## CONTENTS

### IN THIS ISSUE
Highlighted research articles .......................... 1

### NEWS IN BRIEF
Important news stories affecting the community .......... 6

### NEWS IN DEPTH
A Deep Dive into Immunotherapy Resistance .......... 10

### RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature ............... 11

### ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.

### VIEWS
**In The Spotlight**

Evading the STING: LKB1 Loss Leads to STING Silencing and Immune Escape in KRAS-Mutant Lung Cancers .................. 16
C.M.D. Corte and L.A. Byers
See article, p. 34

Something Old, Something New: The Tumor Microenvironment Comes of Age .................. 19
K.L. Marie and G. Merlino
See article, p. 64
See article, p. 82

Circulating Tumor Cells: Come Together, Right Now, Over Metastasis .................. 22
P. Rodrigues and S. Vanharanta
See article, p. 96

### MINI REVIEW
The Biology of m6A RNA Methylation in Normal and Malignant Hematopoiesis ........ 25
L.P. Vu, Y. Cheng, and M.G. Kharas

### RESEARCH BRIEF
Suppression of STING Associated with LKB1 Loss in KRAS-Driven Lung Cancer .............. 34
Précis: Loss of LKB1 in KRAS-mutant lung cancer results in SAM-mediated activation of DNMT1 and EZH2, which subsequently represses the expression of STING and PD-L1 to promote immune escape.
See commentary, p. 16

### RESEARCH ARTICLES
Genome-Informed Targeted Therapy for Osteosarcoma ........ 46
Précis: Genomic characterization and the establishment of patient-derived xenografts identify therapeutic targets within recurrent SCNs in osteosarcoma subclasses.

Remodeling of the Collagen Matrix in Aging Skin Promotes Melanoma Metastasis and Affects Immune Cell Motility .............. 64
Précis: Loss of the cross-linking protein HAPLN1 in skin fibroblasts during aging results in changes to the extracellular matrix architecture that enhance melanoma cell invasion but impair immune cell infiltration.
See commentary, p. 19
Age-Related Changes in HAPLN1 Increase Lymphatic Permeability and Affect Routes of Melanoma Metastasis


Précis: Changes in ECM degradation and lymphatic vasculature permeability during aging are mediated by the cross-linking protein HAPLN1 and determine the route of metastatic dissemination.

See commentary, p. 19

Homophilic CD44 Interactions Mediate Tumor Cell Aggregation and Polyclonal Metastasis in Patient-Derived Breast Cancer Models


Précis: Intercellular homophilic CD44 interaction-mediated tumor cell aggregation recruits PAK2 and activates the PAK2 signaling pathway to drive tumorigenesis and polyclonal metastasis.

See commentary, p. 22

Spatiotemporal Loss of NF1 in Schwann Cell Lineage Leads to Different Types of Cutaneous Neurofibroma Susceptible to Modification by the Hippo Pathway


Précis: Inactivation of Nf1 in a Hoxb7-expressing cell lineage faithfully models neurofibromagenesis and provides insights into the developmental origin of both plexiform and cutaneous neurofibroma.

Cellular Origin, Tumor Progression, and Pathogenic Mechanisms of Cutaneous Neurofibromas Revealed by Mice with Nf1 Knockout in Boundary Cap Cells


Précis: Loss of Nf1 in Prss56-expressing boundary cap cells recapitulates both cutaneous and plexiform neurofibroma and provides insight into neurofibromagenesis.

Acknowledgment to Reviewers

Kitajima and colleagues found that KRAS-mutant/LKB1-null (KL) lung cancers exhibit upregulation of genes associated with oxidative stress and downregulation of genes involved in interferon signaling, including TMEM173, which encodes the dsDNA sensor STING. A screen of epigenetic inhibitors revealed that inhibiting DNMT1 and EZH2 restored STING expression in STING-low KL cell lines, and the binding of DNMT1 to the TMEM173 promoter was increased in STING-null KL cell lines compared to STING-low KL cell lines. Ectopic expression of LKB1 combined with inhibition of DNMT1 restored STING expression and pathway activation, and a STING agonist restored PD-L1 expression in KL cell lines. Collectively, these findings demonstrate that LKB1 negatively regulates STING in KRAS-driven lung cancer and suggest potential therapeutic strategies for patients with KRAS-mutant/LKB1-null lung cancer. For details, please see the article by Kitajima and colleagues on page 34.

ON THE COVER

Kitajima and colleagues found that KRAS-mutant/LKB1-null (KL) lung cancers exhibit upregulation of genes associated with oxidative stress and downregulation of genes involved in interferon signaling, including TMEM173, which encodes the dsDNA sensor STING. A screen of epigenetic inhibitors revealed that inhibiting DNMT1 and EZH2 restored STING expression in STING-low KL cell lines, and the binding of DNMT1 to the TMEM173 promoter was increased in STING-null KL cell lines compared to STING-low KL cell lines. Ectopic expression of LKB1 combined with inhibition of DNMT1 restored STING expression and pathway activation, and a STING agonist restored PD-L1 expression in KL cell lines. Collectively, these findings demonstrate that LKB1 negatively regulates STING in KRAS-driven lung cancer and suggest potential therapeutic strategies for patients with KRAS-mutant/LKB1-null lung cancer. For details, please see the article by Kitajima and colleagues on page 34.