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## METABOLISM AND CHEMICAL BIOLOGY

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These findings highlight the metabolic dependence of IDH2 on the serine biosynthesis pathway, adding an important layer to the connection between TCA cycle and glycolysis, which can be translated into novel targeted therapies.

1445  Subcellular Distribution of p53 by the p53-Responsive IncRNA N4AT1 Determines Chemotherapeutic Response in Neuroblastoma

Sanhita Mitra, Somsundar Veppil Muralidharan, Micor Di Marco, Prasanna Kumar Juvuna, Subazini Thankaswamy Kosalai, Silke Reischl, Daniel Jachimowicz, Santhial Subhash, Ivan Raimondi, Leo Kurian, Maite Huarte, Per Kogner, Matthias Fischer, John Inge Johnsen, Tanmoy Mondal, and Chandrasekhar Kanduri

This study shows how a p53-responsive IncRNA mediates chemotherapeutic response by modulating nuclear p53 pathways and identifies a potential treatment strategy for patients with high-risk neuroblastoma.

1456  Serine-Threonine Kinase TAO3-Mediated Trafficking of Endosomes Containing the Invadopodia Scaffold TKS5a Promotes Cancer Invasion and Tumor Growth


An unbiased screening approach identifies TAO3 as a regulator of invadopodia formation and function, supporting clinical development of this class of target.

1460  HDAC5 Loss Impairs RB Repression of Pro-Oncogenic Genes and Confers CDK4/6 Inhibitor Resistance in Cancer

Yingke Zhou, Xin Jin, Jian Ma, Donglin Ding, Zhenlin Huang, Haoyue Sheng, Yujian Yan, Yunqian Pan, Ting Wei, Liguo Wang, Heshui Wu, and Haojie Huang

This study defines a previously uncharacterized role of HDAC5 in tumor suppression and provides a viable strategy to overcome CDK4/6 inhibitor resistance in HDAC5-deficient cancer.
TUMOR BIOLOGY AND IMMUNOLOGY

1500 A lncRNA TCL6-miR-155 Interaction Regulates the Src-Akt-EMT Network to Mediate Kidney Cancer Progression and Metastasis
Priyanka Kulkarni, Pritha Dasgupta, Yutaka Hashimoto, Marisa Shina, Varahram Sharharyari, Z. Laura Tabatabai, Soichiro Yamamura, Yuichiro Tanaka, Sharanjot Saini, Rajvir Dahia, and Shahana Majid
This study’s investigation of noncoding RNA interactions in renal cell carcinoma identify miRNA-155-lncRNA TCL6-miR-155-mediated regulation of the Src-Akt-EMT network as a novel mechanism of disease progression and metastasis.

1513 Oncogenic Ras Disrupts Epithelial Integrity by Activating the Transmembrane Serine Protease Hepsin
Topi A. Tervonen, Shishir M. Pant, Denis Belitkin, Johanna I. Englund, Katja närhi, Caj Haglund, Panu E. Kovanen, Emmy W. Verschuren, and Juha Klefström
These findings identify the cell-surface serine protease hepsin as a potential therapeutic target for its role in oncogenic Ras-mediated deregulation of epithelial cell–cell and cell–matrix interactions and cohesion of epithelial structure.

1528 Therapy-Induced Transdifferentiation Promotes Glioma Growth Independent of EGFR Signaling
Hwanhee Oh, Inah Hwang, Ja-Young Jang, Lingxiang Wu, Dongqing Cao, Jun Yao, Haoqiang Ying, Jian Yi Li, Yu Yao, Baoli Hu, Qianghu Wang, Hongwu Zheng, and Jihye Paik
This study demonstrates that molecular reprogramming and lineage transdifferentiation underlie anti-EGFR therapy resistance and are clinically relevant to the development of new combinatorial targeting strategies against malignant gliomas with aberrant EGFR signaling.

1540 The BRCA1 Pseudogene Negatively Regulates Antitumor Responses through Inhibition of Innate Immune Defense Mechanisms
Yoo Jane Han, Jing Zhang, Jung-Hyun Lee, Jennifer M. Mason, Olga Karginova, Tosio F. Yoshimatsu, Qinhuo Yao, Ian Hurley, Laia Paré Brunet, Aleix Prat, Kannanganattu V. Prasanth, Michaela U. Gack, and Olufunmilayo I. Olopade
This study identifies a novel mechanism of innate immunity driven by a host pseudogene RNA that inhibits innate immune defense mechanisms and antitumor responses through regulation of antiviral gene expression.

1552 Bladder Tumor Subtype Commitment Occurs in Carcinoma In Situ Driven by Key Signaling Pathways Including ECM Remodeling
Adrian Wullweber, Reiner Strick, Fabienne Lange, Danijel Sakić, Helge Taubert, Sven Wach, Bernd Wullich, Simone Bertz, Veronika Weyerer, Robert Stoehr, Johannes Breyer, Maximilian Burger, Arndt Hartmann, Pamela L. Strissel, and Markus Eckstein
This study demonstrates that CIS is the stage of commitment for determining MIBC tumor subtype, which is relevant for patient prognosis and therapy response.

1567 Mesenchymal Stem Cell–Secreted Extracellular Vesicles Instruct Stepwise Dedifferentiation of Breast Cancer Cells into Dormancy at the Bone Marrow Perivascular Region
These findings describe how the initial process of dormancy and dedifferentiation of breast cancer cells at the bone marrow perivascular niche requires mesenchymal stem cell–derived exosomes, indicating a potential target for therapeutic intervention.

1583 Ferroptosis Inducers Are a Novel Therapeutic Approach for Advanced Prostate Cancer
Ali Ghoochani, En-Chi Hsu, Merve Aslan, Meghan A. Rice, Holly M. Nguyen, James D. Brooks, Eva Corey, Ramasamy Paulmurugan, and Tanya Stoyanova
These findings reveal that induction of ferroptosis is a new therapeutic strategy for advanced prostate cancer as a monotherapy and in combination with second-generation antianaglogens.

1595 EMT Transcription Factor ZEB1 Represses the Mutagenic POLQ-Mediated End-Joining Pathway in Breast Cancers
Mélanie K. Prodhomme, Roxane M. Pommier, Camille Franchet, Frédérique Fauvet, Valérie Bergoglio, Pierre Brousset, Anne-Pierre Morel, Anne-Céline Brunac, Moïgan Devouassoux-Shisheboran, Virginie Petrilli, Caroline Moyret-Lalle, Jean-Sébastien Hoffmann, Alain Puisieux, and Agnès Tissier
These findings uncover an original mechanism of TMEJ regulation, highlighting ZEB1 as a key player in genome stability during cancer progression via its repression of POLQ.

See related commentary, p. 1441
Light at Night and Risk of Pancreatic Cancer in the NIH-AARP Diet and Health Study
Qian Xiao, Rena R. Jones, Peter James, and Rachael Z. Stolzenberg-Solomon

Our study suggests that higher LAN is a risk factor for pancreatic cancer, contributing to the growing literature that demonstrates the potentially adverse health effects of light pollution.

Retraction
Retraction: A Glycolytic Mechanism Regulating an Angiogenic Switch in Prostate Cancer

ABOUT THE COVER
Association of breast cancer subtypes with distinct metabolic phenotypes identified isocitrate dehydrogenase 2 (IDH2) as a key player in triple-negative breast cancer (TNBC) and HER2 subtypes. Wild-type IDH2 promoted cell proliferation, anchorage-independent growth, glycolysis, mitochondrial respiration, and antioxidant defense, thus revealing its protumorigenic role in TNBC cells. Serine biosynthesis pathway proteins were found to be metabolic synthetic dosage lethal partners of IDH2. Pharmacological inhibition of PHGDH sensitized cells with high IDH2 and inhibited tumor growth in vivo, emphasizing PHGDH inhibition as a therapeutic approach for triple-negative breast tumors with high IDH2. For details, see article by Barnabas and colleagues on page 1443.
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