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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.
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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.

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.

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.

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.

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.

Preclinical studies suggest that BRAFV600E-positive pediatric central nervous system (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. 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.
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