

# CANCER RESEARCH

# TABLE OF CONTENTS

## IN THE SPOTLIGHT

- 179**     **Harnessing p53 to Improve Immunotherapy for Lung Cancer Treatment**  
Xiaoteng Niu and Luis Martinez
- 181**     **Myeloid Cells Pave the Metastatic Road in Breast Cancer**  
Daniel E. Michaud and Jennifer L. Guerriero

## CANCER HALLMARKS REVIEW

- 184**     **Lineage Plasticity: The New Cancer Hallmark on the Block**  
Arnav Mehta and Ben Z. Stanger

## RESOURCE REPORT

- 192**     **Integration of Pan-Cancer Single-Cell and Spatial Transcriptomics Reveals Stromal Cell Features and Therapeutic Targets in Tumor Microenvironment**  
Yanhua Du, Jintong Shi, Jiabin Wang, Zhenzhen Xun, Zhuo Yu, Hongxiang Sun, Rujuan Bao, Junke Zheng, Zhigang Li, and Youqiong Ye
- Comprehensive characterization of tumor-associated nonimmune stromal cells provides a robust resource for dissecting tumor microenvironment complexity and guiding stroma-targeted therapy development across multiple human cancer types.

## CANCER BIOLOGY

- 211**     **Erythroid Differentiation Enhances RNA Mis-Splicing in *SF3B1*-Mutant Myelodysplastic Syndromes with Ring Sideroblasts**  
Pedro L. Moura, Teresa Mortera-Blanco, Isabel J. Hofman, Gabriele Todisco, Warren W. Kretzschmar, Ann-Charlotte Björklund, Maria Creignou, Michael Hagemann-Jensen, Christoph Ziegenhain, David Cabrerizo Granados, Indira Barbosa, Gunilla Walldin, Monika Jansson, Neil Ashley, Adam J. Mead, Vanessa Lundin, Marios Dimitriou, Tetsuichi Yoshizato, Petter S. Woll, Seishi Ogawa, Rickard Sandberg, Sten Eirik W. Jacobsen, and Eva Hellström-Lindberg
- Ring sideroblast isolation combined with state-of-the-art multiomics identifies survival mechanisms underlying *SF3B1*-mutant erythropoiesis and establishes an active role for erythroid differentiation and ring sideroblasts themselves in *SF3B1*-mutant myelodysplastic syndrome pathogenesis.

- 226**     **Small Cell Lung Cancer Plasticity Enables NFIB-Independent Metastasis**  
Julie H. Ko, Kyle E. Lambert, Debadrita Bhattacharya, Myung Chang Lee, Caterina I. Colón, Haley Hauser, and Julien Sage
- Small cell lung cancer cells overcome deficiency of the prometastatic oncogene NFIB to gain metastatic potential through various molecular mechanisms, which may represent targets to block progression of this fatal cancer type.

- 241**     **The Chromatin Remodeler CHD4 Sustains Ewing Sarcoma Cell Survival by Controlling Global Chromatin Architecture**  
Joana Graca Marques, Blaz Pavlovic, Quy A. Ngo, Gloria Pedot, Michaela Roemmele, Larissa Volken, Samanta Kisele, Romain Perbet, Marco Wachtel, and Beat W. Schäfer
- CRISPR/Cas9 screening in Ewing sarcoma identifies a dependency on CHD4, which is crucial for maintenance of chromatin architecture to suppress DNA damage and a promising therapeutic target for DNA damage repair-deficient malignancies.

## CANCER IMMUNOLOGY

- 258**     **Spatial and Single-Cell Transcriptomics Reveal a Cancer-Associated Fibroblast Subset in HNSCC That Restricts Infiltration and Antitumor Activity of CD8<sup>+</sup> T Cells**  
Chuwen Li, Haiyan Guo, Peisong Zhai, Ming Yan, Chun Liu, Xiaoning Wang, Chaoji Shi, Jiang Li, Tong Tong, Zhiyuan Zhang, Hailong Ma, and Jianjun Zhang
- Spatial analysis identifies IFN-induced MHC-I<sup>hi</sup>Gal9<sup>+</sup> CAFs that form a trap for CD8<sup>+</sup> T cells, providing insights into the complex networks in the tumor microenvironment that regulate T-cell infiltration and function.
- 276**     **HSF1 Inhibits Antitumor Immune Activity in Breast Cancer by Suppressing CCL5 to Block CD8<sup>+</sup> T-cell Recruitment**  
Curteisha Jacobs, Sakhi Shah, Wen-Cheng Lu, Haimanti Ray, John Wang, Natasha Hockaden, George Sandusky, Kenneth P. Nephew, Xin Lu, Sha Cao, and Richard L. Carpenter
- The stress-responsive transcription factor HSF1 reduces CD8<sup>+</sup> T-cell infiltration in breast tumors to prevent immune-mediated killing, indicating that cellular stress responses affect tumor-immune interactions and that targeting HSF1 could improve immunotherapies.

# TABLE OF CONTENTS

## CANCER METABOLISM AND MOLECULAR MECHANISMS

### 291 **Metabolomic Rewiring Promotes Endocrine Therapy Resistance in Breast Cancer**

Songyeon Ahn, Jun Hyoung Park, Sandra L. Grimm, Danthasinghe Waduge Badrajee Piyarathna, Tagari Samanta, Vasanta Putluri, Dereck Mezquita, Suzanne A.W. Fuqua, Nagireddy Putluri, Cristian Coarfa, and Benny Abraham Kaiparettu

Increased fatty acid oxidation induced by endocrine therapy activates Src signaling to promote endocrine resistance in breast cancer, which can be overcome using clinically approved therapies targeting FAO and Src.

### 305 **Glucose Deprivation Promotes Pseudohypoxia and Dedifferentiation in Lung Adenocarcinoma**

Pasquale Saggese, Aparamita Pandey, Martín Alcaraz Jr, Eileen Fung, Abbie Hall, Jane Yanagawa, Erika F. Rodriguez, Tristan R. Grogan, Giorgio Giurato, Giovanni Nassa, Annamaria Salvati, Orian S. Shirihai, Alessandro Weisz, Steven M. Dubinett, and Claudio Scafoglio

Epigenetic adaptation allows cancer cells to overcome the tumor-suppressive effects of glucose restriction by inducing dedifferentiation and an aggressive phenotype, which could help design better metabolic treatments.

### 328 **CircMMP2(6,7) Cooperates with $\beta$ -Catenin and PRMT5 to Disrupt Bone Homeostasis and Promote Breast Cancer Bone Metastasis**

Yingru Xu, Xincheng Li, Shuxia Zhang, Miaoling Tang, Ruyuan Yu, Xinyi Liao, Ziwen Li, Man Li, Suwen Chen, Wanying Qian, Libing Song, Zunfu Ke, and Jun Li

Upregulation of bone-remodeling factors S100A4 and LGALS3 mediated by a circMMP2(6,7)/ $\beta$ -catenin/PRMT5 complex generates a niche that supports breast cancer bone metastasis, identifying PRMT5 as a promising target for treating metastasis.

## ABOUT THE COVER

The status of intratumoral CD8<sup>+</sup> T cells is one of the determinants of immunotherapy efficiency. Cancer-associated fibroblasts interact with CD8<sup>+</sup> T cells to impact T-cell distribution and function. The cover image depicts a subset of cancer-associated fibroblasts expressing high levels of CXCLs and MHC class I molecules that trap CD8<sup>+</sup> T cells and induce dysfunction of pre-effector CD8<sup>+</sup> T cells via galectin-9. For details, see article by Li and colleagues on p. 258.

doi: 10.1158/0008-5472.CAN-84-2-CVR

