Autophagy Inhibition Improves Chemosensitivity in BRAFV600E Brain Tumors


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


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

In The Spotlight

SPSB1 May Have MET Its Match during Breast Cancer Recurrence

Y. Qin and S.S. McAllister

See article, p. 790

BluepRINT for Moderate-to-Low Penetration Cancer Susceptibility Genes Needed: Breast Cancer and Beyond

J. Ngeow and C. Eng

See article, p. 804

A Little pRB Can Lead to Big Problems

P.W. Hinds

See article, p. 840

Targeting Mitochondrial Metabolism by Inhibiting Autophagy in BRAF-Driven Cancers

A.M. Strohecker and E. White

See article, p. 766
Mulcahy Levy and colleagues report that autophagy is increased in 
BRAF\textsuperscript{V600E}-positive pediatric central nervous system (CNS) tumors, sug-
gestting 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 autophagy inhibitor vemurafenib in BRAF-mutant CNS tumor 
cells. The addition of chloroquine to vemurafenib overcame vemurafenib resis-
tance in primary BRAF-mutant pleomorphic xanthoastrocytoma cells, and com-
bined 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.

Haploinsufficiency of an 
RB-E2F1-Condensin II Complex 
Leads to Aberrant Replication 
and Aneuploidy .......................... 840

C.H. Coschi, C.A. Ishak, D. Gallo, A. Marshall, S. Talluri, 
J. Wang, M.J. Cecchini, A.L. Martens, V. Percy, 
I. Welch, P.C. Boutros, G.W. Brown, and F.A. Dick

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