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- These findings in mice show that, in addition to accidental mutations, cancer risk is determined by networks of individual gene variants.

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- 50 **Transcriptional Repression of SIRT3 Potentiates Mitochondrial Aconitase Activation to Drive Aggressive Prostate Cancer to the Bone**
Abhisha Sawant Dessai, Mayrel Palestino Dominguez, Uan-I Chen, John Hasper, Christian Prechtel, Cuijuan Yu, Eriko Katsuta, Tao Dai, Bokai Zhu, Sung Yun Jung, Nagireddy Putluri, Kazuaki Takabe, Xiang H.-F. Zhang, Bert W. O'Malley, and Subhamoy Dasgupta
- This study highlights the importance of mitochondrial aconitase activity in the development of advanced metastatic prostate cancer and suggests that blocking SRC-2 to enhance *SIRT3* expression may be therapeutically valuable.
- 64 **A Notch-Dependent Inflammatory Feedback Circuit between Macrophages and Cancer Cells Regulates Pancreatic Cancer Metastasis**
Yawen Geng, Jie Fan, Lianyu Chen, Chenyue Zhang, Chao Qu, Ling Qian, Kun Chen, Zhiqiang Meng, Zhen Chen, and Peng Wang
- This study provides potential therapeutic targets and robust preclinical evidence for PDAC treatment by interrupting feedback signaling between cancer cells and macrophages with targeted inhibitors.
- 77 **NSD3-Induced Methylation of H3K36 Activates NOTCH Signaling to Drive Breast Tumor Initiation and Metastatic Progression**
Ga-Young Jeong, Mi Kyung Park, Hee-Joo Choi, Hee Woon An, Young-Un Park, Hyung-Jun Choi, Jin Park, Hyung-Yong Kim, Taekwon Son, Ho Lee, Kyueng-Whan Min, Young-Ha Oh, Jeong-Yeon Lee, and Gu Kong
- This study demonstrates the functional significance of histone methyltransferase NSD3 in epigenetic regulation of breast cancer stemness, EMT, and metastasis, suggesting NSD3 as an actionable therapeutic target in metastatic breast cancer.

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This study elucidates that *de novo* expression of MUC5AC promotes cancer cell stemness during Kras-driven pancreatic tumorigenesis and can be targeted for development of a novel therapeutic regimen.

103 Design and Functional Validation of a Mutant Variant of the lncRNA *HOTAIR* to Counteract Snail Function in Epithelial-to-Mesenchymal Transition

Cecilia Battistelli, Sabrina Garbo, Veronica Riccioni, Claudia Montaldo, Laura Santangelo, Andrea Vandelli, Raffaele Strippoli, Gian Gaetano Tartaglia, Marco Tripodi, and Carla Cicchini
This study defines an innovative RNA-based strategy to interfere with a pivotal function of the tumor-related lncRNA *HOTAIR*, comprising a dominant negative mutant that was computationally designed and that impairs epithelial-to-mesenchymal transition.

114 Hypoxic Glioma Stem Cell-Derived Exosomes Containing Linc01060 Promote Progression of Glioma by Regulating the MZF1/c-Myc/HIF1 α Axis

Junjun Li, Tingting Liao, Hongya Liu, Hongliang Yuan, Taohui Ouyang, Jiajing Wang, Songshan Chai, Jinsong Li, Jingchao Chen, Xiang Li, Hongyang Zhao, and Nanxiang Xiong
These findings suggest that inhibition of Linc01060-containing exosomes or targeting the Linc01060/MZF1/c-Myc/HIF1 α axis may be an effective therapeutic strategy in glioma.

TUMOR BIOLOGY AND IMMUNOLOGY

129 The Amino-Terminal Oligomerization Domain of Angiopoietin-2 Affects Vascular Remodeling, Mammary Gland Tumor Growth, and Lung Metastasis in Mice

Emmi Kapiainen, Minna K. Kihlström, Riikka Pietilä, Mika Kaakinen, Veli-Pekka Ronkainen, Hongmin Tu, Anne Heikkinen, Raman Devarajan, Ilkka Miinalainen, Anna Laitakari, Mohammadhassan Ansarizadeh, Qin Zhang, Gong-Hong Wei, Lloyd Ruddock, Taina Pihlajaniemi, Harri Elamaa, and Lauri Eklund
This study identifies the role of the N-terminal oligomerization domain of angiopoietin-2 in vascular remodeling and lung metastasis and provides new insights into mechanisms underlying the versatile functions of angiopoietin-2 in cancer.

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144 Lipopolysaccharide-Mediated Chronic Inflammation Promotes Tobacco Carcinogen-Induced Lung Cancer and Determines the Efficacy of Immunotherapy

Chia-Hsin Liu, Zhong Chen, Kong Chen, Fu-Tien Liao, Chia-En Chung, Xiaoping Liu, Yu-Chun Lin, Phouthone Keohavong, George D. Leikauf, and Yuanpu Peter Di
This study identifies an immune gene signature that predicts treatment responses and survival in patients with tobacco carcinogen-induced lung cancer receiving immune checkpoint blockade therapy.

158 Enhanced Efficacy of Simultaneous PD-1 and PD-L1 Immune Checkpoint Blockade in High-Grade Serous Ovarian Cancer

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This study indicates that increased efficacy of immune therapies in ovarian cancer is driven by state changes of NK and small subsets of CD8 T cells into active and cytotoxic states.

174 ZMYND8 Expression in Breast Cancer Cells Blocks T-Lymphocyte Surveillance to Promote Tumor Growth

Yong Wang, Maowu Luo, Yan Chen, Yijie Wang, Bo Zhang, Zhenhua Ren, Lei Bao, Yanan Wang, Jennifer E. Wang, Yang-Xin Fu, Weibo Luo, and Yingfei Wang
These findings show that ZMYND8 is a new negative and intrinsic regulator of the innate immune response in breast tumor cells, and that ZMYND8 may be a possible target for antitumor immunotherapy.

TRANSLATIONAL SCIENCE

187 Hormonal Regulation of Semaphorin 7a in ER⁺ Breast Cancer Drives Therapeutic Resistance

Lyndsey S. Crump, Garhett L. Wyatt, Taylor R. Rutherford, Jennifer K. Richer, Weston W. Porter, and Traci R. Lyons
SEMA7A predicts for and likely contributes to poor response to standard-of-care therapies, suggesting that patients with SEMA7A⁺ER⁺ tumors may benefit from alternative therapeutic strategies.

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These data demonstrate a novel oncogenic role for PAK4 in rhabdomyosarcoma and show that targeting PAK4 activity is a promising viable therapeutic option for advanced rhabdomyosarcoma.

CONVERGENCE AND TECHNOLOGIES

213 Activatable Zymography Probes Enable *In Situ* Localization of Protease Dysregulation in Cancer

Ava P. Soleimany, Jesse D. Kirkpatrick, Susan Su, Jaideep S. Dudani, Qian Zhong, Ahmet Bekdemir, and Sangeeta N. Bhatia

Visualization of protease activity within the native tissue context using AZPs provides new biological insights into protease dysregulation in cancer and guides the design of conditional diagnostics and therapeutics.

225 Acknowledgment to Reviewers

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ABOUT THE COVER

Quantitative analysis of lung metastases in mouse cancer models can be troublesome, often requiring laborious tissue sectioning. In a B16F10 melanoma cell colonization model, cells were injected into tail veins of mice and their lungs collected after two weeks. The left lung lobes were processed, optically cleared, and scanned in 3D using optical projection tomography. This provided a novel method to accurately quantify the volume and number of melanoma cell colonies from whole mouse lungs. For details, see the article by Kapiainen and colleagues on page 129.

