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
Mulcahy Levy and colleagues report that autophagy is increased in  
BRAFV600E-positive pediatric central nervous system (CNS) tumors, sug-
gesting 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 resis-
tance in primary BRAF-mutant pleomorphic xanthoastrocytoma cells, and combi-
ined 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.

A Melanoma Cell State Distinction 
Influences Sensitivity to MAPK 
Pathway Inhibitors ..................... 816 
D.J. Konieczkowski, C.M. Johannessen, 
O. Abudayyeh, J.W. Kim, Z.A. Cooper, A. Piris, 
D.T. Frederick, M. Barzily-Rokni, R. Strausssman, 
Flaherty, J.A. Wargo, P. Tamayo, and L.A. Garraway 
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 
A. Elhammali, J.E. Ippolito, L. Collins, J. Crowley, 
J. Marasa, and D. Piwnica-Worms 
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.

See commentary, p. 764

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