BREAKING INSIGHTS

1 Highlights from Recent Cancer Literature

OBITUARY

3 Takashi Sugimura: In Memoriam (1926–2020)
Susumu Nishimura and Hitoshi Nakagama

REVIEWS

5 Rafting Down the Metastatic Cascade: The Role of Lipid Rafts in Cancer Metastasis, Cell Death, and Clinical Outcomes
Joshua D. Greenlee, Tejas Subramanian, Kevin Liu, and Michael R. King

18 Targeting CDK12 for Cancer Therapy: Function, Mechanism, and Drug Discovery
Hui Liu, Kangdong Liu, and Zigang Dong

27 Splenic Hematopoietic and Stromal Cells in Cancer Progression
Jonas Steenbrugge, Emiel A. De Jaeghere, Evelyne Meyer, Hannelore Denys, and Olivier De Wever

CANCER RESEARCH HIGHLIGHTS

35 Alternatively Spliced Form of Angiopoietin-2 as a New Vascular Rheostat
Miki Kamiyama and Hellmut G. Augustin
See related article, p. 129

MOLECULAR CELL BIOLOGY

50 Transcriptional Repression of SIRT3 Potentiates Mitochondrial Aconitase Activation to Drive Aggressive Prostate Cancer to the Bone
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.
TABLE OF CONTENTS

91 Secretory Mucin SAC Promotes Neoplastic Progression by Augmenting KLF4-Mediated Pancreatic Cancer Cell Stemness
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, 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/HIF1α 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/HIF1α axis may be an effective therapeutic strategy in glioma.

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.

See related commentary, p. 35

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
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.

TUMOR BIOLOGY AND IMMUNOLOGY

187 Hormonal Regulation of Semaphorin 7a in ER+ Breast Cancer Drives Therapeutic Resistance
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.
### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>Targeting PAK4 Inhibits Ras-Mediated Signaling and Multiple Oncogenic Pathways in High-Risk Rhabdomyosarcoma</td>
<td>Atreyi Dasgupta, Laura Sierra, Susan V. Tsang, Lyazat Kurenbekova, Tajhal Patel, Kimal Rajapakse, Ryan L. Shuck, Nino Rainusso, Yosef Landesman, Thaddeus Unger, Cristian Coarfa, and Jason T. Yustein</td>
</tr>
<tr>
<td>213</td>
<td>Activatable Zymography Probes Enable In Situ Localization of Protease Dysregulation in Cancer</td>
<td>Ava P. Soleimany, Jesse D. Kirkpatrick, Susan Su, Jaideep S. Dudani, Qian Zhong, Ahmet Bekdemir, and Sangeeta N. Bhatia</td>
</tr>
<tr>
<td>225</td>
<td>Acknowledgment to Reviewers</td>
<td></td>
</tr>
</tbody>
</table>

**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.
81 (1)


<table>
<thead>
<tr>
<th>Updated version</th>
<th>Access the most recent version of this article at: <a href="http://cancerres.aacrjournals.org/content/81/1">http://cancerres.aacrjournals.org/content/81/1</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>E-mail alerts</td>
<td>Sign up to receive free email-alerts related to this article or journal.</td>
</tr>
<tr>
<td>Reprints and Subscriptions</td>
<td>To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at <a href="mailto:pubs@aacr.org">pubs@aacr.org</a>.</td>
</tr>
<tr>
<td>Permissions</td>
<td>To request permission to re-use all or part of this article, use this link <a href="http://cancerres.aacrjournals.org/content/81/1">http://cancerres.aacrjournals.org/content/81/1</a>. Click on &quot;Request Permissions&quot; which will take you to the Copyright Clearance Center's (CCC) Rightslink site.</td>
</tr>
</tbody>
</table>