

BREAKING INSIGHTS

- 2445** Highlights from Recent Cancer Literature

REVIEW

- 2447** Can Exercise-Induced Modulation of the Tumor Physiologic Microenvironment Improve Antitumor Immunity?

Xiaojie Zhang, Kathleen A. Ashcraft, Allison Betof Warner, Smita K. Nair, and Mark W. Dewhirst

CANCER RESEARCH HIGHLIGHTS

- 2457** Progress in Understanding Complexity and Determinants of Immune-Related Prognostic Subsets in Primary Melanoma

Andrea Anichini

See related article, p. 2684

- 2460** Phosphatase 1 Nuclear Targeting Subunit, a Novel DNA Repair Partner of PARP1

Junko Murai and Yves Pommier

See related article, p. 2526

CONTROVERSY AND CONSENSUS

- 2462** Liquid Biopsy: Is There an Advantage to Analyzing Circulating Exosomal DNA Compared to cfDNA or Are They the Same?

Christoph Kahlert

GENOME AND EPIGENOME

- 2466** Hemap: An Interactive Online Resource for Characterizing Molecular Phenotypes across Hematologic Malignancies



Petri Pölönen, Juha Mehtonen, Jake Lin, Thomas Liuksiala, Sergei Häyrynen, Susanna Teppo, Artturi Mäkinen, Ashwini Kumar, Disha Malani, Virva Pohjolainen, Kimmo Porkka, Caroline A. Heckman, Patrick May, Ville Hautamäki, Kirsi J. Granberg, Olli Lohi, Matti Nykter, and Merja Heinäniemi

Significance: This study describes a data resource for researching derailed cellular pathways and candidate drug targets across hematological malignancies.

METABOLISM AND CHEMICAL BIOLOGY

- 2480** Long Noncoding RNA MALAT1 Regulates Cancer Glucose Metabolism by Enhancing mTOR-Mediated Translation of TCF7L2

Pushkar Malakar, Ilan Stein, Amijai Saragovi, Roni Winkler, Noam Stern-Ginossar, Michael Berger, Eli Pikarsky, and Rotem Karni

Significance: These findings show that lncRNA MALAT1 contributes to HCC development by regulating cancer glucose metabolism, enhancing glycolysis, and inhibiting gluconeogenesis via elevated translation of the transcription factor TCF7L2.

- 2494** Free Fatty Acids Rewire Cancer Metabolism in Obesity-Associated Breast Cancer via Estrogen Receptor and mTOR Signaling

Zeynep Madak-Erdogan, Shoham Band, Yiru C. Zhao, Brandi P. Smith, Eylem Kulkoyluoglu-Cotul, Qianying Zuo, Ashlie Santaliz Casiano, Kinga Wrobel, Gianluigi Rossi, Rebecca L. Smith, Sung Hoon Kim, John A. Katzenellenbogen, Mariah L. Johnson, Meera Patel, Natascia Marino, Anna Maria V. Stornio, and Jodi A. Flaws

Significance: These findings show that obesity-associated changes in certain blood metabolites rewire metabolic programs in cancer cells, influence mammary epithelial cell tumorigenicity and aggressiveness, and increase breast cancer risk.

MOLECULAR CELL BIOLOGY

- 2511** Elevated Heme Synthesis and Uptake Underpin Intensified Oxidative Metabolism and Tumorigenic Functions in Non-Small Cell Lung Cancer Cells



Sagar Sohoni, Poorva Ghosh, Tianyuan Wang, Sarada Preeti Kalainayakan, Chantal Vidal, Sanchareeka Dey, Purna Chaitanya Konduri, and Li Zhang

Significance: These findings show that elevated heme availability due to increased heme synthesis and uptake causes intensified oxygen consumption and ATP generation, promoting tumorigenic functions and tumor growth in NSCLC.

- 2526** Phosphatase 1 Nuclear Targeting Subunit Mediates Recruitment and Function of Poly (ADP-Ribose) Polymerase 1 in DNA Repair

Feifei Wang, Songli Zhu, Laura A. Fisher, Ling Wang, Nicholas J. Eurek, James K. Wahl III, Li Lan, and Aimin Peng

Significance: These findings reveal PNUTS as an essential functional partner of PARP1 in DNA repair and suggest its inhibition as a potential therapeutic strategy in conjunction with DNA-damaging agents or PARP inhibitors.

See related commentary, p. 2460

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- 2536** **Temozolomide Treatment Induces lncRNA MALAT1 in an NF- κ B and p53 Codependent Manner in Glioblastoma**
David J. Voce, Giovanna M. Bernal, Longtao Wu, Clayton D. Crawley, Wei Zhang, Nassir M. Mansour, Kirk E. Cahill, Szymon J. Szymura, Abhineet Uppal, David R. Raleigh, Ruben Spretz, Luis Nunez, Gustavo Larsen, Nikolai N. Khodarev, Ralph R. Weichselbaum, and Bakhtiar Yamini
Significance: These findings identify NF- κ B and p53 as regulators of the lncRNA MALAT1 and suggest MALAT1 as a potential target for the chemosensitization of GBM.
- 2549** **Regulation of miRNA Biogenesis and Histone Modification by K63-Polyubiquitinated DDX17 Controls Cancer Stem-like Features**
Shih-Han Kao, Wei-Chung Cheng, Yi-Ting Wang, Han-Tsang Wu, Han-Yu Yeh, Yu-Ju Chen, Ming-Hsui Tsai, and Kou-Juei Wu
Significance: Hypoxia-induced polyubiquitination of DDX17 controls its dissociation from the pri-miRNA–Drosha–DCGR8 complex to reduce anti-stemness miRNA biogenesis and association with YAP and p300 to enhance transcription of stemness-related genes.
- 2564** **Genome-Wide Interrogation of Human Cancers Identifies EGLN1 Dependency in Clear Cell Ovarian Cancers**
Colles Price, Stanley Gill, Zandra V. Ho, Shawn M. Davidson, Erin Merkel, James M. McFarland, Lisa Leung, Andrew Tang, Maria Kost-Alimova, Aviad Tsherniak, Oliver Jonas, Francisca Vazquez, and William C. Hahn
Significance: These findings reveal a differential dependency of clear cell ovarian cancers on EGLN1, thus identifying EGLN1 as a potential therapeutic target in clear cell ovarian cancer patients.
- 2580** **Activation of MAPK Signaling by CXCR7 Leads to Enzalutamide Resistance in Prostate Cancer**
Shangze Li, Ka-wing Fong, Galina Gritsina, Ali Zhang, Jonathan C. Zhao, Jung Kim, Adam Sharp, Wei Yuan, Caterina Aversa, Ximing J. Yang, Peter S. Nelson, Felix Y. Feng, Arul M. Chinnaiyan, Johann S. de Bono, Colm Morrissey, Matthew B. Rettig, and Jindan Yu
Significance: These findings identify CXCR7-mediated MAPK activation as a mechanism of resistance to second-generation antiandrogen therapy, highlighting the therapeutic potential of MAPK/ERK inhibitors in CRPC.
- 2593** **NFAT1-Mediated Regulation of NDEL1 Promotes Growth and Invasion of Glioma Stem-like Cells**
Yang Jiang, Yifu Song, Run Wang, Tianhao Hu, Di Zhang, Zixun Wang, Xinxin Tie, Minghao Wang, and Sheng Han
Significance: NFAT1 controls the growth and invasion of GSCs, partially by regulating NDEL1. Targeting the NFAT1–NDEL1 axis might provide opportunities in treating patients with glioma.

- 2604** **Retinoic Acid–Related Orphan Receptor C Regulates Proliferation, Glycolysis, and Chemoresistance via the PD-L1/ITGB6/STAT3 Signaling Axis in Bladder Cancer**
Dalong Cao, Zihao Qi, Yangyang Pang, Haoran Li, Huyang Xie, Junlong Wu, Yongqiang Huang, Yao Zhu, Yijun Shen, Yiping Zhu, Bo Dai, Xin Hu, Dingwei Ye, and Ziliang Wang
Significance: These findings suggest that RORC-mediated regulation of a PD-L1/ITGB6/FAK/STAT3 signaling axis in bladder cancer provides several potential therapeutic targets to prevent tumor progression.

TUMOR BIOLOGY AND IMMUNOLOGY

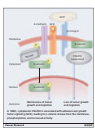
- 2619** **PDLIM2 Is a Marker of Adhesion and β -Catenin Activity in Triple-Negative Breast Cancer**
Orla T. Cox, Shelley J. Edmunds, Katja Simon-Keller, Bo Li, Bruce Moran, Niamh E. Buckley, Milan Bustamante-Garrido, Nollaig Healy, Ciara H. O'Flanagan, William M. Gallagher, Richard D. Kennedy, René Bernards, Carlos Caldas, Suet-Feung Chin, Alexander Marx, and Rosemary O'Connor
Significance: This study shows that PDLIM2 expression defines a subset of triple-negative breast cancer that may benefit from targeting the β -catenin and adhesion signaling pathways.
- 2634** **Cross-Talk between Receptor Tyrosine Kinases AXL and ERBB3 Regulates Invadopodia Formation in Melanoma Cells**
Or-Yam Revach, Oded Sandler, Yardena Samuels, and Benjamin Geiger
Significance: These findings uncover a unique interplay between AXL and ERBB3 in invadopodia regulation that points to the need for combined therapy in order to prevent invadopodia-mediated metastasis in melanoma.
- 2649** **MITF Expression Predicts Therapeutic Vulnerability to p300 Inhibition in Human Melanoma**
Edward Kim, Beth E. Zucconi, Muzhou Wu, Sarah E. Nocco, David J. Meyers, Jean S. McGee, Samantha Venkatesh, Daniel L. Cohen, Estela C. Gonzalez, Byungwoo Ryu, Philip A. Cole, and Rhoda M. Alani
Significance: These results show that MITF is a major downstream target of p300 in human melanoma whose expression is predictive of melanoma response to small-molecule inhibition of p300 HAT activity.
- 2662** **Dicer1 Phosphomimetic Promotes Tumor Progression and Dissemination**
Neeraj K. Aryal, Vinod Pant, Amanda R. Wasylshen, Bobbie J. Rimel, Laura Baseler, Adel K. El-Naggar, David G. Mutch, Paul J. Goodfellow, Swathi Arur, and Guillermina Lozano
Significance: This work highlights the relevance of Dicer1 phosphorylation in mammalian tumor development and dissemination.

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2669 Pan-TAM Tyrosine Kinase Inhibitor BMS-777607 Enhances Anti-PD-1 mAb Efficacy in a Murine Model of Triple-Negative Breast Cancer

Canan Kasikara, Viralkumar Davra, David Calianese, Ke Geng, Thomas E. Spires, Michael Quigley, Michael Wichroski, Ganapathy Sriram, Lucia Suarez-Lopez, Michael B. Yaffe, Sergei V. Kotenko, Mariana S. De Lorenzo, and Raymond B. Birge

Significance: These findings show that pan-inhibition of TAM receptors in combination with anti-PD1 may have clinical value as cancer therapeutics to promote an inflammatory tumor microenvironment and improve host antitumor immunity.

2684 Genetic and Environmental Determinants of Immune Response to Cutaneous Melanoma

Joanna Poźniak, Jérémie Nsengimana, Jonathan P. Laye, Sally J. O'Shea, Joey Mark S. Diaz, Alastair P. Droop, Anastasia Fila, Mark Harland, John R. Davies, Tracey Mell, Juliette A. Randerson-Moor, Sathya Muralidhar, Sabrina A. Hogan, Sandra Nicole Freiburger, Mitchell P. Levesque, Graham P. Cook, D. Timothy Bishop, and Julia Newton-Bishop

Significance: These findings identify novel genetic and environmental modulators of the immune response against primary cutaneous melanoma and predict their impact on patient survival.

See related commentary, p. 2457

2697 Extracellular Matrix Protein Tenascin C Increases Phagocytosis Mediated by CD47 Loss of Function in Glioblastoma

Ding Ma, Senquan Liu, Bachchu Lal, Shuang Wei, Shuyan Wang, Daqian Zhan, Hao Zhang, Richard S. Lee, Peisong Gao, Hernando Lopez-Bertoni, Mingyao Ying, Jian Jian Li, John Laterra, Mary Ann Wilson, and Shuli Xia

Significance: These findings link TNC to CD47-driven phagocytosis and demonstrate that TNC affects the anti-tumor function of brain TAM, facilitating the development of novel innate immune system-based therapies for brain tumors.

2709 Solid Tumor-Induced Immune Regulation Alters the GvHD/GvT Paradigm after Allogeneic Bone Marrow Transplantation

Nana Dang, Yuan Lin, Omer Rutgeerts, Xavier Sagaert, An D. Billiau, Mark Waer, and Ben Sprangers

Significance: These findings show that cells such as T cells or macrophages in the bone marrow inoculum may interfere with the systemic and local immune reactivity against tumors.

2722 Inhibition of EphB4-Ephrin-B2 Signaling Reprograms the Tumor Immune Microenvironment in Head and Neck Cancers

Shilpa Bhatia, Ayman Oweida, Shelby Lennon, Laurel B. Darragh, Dallin Milner, Andy V. Phan, Adam C. Mueller, Benjamin Van Court, David Raben, Natalie J. Serkova, Xiao-Jing Wang, Antonio Jimeno, Eric T. Clambey, Elena B. Pasquale, and Sana D. Karam

Significance: These findings present EphB4-ephrin-B2 inhibition as an alternative to anti-PDL1 therapeutics that can be used in combination with radiation to induce an effective antitumor immune response in patients with HNSCC.

2736 Melanoma-Induced Reprogramming of Schwann Cell Signaling Aids Tumor Growth

Galina V. Shurin, Oleg Kruglov, Fei Ding, Yan Lin, Xingxing Hao, Anton A. Keskinov, Zhaoyang You, Anna E. Lokshin, William A. LaFramboise, Louis D. Faló Jr, Michael R. Shurin, and Yuri L. Bunimovich

Significance: These findings reveal a role of the nerve injury response, particularly through functions of activated Schwann cells, in promoting melanoma growth.

TRANSLATIONAL SCIENCE

2748 An HK2 Antisense Oligonucleotide Induces Synthetic Lethality in HK1⁻HK2⁺ Multiple Myeloma



Shili Xu, Tianyuan Zhou, Hanna M. Doh, K Ryan Trinh, Art Catapang, Jason T. Lee, Daniel Braas, Nicholas A. Bayley, Reiko E. Yamada, Alex Vasuthasawat, Joshua P. Sasine, John M. Timmerman, Sarah M. Larson, Youngsoo Kim, A. Robert MacLeod, Sherie L. Morrison, and Harvey R. Herschman

Significance: A first-in-class HK2 antisense oligonucleotide suppresses HK2 expression in cell culture and in vivo, presenting an effective, tolerated combination therapy for preventing progression of HK1⁻HK2⁺ MM tumors.

2761 SWI/SNF-Compromised Cancers Are Susceptible to Bromodomain Inhibitors



Tatiana Shorstova, Maud Marques, Jie Su, Jake Johnston, Claudia L. Kleinman, Nancy Hamel, Sidong Huang, Moulay A. Alaoui-Jamali, William D. Foulkes, and Michael Witcher

Significance: These findings address an unmet clinical need by identifying loss of SMARCA4/A2 as biomarkers of hypersensitivity to BETi.

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CONVERGENCE AND TECHNOLOGIES

- 2775** **Molecular Imaging of Deoxycytidine Kinase Activity Using Deoxycytidine-Enhanced CEST MRI**
Zheng Han, Yuguo Li, Jia Zhang, Jing Liu, Chuheng Chen, Peter C. van Zijl, and Guanshu Liu
Significance: A new molecular MRI method that detects deoxycytidine kinase activity using its natural substrate deoxycytidine has great translational potential for clinical assessment of tumor resistance and prediction of treatment efficacy.

POPULATION AND PREVENTION SCIENCE

- 2784** **Breast Cancer Risk and Insulin Resistance: Post Genome-Wide Gene–Environment Interaction Study Using a Random Survival Forest**
Su Yon Jung, Jeanette C. Papp, Eric M. Sobel, Herbert Yu, and Zuo-Feng Zhang
Significance: These findings identify insulin resistance SNPs in combination with lifestyle as synergistic factors for breast cancer risk, suggesting lifestyle changes can prevent breast cancer in women who carry the risk genotypes.

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ABOUT THE COVER

CXCR7, an atypical chemokine receptor, is upregulated in enzalutamide-resistant prostate cancer. Activated CXCR7 interacts with β -arrestin 2 and internalizes into endosomes, wherein the complex acts as a scaffold protein for MAPK protein assembly. MAPK signaling provides an alternative survival pathway, leading to enzalutamide resistance. Using immunofluorescence, it was found that ectopically expressed CXCR7 localized mainly in the cytoplasmic aggregates, colocalizing with β -arrestin 2 in the endosomes. For details, see article by Li and colleagues on page 2580.

