Autophagy Inhibition Improves Chemosensitivity in BRAFV600E Brain Tumors


Précis: BRAF V600E-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


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


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


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
A Melanoma Cell State Distinction Influences Sensitivity to MAPK Pathway Inhibitors .......... 816
Précis: BRAF-mutant melanoma can be classified into two transcriptional cell states that are defined by MITF and NF-κB activity and are correlated with intrinsic resistance to MAPK inhibition.

A High-Throughput Fluorimetric Assay for 2-Hydroxyglutarate Identifies Zaprinast as a Glutaminase Inhibitor .......... 828
Précis: Zaprinast is an inhibitor of glutaminase that reduces levels of the oncometabolite 2-hydroxyglutarate and shows activity in IDH-mutant and glutamine-addicted cancer cells.

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ON THE COVER
Mulcahy Levy and colleagues report that autophagy is increased in BRAFV600E-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 BRAFV600E-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 BRAFV600E-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.

Haploinsufficiency of an RB-E2F1-Condensin II Complex Leads to Aberrant Replication and Aneuploidy ................. 840
Précis: Loss of one RB1 allele disrupts a pRB-E2F1-condensin II complex that regulates DNA replication and is sufficient to induce replication stress, chromosome structure defects, and aneuploidy.
See commentary, p. 764

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