Autophagy Inhibition Improves Chemosensitivity in BRAFV600E Brain Tumors 773

Précis: BRAFV600E-positive pediatric central nervous system tumor cells are autophagy-dependent and can be effectively targeted with combined chloroquine and vemurafenib therapy.

Obligate Progression Precedes Lung Adenocarcinoma Dissemination 781

Précis: Tumor-cell dissemination is a rate-limiting step in lung cancer metastasis that requires genetic alterations that can be facilitated by p53 loss and is characterized by downregulation of Nkx2-1.

SPSB1 Promotes Breast Cancer Recurrence by Potentiating c-MET Signaling 790

Précis: Upregulation of SPSB1 enhances the survival of residual tumor cells and mediates tumor recurrence by activating c-MET signaling in aggressive breast cancer subtypes. See commentary, p. 760

Rare Mutations in RINT1 Predispose Carriers to Breast and Lynch Syndrome-Spectrum Cancers 804

Précis: Rare variants in RINT1 are associated with increased risk for breast cancer as well as a spectrum of cancers that are associated with DNA mismatch repair defects. See commentary, p. 762
Mulcahy Levy and colleagues report that autophagy is increased in BRAF\textsuperscript{V600E}-positive pediatric central nervous system (CNS) tumors, suggesting that BRAF-mutant CNS tumors may be dependent on autophagy. Indeed, inhibition of autophagy was cytotoxic to BRAF\textsuperscript{V600E}-positive CNS tumor cells, and the autophagy inhibitor chloroquine showed synergistic activity with the BRAF inhibitor vemurafenib in BRAF-mutant CNS tumor cells. The addition of chloroquine to vemurafenib overcame vemurafenib resistance in primary BRAF-mutant pleomorphic xanthoastrocytoma cells, and combined chloroquine and vemurafenib rapidly improved symptoms and led to durable disease stabilization in a patient with vemurafenib-refractory BRAF\textsuperscript{V600E}-positive brainstem ganglioglioma. These findings provide a rationale for combining autophagy inhibitors with BRAF-targeted therapy in patients with BRAF-mutant CNS tumors. For details, please see the article by Mulcahy Levy and colleagues on page 773.