IN THIS ISSUE

Highlighted research articles .......................115

NEWS IN BRIEF

Important news stories affecting the community ..........118

RESEARCH WATCH

Selected highlights of recent articles of exceptional significance from the cancer literature ..............123

ONLINE

For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

VIEWS

In The Spotlight

JAK Mutations as Escape Mechanisms to Anti–PD-1 Therapy ..................128
A. Marabelle, S. Aspeslagh, S. Postel-Vinay, and J.-C. Soria
See article, p. 188

Epigenomic Inactivation of RasGAPs Activates RAS Signaling in a Subset of Luminal B Breast Cancers ......131
R. Sears and J.W. Gray
See article, p. 202

Tuning Chromosomal Instability to Optimize Tumor Fitness ..................134
M.E. Burkard and B.A. Weaver
See article, p. 218

REVIEW

Targeting ALK: Precision Medicine Takes on Drug Resistance .............137
J.J. Lin, G.J. Riely, and A.T. Shaw

RESEARCH BRIEFS

Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax ........156
Précis: The hematologic malignancy blastic plasmacytoid dendritic cell neoplasm is characterized by sensitivity to BCL2 inhibition with venetoclax in vitro, in patient-derived xenografts, and in patients with relapsed/refractory disease.

Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse ............165
Précis: Chemotherapy-induced senescent noncancerous cells promote therapy-associated side effects, tumor metastasis, and relapse.

The Rodent Liver Undergoes Weaning-Induced Involution and Supports Breast Cancer Metastasis ............177
Précis: Weaning-induced liver involution establishes a prometastatic liver microenvironment in rodents, which may explain the increased risk for liver metastasis in patients with postpartum breast cancer.
Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations ....... 188


Précis: Loss-of-function JAK1/2 mutations induce loss of PD-L1 expression to drive primary resistance to anti–PD-1 therapy.

See commentary, p. 128

Shin and colleagues performed whole-exome sequencing of pretreatment biopsies from 23 patients with metastatic melanoma and 16 patients with metastatic colon cancer treated with anti–PD-1 therapy and identified a concomitant loss-of-function JAK1 mutation and amplification of the JAK locus in one of the patients with melanoma and a concomitant homozygous truncating JAK1 mutation and LOH at the JAK1 locus in one of the patients with colon cancer. Loss-of-function JAK1/2 mutations abrogated IFNγ-mediated signaling and subsequent upregulation of PD-L1 in patient-derived melanoma cell lines.

Analysis of the Cancer Cell Line Encyclopedia and The Cancer Genome Atlas databases revealed that truncating JAK1/2 mutations occurred in multiple types of cancer and were associated with significantly decreased overall survival in patients with melanoma or breast, prostate, and lung cancers. These findings describe the mechanism by which loss-of-function kinase mutations induce primary resistance to anti–PD-1 therapy. For details, please see the article by Shin and colleagues on page 188.

APC/C Dysfunction Limits Excessive Cancer Chromosomal Instability ......... 218


Précis: Reduced activity of the APC/C complex induces a mild mitotic delay that reduces segregation errors to allow tumor cells to circumvent the deleterious effects of excessive CIN.

See commentary, p. 134