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Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse ........ 165
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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.

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Loss of RasGAP Tumor Suppressors Underlies the Aggressive Nature of Luminal B Breast Cancers ………… 202


Précis: Expression of the RasGAPs DAB2IP and RASAL2 is concomitantly lost in a subset of aggressive luminal B breast tumors, promoting invasion and metastasis via activation of RAS and NF-κB signaling.

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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.

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ON THE COVER

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