and Cdkn2a to Drive the Development of Pleural Malignant Mesothelioma in Conditional Mouse Models

Anna-Mariya Kukuyan, Eleonora Sementino, Yuwaraj Kadariya, Craig W. Menges, Mitchell Cheung, Yinfei Tan, Kathy Q. Cai, Michael J. Slifker, Suraj Peri, Andres J. Klein-Szanto, Frank J. Rauscher III, and Joseph R. Testa

Significance: Combinatorial deletions of Bap1, Nf2, and Cdkn2a result in aggressive mesotheliomas, with Bap1 loss contributing to tumorigenesis by circumventing PRC2-mediated repression of oncogenic target genes.

4124 Loss of PTEN Accelerates NKX3.1 Degradation to Promote Prostate Cancer Progression

Cai Bowen, Michael C. Ostrowski, Gustavo Leone, and Edward P. Gelmann

Significance: PTEN functions as a phosphatase of NKX3.1, a gatekeeper suppressor of prostate cancer.

4135 p38 Stabilizes Snail by Suppressing DYRK2-Mediated Phosphorylation That Is Required for GSK3 β -TrCP-Induced Snail Degradation

Ki-Jun Ryu, Sun-Mi Park, Seung-Ho Park, In-Kyu Kim, Hyeontak Han, Hyo-Jin Kim, Seon-Hee Kim, Keun-Seok Hong, Hyemin Kim, Minju Kim, Sung-Jin Yoon, Killivalavan Asaithambi, Kon Ho Lee, Jae-Yong Park, Young-Sool Hah, Hee Jun Cho, Jong In Yook, Jung Wook Yang, Gyung-Hyuck Ko, Gyemin Lee, Yang Jae Kang, Cheol Hwangbo, Kwang Dong Kim, Young-Jun Park, and Jiyun Yoo

Significance: These findings identify p38 MAPK as a novel regulator of Snail protein stability and potential therapeutic target in ovarian cancer.

TUMOR BIOLOGY AND IMMUNOLOGY

4149 Remodeling the Tumor Microenvironment Sensitizes Breast Tumors to Anti-Programmed Death-Ligand 1 Immunotherapy



Renee Clift, Jennifer Souratha, Sheryl A. Garrovillo, Susan Zimmerman, and Barbara Blouw

Significance: These findings show removal of hyaluronan in the tumor microenvironment improves immune cells and checkpoint inhibitors access to tumors.

4160 NOTCH Signaling via WNT Regulates the Proliferation of Alternative, CCR2-Independent Tumor-Associated Macrophages in Hepatocellular Carcinoma

Yu-Chen Ye, Jun-Long Zhao, Yi-Tong Lu, Chun-Chen Gao, Yang Yang, Shi-Qian Liang, Ying-Ying Lu, Lin Wang, Shu-Qiang Yue, Ke-Feng Dou, Hong-Yan Qin, and Hua Han

Significance: These findings highlight the role of NOTCH and WNT signaling in regulating TAMs in hepatocellular carcinoma.

4173 EN1 Is a Transcriptional Dependency in Triple-Negative Breast Cancer Associated with Brain Metastasis



Guillermo Peluffo, Ashim Subedee, Nicholas W. Harper, Natalie Kingston, Bojana Jovanović, Felipe Flores, Laura E. Stevens, Francisco Beca, Anne Trinh, Chandra Sekhar Reddy Chilamakuri, Evangelia K. Papachristou, Katherine Murphy, Ying Su, Andriy Marusyk, Clive S. D'Santos, Oscar M. Rueda, Andrew H. Beck, Carlos Caldas, Jason S. Carroll, and Kornelia Polyak

Significance: These findings show that the EN1 transcription factor regulates neurogenesis-related genes and is associated with brain metastasis in triple-negative breast cancer.

4184 Deletion of the Miz-1 POZ Domain Increases Efficacy of Cytarabine Treatment in T- and B-ALL/Lymphoma Mouse Models

Julie Ross, Marissa Rashkovan, Jennifer Fraszczak, Charles Joly-Beauparlant, Charles Vadnais, René Winkler, Arnaud Droit, Christian Kosan, and Tarik Mörröy

Significance: Ablation of the POZ domain of Miz-1 perturbs its interaction with c-MYC and delays the generation of T- and B-cell leukemias and lymphomas.

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- 4196** **Activation of the VEGFC/VEGFR3 Pathway Induces Tumor Immune Escape in Colorectal Cancer**
 Carlotta Tacconi, Federica Ungaro, Carmen Correale, Vincenzo Arena, Luca Massimino, Michael Detmar, Antonino Spinelli, Michele Carvello, Massimiliano Mazzone, Ana I. Oliveira, Federica Rubbino, Valentina Garlatti, Salvatore Spanò, Enrico Lugli, Federico S. Colombo, Alberto Malesci, Laurent Peyrin-Biroulet, Stefania Vetrano, Silvio Danese, and Silvia D'Alessio

Significance: The prolymphangiogenic factor VEGFC is abundant in colorectal cancer and activates VEGFR3 present on cancer-associated macrophages and lymphatic vessels; activation of VEGFR3 signalling fosters cancer immune escape, resulting in enhanced tumor growth.

- 4211** **Sphingosine Kinase 1 Signaling Promotes Metastasis of Triple-Negative Breast Cancer**
 Sunil Acharya, Jun Yao, Ping Li, Chenyu Zhang, Frank J. Lowery, Qingling Zhang, Hua Guo, Jingkun Qu, Fei Yang, Ignacio I. Wistuba, Helen Piwnica-Worms, Aysegul A. Sahin, and Dihua Yu

Significance: SPHK1 is overexpressed in TNBC and promotes metastasis; targeting SPHK1 or its downstream target NFκB with clinically available inhibitors could be effective for inhibiting TNBC metastasis.

- 4227** **Transcriptomic Differences between Primary Colorectal Adenocarcinomas and Distant Metastases Reveal Metastatic Colorectal Cancer Subtypes**
 Yasmin Kamal, Stephanie L. Schmit, Hannah J. Hoehn, Christopher I. Amos, and H. Robert Frost

Significance: These findings identify a colorectal adenocarcinoma metastasis-specific gene-expression signature that is free from potentially confounding background signals coming from treatment exposure and the normal host tissue that the metastasis is now situated within.

- 4242** **The Highly Recurrent PP2A Aα-Subunit Mutation P179R Alters Protein Structure and Impairs PP2A Enzyme Function to Promote Endometrial Tumorigenesis**

Sarah E. Taylor, Caitlin M. O'Connor, Zhizhi Wang, Guobo Shen, Haichi Song, Daniel Leonard, Jaya Sangodkar, Corinne LaVasseur, Stefanie Avril, Steven Waggoner, Kristine Zanotti, Amy J. Armstrong, Christa Nagel, Kimberly Resnick, Sareena Singh, Mark W. Jackson, Wenqing Xu, Shozeb Haider, Analisa DiFeo, and Goutham Narla

Significance: This study characterizes a highly recurrent, disease-specific PP2A PPP2R1A mutation as a driver of endometrial carcinoma and a target for novel therapeutic development.

See related commentary, p. 4009

TRANSLATIONAL SCIENCE

- 4258** **Chromosome 12p Amplification in Triple-Negative/BRCA1-Mutated Breast Cancer Associates with Emergence of Docetaxel Resistance and Carboplatin Sensitivity**



Jorge Gómez-Miragaya, Ander Díaz-Navarro, Raul Tonda, Sergi Beltran, Luis Palomero, Marta Palafox, Lacey E. Dobrolecki, Chen Huang, Suhas Vasaikar, Bing Zhang, Gerburg M. Wulf, Alejandro Collado-Sole, Eva M. Trinidad, Purificación Muñoz, Laia Paré, Aleix Prat, Alejandra Bruna, Carlos Caldas, Joaquín Arribas, María Teresa Soler-Monso, Anna Petit, Judith Balmaña, Cristina Cruz, Violeta Serra, Miguel Angel Pujana, Michael T. Lewis, Xose S. Puente, and Eva González-Suárez

Significance: Chr12p copy number gains indicate rapid emergence of resistance to docetaxel and increased sensitivity to carboplatin, therefore sequential docetaxel/carboplatin treatment could improve survival in TNBC/BRCA1 patients.

- 4271** **A Peptide Probe Enables Photoacoustic-Guided Imaging and Drug Delivery to Lung Tumors in K-ras^{LAZ} Mutant Mice**

Hyunkyung Jung, Sungjo Park, Gowri Rangaswamy Gunassekaran, Mansik Jeon, Young-Eun Cho, Moon-Chang Baek, Jae Yong Park, Gayong Shim, Yu-Kyoung Oh, In-San Kim, Chulhong Kim, and Byunghoon Lee

Significance: These findings present a new tumor-targeting probe for photoacoustic-guided detection and drug delivery.

- 4283** **ATP-Competitive Inhibitors Midostaurin and Avapritinib Have Distinct Resistance Profiles in Exon 17-Mutant KIT**

Beth Apsel Winger, Wilian A. Cortopassi, Diego Garrido Ruiz, Lucky Ding, Kibeom Jang, Ariel Leyte-Vidal, Na Zhang, Rosaura Esteve-Puig, Matthew P. Jacobson, and Neil P. Shah

Significance: This study identifies potential problematic kinase domain mutations for next generation KIT inhibitors midostaurin and avapritinib.

CONVERGENCE AND TECHNOLOGIES

- 4293** **Toward Personalized Computer Simulation of Breast Cancer Treatment: A Multiscale Pharmacokinetic and Pharmacodynamic Model Informed by Multitype Patient Data**

Xiaoran Lai, Oliver M. Geier, Thomas Fleischer, Øystein Garred, Elin Borgen, Simon W. Funke, Surendra Kumar, Marie E. Rognes, Therese Seierstad, Anne-Lise Børresen-Dale, Vessela N. Kristensen, Olav Engebraaten, Alvaro Köhn-Luque, and Arnoldo Frigessi

Significance: Mathematical modeling is used to validate possible mechanisms of tumor growth, resistance, and treatment outcome.

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EDITOR'S NOTES

- 4305** Editor's Note: Toll-Like Receptors on Tumor Cells Facilitate Evasion of Immune Surveillance
Bo Huang, Jie Zhao, Hongxing Li, Kai-Li He, Yibang Chen, Lloyd Mayer, Jay C. Unkeless, and Huabao Xiong

- 4306** Editor's Note: *Listeria monocytogenes* Promotes Tumor Growth via Tumor Cell Toll-Like Receptor 2 Signaling
Bo Huang, Jie Zhao, Shiqian Shen, Hongxing Li, Kai-Li He, Guan-Xin Shen, Lloyd Mayer, Jay Unkeless, Dong Li, Ye Yuan, Gui-Mei Zhang, Huabao Xiong, and Zuo-Hua Feng

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ABOUT THE COVER

YAP nuclear translocation and activation regulate cellular proliferation and growth of some solid tumors. Rab11, a family of small GTPases that control the recycling endosome-mediated protein trafficking, restrains YAP localization at apical junctions and cytoplasm in mature epithelial cells. During colonic tumorigenesis, loss of Rab11 function diminishes Hippo kinase activities, leading to increased YAP nuclear translocation and accelerated tumor growth. For details, see article by D'Agostino and colleagues on page 4099.

