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 Mehtomen, Jake Lin, Thomas Liukslaiia, Sergei Hayynen, Susanna Teppo, Atturi Mäkinen, Ashwini Kumar, Disha Malani, Virva Pohjolainen, Kimmo Porrka, Caroline A. Heckman, Patrick May, Ville Hautamäki, Kirsi I. Granberg, Olli Lohi, Matti Nykter, and Merja Heinaniemi
Significance: This study describes a data resource for researching detailed 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 IncRNA 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 Rosti, Rebecca L. Smith, Sung Hoon Kim, John A. Katzenellenbogen, Mariah L. Johnson, Meera Patel, Natasia Marino, Anna Maria V. Storniolo, 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, Poovala Ghosh, Tianyuan Wang, Sarada Preeta Kalainayakan, Chantal Vidal, Sanchareeka Dey, Purva Chaitanya Konduiri, 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 IncRNA MALAT1 in an NF-κB and p53 Codependent Manner in Glioblastoma  

Significance: These findings identify NF-κB and p53 as regulators of the IncRNA MALAT1 and suggest MALAT1 as a potential target for the chemosensitzation of GBM.

2549  Regulation of miRNA Biogenesis and Histone Modification by K63-Polyubiquitinated DDX17 Controls Cancer Stem-like Features  
Shih-Han Kao, Wei-Chang Cheng, Yi-Ting Wang, Han-Tsang Wu, Han-Yu Yeh, Yu-Ju Chen, Ming-Hsui Tsai, and Kou-Juey 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, Colles Price, Stanley Gill, Zandra V. Ho, and Konstantinos Natsis

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, Calina Grigola, 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, and William C. Hahn

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 Flu, 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, Zhiyuan Qin, Gang Liu, 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  

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  
Aviad Tsherniak, Oliver Jonas, Francisca Vazquez, and William C. Hahn

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  
Guillermina Lozano, David G. Mutch, Paul J. Goodfellow, Swathi Arur, and Benjamin Geiger

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  

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, Viral Kumar Davra, David Callanese, Ke Geng, Thomas E. Spires, Michael Quigley, Michael Wichirski, Ganapathy Sridram, 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

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, Senqun Liu, Bachehu Liu, Shuang Wei, Shuyan Wang, Daqian Zhan, Hao Zhang, Richard S. Lee, Peisong Cao, Hernandez Lopez-Bertoni, Mengyao Ying, Jian Juan Li, John Laterra, Mary Ann Wilson, and Shuli Xia

Significance: These findings link TNC to CD47-driven phagocytosis and demonstrate that TNC affects the antitumor 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, Ozmer 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 Microenvironment in Head and Neck Cancers

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

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. Bayle, 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. Hershman

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.
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.

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.