

## CANCER RESEARCH

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## GENOME AND EPIGENOME

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Yanli Liu, Bingqian Guo, Estrella Aguilera-Jimenez, Vivian S. Chu, Jin Zhou, Zhong Wu, Joshua M. Francis, Xiaojun Yang, Peter S. Choi, Swneke D. Bailey, and Xiaoyang Zhang  
An integrative 3D genomics methodology delineates mechanisms underlying the function of KLF5 in multiple epithelial cancers and suggests potential strategies to target cancers with aberrantly activated KLF5.

## METABOLISM AND CHEMICAL BIOLOGY

**5478** Brain Tumor Stem Cell Dependence on Glutaminase Reveals a Metabolic Vulnerability through the Amino Acid Deprivation Response Pathway

**A C** Ian J. Restall, Orsolya Cseh, Laura M. Richards, Trevor J. Pugh, H. Artee Luchman, and Samuel Weiss  
Glioblastoma brain tumor stem cells with low astrocytic glutamate transporter expression are dependent on GLS to maintain intracellular glutamate to prevent the amino acid deprivation response and cell death.

**5491** Endocytosis-Mediated Replenishment of Amino Acids Favors Cancer Cell Proliferation and Survival in Chromophobe Renal Cell Carcinoma

**A C** Yi Xiao, Anja Rabien, René Buschow, Vyacheslav Amtislavskiy, Jonas Busch, Ergin Kilic, Sonia L. Villegas, Bernd Timmermann, Moritz Schütte, Thorsten Mielke, Marie-Laure Yaspo, Klaus Jung, and David Meierhofer  
This study reveals macropinocytosis as an important process utilized by chRCC to gain extracellular nutrients in a p53-independent manner.

## MOLECULAR CELL BIOLOGY

**5502** YAP Orchestrates Heterotypic Endothelial Cell Communication via HGF/c-MET Signaling in Liver Tumorigenesis

Stefan Thomann, Sofia M.E. Weiler, Simone Marquard, Fabian Rose, Claudia R. Ball, Marcell Tóth, Teng Wei, Carsten Sticht, Sarah Fritzsche, Stephanie Roessler, Carolina De La Torre, Eduard Ryschich, Olga Ermakova, Carolin Mogler, Daniel Kazdal, Norbert Gretz, Hanno Glimm, Eugen Rempel, Peter Schirmacher, and Kai Breuhahn

YAP-dependent changes of the liver vascular niche comprise the formation of heterologous communication hubs in which tumor cell-derived factors modify the cross-talk between EC subpopulations.

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**5515**    **Loss of Fbxw7 Impairs Development of and Induces Heterogeneous Tumor Formation in the Mouse Mammary Gland**

Ichiro Onoyama, Shogo Nakayama, Hideyuki Shimizu, and Keiichi I. Nakayama

Mammary gland-specific ablation of Fbxw7 in mice results in defective gland development and spontaneous mammary tumor formation reminiscent of human basal-like carcinoma with intratumoral heterogeneity.

**5531**    **Transient Activation of the Hedgehog-Gli Pathway Rescues Radiotherapy-Induced Dry Mouth via Recovering Salivary Gland Resident Macrophages**

Qingguo Zhao, Linying Zhang, Bo Hai, Jun Wang, Courtney L. Baetge, Michael A. Deveau, Geoffrey M. Kapler, Jian Q. Feng, and Fei Liu

These findings illuminate a novel direction for developing effective treatment of irreversible dry mouth, which is common after radiotherapy for head and neck cancer and for which no effective treatments are available.

See related commentary, p. 5462

**5543**    **Transcriptional Activation of MYC-Induced Genes by GCN5 Promotes B-cell Lymphomagenesis**

**A C**

Aimee T. Farria, Joshua B. Plummer, Andrew P. Salinger, Jianjun Shen, Kevin Lin, Yue Lu, Kevin M. McBride, Evangelia Koutelou, and Sharon Y.R. Dent

Our results provide important proof of principle for Gcn5 functions in formation and progression of Myc-driven cancers, suggesting that GCN5 may be a viable target for development of new cancer therapies.

## TUMOR BIOLOGY AND IMMUNOLOGY

**5554**    **Peritoneal Spread of Ovarian Cancer Harbors Therapeutic Vulnerabilities Regulated by FOXM1 and EGFR/ERBB2 Signaling**

Deepak Parashar, Bindu Nair, Anjali Geethadevi, Jasmine George, Ajay Nair, Shirng-Wern Tsaih, Ishaque P. Kadamberi, Gopa Kumar Gopinadhan Nair, Yiling Lu, Ramani Ramchandran, Denise S. Uyar, Janet S. Rader, Prahlad T. Ram, Gordon B. Mills, Sunila Pradeep, and Pradeep Chaluvally-Raghavan

This study describes the mechanism exhibited by ovarian cancer cells required for adherent cell transition to nonadherent form during peritoneal spread and metastasis.

**5569**    **A Wnt-Induced Phenotypic Switch in Cancer-Associated Fibroblasts Inhibits EMT in Colorectal Cancer**

Mohammed H. Mosa, Birgitta E. Michels, Constantin Menche, Adele M. Nicolas, Tahmineh Darvishi, Florian R. Greten, and Henner F. Farin

This study provides evidence for Wnt-induced functional diversity of colorectal cancer-associated fibroblasts, representing a non-cell autonomous mechanism for colon cancer progression.

**5583**    **Tumor Fibroblast-Derived FGF2 Regulates Expression of SPRY1 in Esophageal Tumor-Infiltrating T Cells and Plays a Role in T-cell Exhaustion**

Qing-yun Chen, Yi-ni Li, Xin-yue Wang, Xu Zhang, Yi Hu, Lei Li, Da-qin Suo, Ke Ni, Zhuo Li, Jia-rong Zhan, Ting-ting Zeng, Ying-hui Zhu, Yan Li, Li-jia Ma, and Xin-Yuan Guan

These findings reveal FGF2 as an important regulator of SPRY1 expression involved in establishing the dysfunctional state of CD8<sup>+</sup> T cells and suggest that inhibition of FGF2 has potential clinical value in ESCC.

## TRANSLATIONAL SCIENCE

**5597**    **Inhibition of IL1 $\beta$  by Canakinumab May Be Effective against Diverse Molecular Subtypes of Lung Cancer: An Exploratory Analysis of the CANTOS Trial**

**A C**

Connie C. Wong, Jason Baum, Angela Silvestro, Michael T. Beste, Bharani Bharani-Dharan, Siyan Xu, Ying A. Wang, Xiaoshan Wang, Margaret F. Prescott, Lynne Krajcovich, Margaret Dugan, Paul M. Ridker, Anne-Marie Martin, and Eric C. Svensson

These findings suggest that targeting the IL1 $\beta$  inflammatory pathway might be critical in reducing tumor-promoting inflammation and lung cancer incidence.

**5606**    **Cancers from Novel *Pole*-Mutant Mouse Models Provide Insights into Polymerase-Mediated Hypermutagenesis and Immune Checkpoint Blockade**

Melissa A. Galati, Karl P. Hodel, Miki S. Gams, Sumedha Sudhaman, Taylor Bridge, Walter J. Zahurancik, Nathan A. Ungerleider, Vivian S. Park, Ayse B. Ercan, Lazar Joksimovic, Iram Siddiqui, Robert Siddaway, Melissa Edwards, Richard de Borja, Dana Elshaer, Jiil Chung, Victoria J. Forster, Nuno M. Nunes, Melyssa Aronson, Xia Wang, Jagadeesh Ramdas, Andrea Seeley, Tomasz Sarosiek, Gavin P. Dunn, Jonathan N. Byrd, Oz Mordechai, Carol Durno, Alberto Martin, Adam Shlien, Eric Bouffet, Zucui Suo, James G. Jackson, Cynthia E. Hawkins, Cynthia J. Guidos, Zachary F. Pursell, and Uri Tabori

Two mouse models of polymerase exonuclease deficiency shed light on mechanisms of mutation accumulation and considerations for immunotherapy.

See related commentary, p. 5459

**5619**    **The Functional Landscape of Patient-Derived RNF43 Mutations Predicts Sensitivity to Wnt Inhibition**

Jia Yu, Permeen A. Mohamed Yusoff, Daniëlle T.J. Woutersen, Pamela Goh, Nathan Harmston, Ron Smits, David M. Epstein, David M. Virshup, and Babita Madan

Systematic examination of patient-derived RNF43 mutations identifies rules to guide patient selection, including that truncation or point mutations in well-defined functional domains sensitize cancers to PORCN inhibitors.

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## 5633 RIG-I-Like Receptor LGP2 Is Required for Tumor Control by Radiotherapy

Wenxin Zheng, Diana Rose E. Ranoa, Xiaona Huang, Yuzhu Hou, Kaiting Yang, Elizabeth C. Poli, Michael A. Beckett, Yang-Xin Fu, and Ralph R. Weichselbaum

These findings reveal an essential role of LGP2 in promoting antitumor immunity after radiotherapy and provides a new strategy to enhance radiotherapy.

## CONVERGENCE AND TECHNOLOGIES

## 5642 STAT3-Mediated Astrocyte Reactivity Associated with Brain Metastasis Contributes to Neurovascular Dysfunction

**AC**

Manuel Sarmiento Soto, James R. Larkin, Chris Martin, Alexandre A. Khrapitchev, Melissa Maczka,

Vasiliki Economopoulos, Helen Scott, Carole Escartin, Gilles Bonvento, Sébastien Serres, and Nicola R. Sibson

These findings demonstrate that selectively targeting STAT3-mediated astrocyte reactivity ameliorates the cerebrovascular dysfunction associated with brain metastasis, providing a potential therapeutic avenue for improved patient outcome.

**AC** AC icon indicates Author Choice

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## ABOUT THE COVER

Ovarian cancer cells rely on differential signaling of EGFR/ERBB2- or FOXM1-activated pathways when cancer cells become spheroids or when they attach to the mesothelium on distant organs, respectively. Using immunofluorescence, the authors photographed GFP-labeled ovarian cancer cells (green) that were grown on the RFP-labeled mesothelial cells (red). Ovarian cancer cells were then sorted, and gene expression signatures for both adherent and nonadherent cells were determined. The authors further identified that ZEB1 is an important regulator of EGFR, ERBB2, and FOXM1, which are critical for the transition between adherent and nonadherent forms of cells. For details, see the article by Parashar and colleagues on page 5554.

