BREAKING INSIGHTS

4443 Highlights from Recent Cancer Literature

PRIORITY REPORTS

4445 Kras and Tp53 Mutations Cause Cholangiocyte- and Hepatocyte-Derived Cholangiocarcinoma

Significance: The histopathogenesis of biliary tract cancer, driven by Tp53 and Kras mutations, can be differentially impacted by the cell of origin within the mature liver as well by major epidemiological risk factors.

4452 Recurrent RARB Translocations in Acute Promyelocytic Leukemia Lacking RARA Translocation

Significance: These findings report a novel and distinct genetic subtype of acute promyelocytic leukemia (APL) by illustrating that the majority of APL without RARA translocations harbor RARB translocations.

4459 Aberrant FGFR Tyrosine Kinase Signaling Enhances the Warburg Effect by Reprogramming LDH Isoform Expression and Activity in Prostate Cancer
Junchen Liu, Guo Chen, Zexhen Liu, Shaoyou Liu, Zhiduan Cai, Pan You, Yuepeng Ke, Li Lai, Yun Huang, Hongchang Gao, Liangcai Zhao, Helene Pelicano, Peng Huang, Wallace L. McKeehan, Chin-Lee Wu, Cong Wang, Weide Zhong, and Fen Wang

Significance: FGF signaling drives the Warburg effect through differential regulation of LDHA and LDHB, thereby promoting the progression of prostate cancer.

4471 PDSS2 Deficiency Induces Hepatocarcinogenesis by Decreasing Mitochondrial Respiration and Reprogramming Glucose Metabolism
Yan Li, Shuhai Lin, Lei Li, Zhi Tang, Yumin Hu, Xiaojiao Ban, Tingting Zeng, Ying Zhou, Yinghui Zhu, Song Gao, Wen Deng, Xiaoshi Zhang, Dan Xie, Yunfei Yuan, Peng Huang, Jinjun Li, Zongwei Cai, and Xin-Yuan Guan

Significance: Downregulation of PDSS2 is a driving factor in hepatocellular carcinoma tumorigenesis.

4482 Enhanced Glycolysis Supports Cell Survival in EGFR-Mutant Lung Adenocarcinoma by Inhibiting Autophagy-Mediated EGFR Degradation
Ji Hye Kim, Boas Nam, Yun Jung Choi, Seon Ye Kim, Jung-Eun Lee, KI Jung Sung, Woo Sung Kim, Chang-Min Choi, Eun-Ju Chang, Jae Soo Koh, Joon Seon Song, Shinkyo Yoon, Jae Cheol Lee, Jin Ryung Rho, and Jaelyoung Son

Significance: Enhanced glycolysis by EGFR mutation is required for maintaining EGFR levels via inhibition of JNK-induced autophagy. This provides a promising rationale for use of JNK activators in patients with EGFR-mutated NSCLC.

METABOLISM AND CHEMICAL BIOLOGY

4497 R-spondin3 Is Associated with Basal-Progenitor Behavior in Normal and Tumor Mammary Cells
Johanna M. Tocci, Carla M. Felcher, Martín E. García Sol/a, María Victoria Goddio, Maria Noel Zimberlin, Natalia Rubinstein, Anabella Srebrow, Omar A. Coso, Martin C. Abba, Roberto P. Meis, and Edith C. Kordon

Significance: These findings identify RSPO3 as a potential therapeutic target in basal-like breast cancers.

4512 DDX3 Activates CBC-eIF3–Mediated Translation of uORF-Containing Oncogenic mRNAs to Promote Metastasis in HNSCC
Hung-Hsi Chen, Hsin-I. Yu, Muh-Hwa Yang, and Woan-Yuh Tarn

Significance: The discovery of DDX3-mediated expression of oncogenic uORF-containing genes expands knowledge on translational control mechanisms and provides potential targets for cancer therapy.
Expression of Long Noncoding RNA YIYA Promotes Glycolysis in Breast Cancer

Zhen Xing, Yanyan Zhang, Ke Liang, Liang Yan, Yu Xiang, Chunli Li, Qingsong Hu, Feng Jin, Vasanta Putluri, Nagireddy Putluri, Cristian Coasa, Arun Sreekumar, Peter K. Park, Tina K. Nguyen, Shouyu Wang, Jianwei Zhou, Yan Zhou, Jeffrey R. Marks, David H. Hawke, Mien-Chie Hung, Liuqing Yang, Leng Han, Haoqiang Ying, and Chunru Lin

Significance: These findings offer a first glimpse into how a long-coding RNA influences cancer metabolism to drive tumor growth.

The Endosomal Protein CEMIP Links WNT Signaling to MEK1–ERK1/2 Activation in Selumetinib-Resistant Intestinal Organoids

Hong Quan Duong, Ivan Nemazanyy, Florian Rambow, Seng Chuan Tang, Sylvain Delaunay, Lars Tharun, Alexandra Florin, Reinhard Büttner, Daniel Vandaele, Pierre Close, Jean-Christophe Marine, Kateryna Shostak, and Alain Chariot

Significance: MEK1 inhibitor-resistant colorectal cancer relies on the scaffold and endosomal protein CEMIP to maintain ERK1/2 signaling and Myc-driven transcription.

Transcription Factor YY1 Promotes Cell Proliferation by Directly Activating the Pentose Phosphate Pathway

Shourong Wu, Huimin Wang, Yanjun Li, Yudan Xie, Can Huang, Hezhao Zhao, Makoto Miyagishi, and Vivi Kasim

Significance: This study reveals a novel role for YY1 in regulating G6PD and activating the pentose phosphate pathway, linking its function in tumorigenesis to metabolic reprogramming.

Long Noncoding RNA CRYBG3 Blocks Cytokinesis by Directly Binding G-Actin

Hailong Pei, Wentao Hu, Ziyang Guo, Huaiyuan Chen, Ji Ma, Weidong Mao, Bingyan Li, Aiqing Wang, Jianmei Wan, Jian Zhang, Jing Nie, Guangming Zhou, and Tom K. Hei

Significance: Identification of the long noncoding RNA LNC CRYBG3 as a mediator of microfilament disorganization marks it as a novel therapeutic antitumor strategy.

CD4+ T-cell–Mediated Rejection of MHC Class II–Positive Tumor Cells Is Dependent on Antigen Secretion and Indirect Presentation on Host APCs

Ole Audun W. Haasth, Marte Fauskanger, Melanie Manzke, Katrin U. Lundin, Alexandre Corhay, Bjarne Bogen, and Anders A. Tveita

Significance: Elimination of tumors by CD4+ T cells recognizing secreted tumor neoantigens can occur in the absence of tumor cell-intrinsic MHC II expression, highlighting the potential clinical relevance of indirect antigen recognition by tumor-infiltrating APC.

Hypoxic Tumor-Derived Exosomal miR-301a Mediates M2 Macrophage Polarization via PTEN/PI3Kg to Promote Pancreatic Cancer Metastasis

Xiaofeng Wang, Guangtao Luo, Kumdong Zhang, Jun Cao, Chen Huang, Tao Jiang, Bingya Liu, Liping Su, and Zhengjun Qiu

Significance: These findings identify an exosomal miRNA critical for microenvironmental cross-talk that may prove to be a potential target for diagnosis and treatment of pancreatic cancer.

Inactivation of Citron Kinase Inhibits Medulloblastoma Progression by Inducing Apoptosis and Cell Senescence

Gianmarco Pallavicini, Francesco Sgrò, Francesca Garello, Martia Falcone, Valeria Bitonto, Gaia E. Betto, Federico T. Bianchi, Marta Gai, Alessandra M.A. Chiotto, Miriam Filippi, Juan C. Cutrin, Ugo Ala, Enzo Terreno, Emilia Turco, and Ferdinando Di Cunto

Significance: In vitro and in vivo proof of concept identifies citron kinase protein as a suitable target for medulloblastoma treatment.

Attenuated TRAF3 Fosters Activation of Alternative NF-κB and Reduced Expression of Antiviral Interferon, TP53, and RB to Promote HPV-Positive Head and Neck Cancers


Significance: These findings report the functional role of TRAF3 as a tumor suppressor that modulates the malignant phenotype of HPV+ head and neck cancers.
Mapping the HLA Ligandome of Colorectal Cancer Reveals an Imprint of Malignant Cell Transformation

Significance: Cancer-associated pathways are reflected in the antigenic landscape of colorectal cancer, suggesting that tumor-specific antigens do not necessarily have to be mutation-derived but may also originate from other alterations in cancer cells.

Tipifarnib Inhibits HRAS-Driven Dedifferentiated Thyroid Cancers
Brian R. Uitten, Vanessa Dos Anjos, Maria E.R. Garcia-Rendueles, Jeffrey A. Knauf, Gnana P. Krishnamoorthy, Mahesh Saezema, Umeshkumar K. Bhanot, Nicholas D. Socci, Alan L. Ho, Ronald Gosselien, and James A. Fajin

Significance: Tipifarnib effectively inhibits oncogenic HRAS-driven tumorigenesis and abrogating adaptive signaling improves responses. NF1 and GNAS mutations drive acquired resistance to Hras inhibition, supporting the on-target effects of the drug.

The Canonical Wnt Pathway Drives Macropinocytosis in Cancer

Significance: The Wnt pathway drives macropinocytosis in cancer cells, thereby contributing to cancer growth in nutrient-deficient conditions and, in the context of colon cancer, to the early phases of oncogenesis.

Epithelial–Mesenchymal Transition in Human Prostate Cancer Demonstrates Enhanced Immune Evasion Marked by IDO1 Expression
Kimberley Kolijn, Esther J. Verhoef, Marcel Smid, René Böttcher, Guido W. Jenster, Reno Debets, and Geert J.H. van Leenders

Significance: These findings demonstrate EMT is linked to an immunosuppressive environment in clinical prostate cancer, suggesting that patients with prostate cancer can potentially benefit from combinational drug therapy.

SHP-1 Acts as a Tumor Suppressor in Hepatocarcinogenesis and HCC Progression
Liang-Zhi Ren, Kai Ding, Ze-Rui Wang, Chen-Hong Ding, Shuo-Juan Lei, Jin-Pei Liu, Chuan Yin, Ping-Fang Hu, Jin Ding, Wan-Sheng Chen, Xin Zhang, and Wei-Fen Xie

Significance: The nonreceptor protein tyrosine phosphatase SHP-1 acts as a tumor suppressor in hepatocellular carcinoma.

Circulating Tumor Cells Undergoing EMT Provide a Metric for Diagnosis and Prognosis of Patients with Hepatocellular Carcinoma
Lu-Nan Qi, Bang-De Xiang, Fei-Xiang Wu, Jia-Zhou Ye, Jian-Hong Zhong, Yan-Yan Wang, Yuan-Yuan Chen, Zu-Shan Chen, Liang Ma, Jie Chen, Wen-Feng Gong, Ze-Guang Han, Yan Lu, Jin-Jie Shang, and Le-Qun Li

Significance: In liver cancer, CTC examination may represent an important “liquid biopsy” tool to detect both early disease and recurrent or metastatic disease, providing cues for early intervention or adjuvant therapy.
CD271⁺ Cells Are Diagnostic and Prognostic and Exhibit Elevated MAPK Activity in SHH Medulloblastoma

Lisa Liang, Ludivine Goudière-Morrison, Nazanian Tatari, Margaret Stromnecki, Agnes Frenouza, Christopher J. Porter, Marc R. Del Bigio, Cynthia Hawkins, Jennifer A. Chan, Timothy C. Ryken, Michael D. Taylor, Vijay Ramaswamy, and Tamra E. Werbowetski-Ogilvie

Significance: This study identifies CD271 as a specific and novel biomarker of SHH-type medulloblastoma and that targeting CD271⁺ cells through MEK inhibition represents a novel therapeutic strategy for the treatment of SHH medulloblastoma.

EWS/ETS-Driven Ewing Sarcoma Requires BET Bromodomain Proteins


Significance: These findings reveal the dependency of EWS/ETS transcription factors on BET epigenetic reader proteins and demonstrate the potential of BET inhibitors for the treatment of Ewing sarcoma.

Combined MR Imaging of Oxygen Consumption and Supply Reveals Tumor Hypoxia and Aggressiveness in Prostate Cancer Patients

Tord Hompland, Knut Håkon Hole, Harald Bull Ragnum, Eva-Katrine Aarnes, Ljiljana Vlatkovic, A. Katherine Lie, Sebastian Patzke, Bjørn Bremnhovd, Therese Seienstad, and Heidi Lyng

Significance: These findings present a novel imaging strategy that indirectly measures tumor hypoxia and has potential application in a wide variety of solid tumors and other imaging modalities.

Correction: Significance of MAD2 Expression to Mitotic Checkpoint Control in Ovarian Cancer Cells

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ABOUT THE COVER

Tumor microheterogeneity is common and subclones in primary tumors are potential mediators of tumor progression. Laser capture microdissection was used to isolate foci of residual tumor (purple and green) that remained after regression of the bulk tumor (red) in radical prostatectomy specimens from patients with prostate cancer treated for 6 months with neoadjuvant intensive androgen deprivation therapy. Whole exome sequencing identified foci-specific oncogenic alterations, including losses of RB1, BRCA2, or PTEN, indicating that the tumor prior to therapy contained subclones that were castration-resistant by distinct mechanisms. These subclones may evolve further and may be the origin of metastatic castration-resistant prostate cancer, and their early detection may allow for more effective adjuvant therapy. For details, see article by Sowalsky and colleagues on page 4716.