Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax


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


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


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


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

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


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.

See commentary, p. 131

ON THE COVER
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.

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