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- Restricted Expression of miR-30c-2-3p and miR-30a-3p in Clear Cell Renal Cell Carcinomas Enhances HIF2α Activity ............ 53
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- MAP Kinase Pathway Alterations in BRAF-Mutant Melanoma Patients with Acquired Resistance to Combined RAF/MEK Inhibition ............ 61
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Using data from a high-throughput drug screen, Faber and colleagues found that AZD8055, an inhibitor of mTOR complexes 1 and 2 (TORC1/2), cooperated with the BCL-2/BCL-XL inhibitor ABT-263 to induce cell-cycle arrest and apoptosis specifically in KRAS- and BRAF-mutant colorectal cancer cell lines. This genotype selectivity was mediated by suppression of the antiapoptotic protein MCL-1 and disruption of BIM–MCL-1 complexes in response to TORC1/2 inhibition, which sensitized KRAS-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in KRAS-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with KRAS- and BRAF-mutant colorectal cancer. For details, please see the article by Faber and colleagues on page 42.

A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition


See commentary, p. 27

Research Articles

Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy


Précis: Acquired BRAF inhibitor resistance is driven by heterogeneous genetic alterations that promote MAPK reactivation, PI3K–AKT upregulation, and branched clonal evolution.

See commentary, p. 27

The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma


Précis: Whole-exome sequencing identifies diverse mechanisms of resistance to vemurafenib or dabrafenib, many of which result in MAPK pathway reactivation.

See commentary, p. 27

Defective stromal remodeling and neutrophil extracellular traps in lymphoid tissues favor the transition from autoimmunity to lymphoma


Précis: Loss of the matricellular protein SPARC leads to altered stromal remodeling and abnormal neutrophil activity that exacerbate autoimmunity and promote B-cell transformation.

See commentary, p. 25

The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma


Précis: Whole-exome sequencing identifies diverse mechanisms of resistance to vemurafenib or dabrafenib, many of which result in MAPK pathway reactivation.

See commentary, p. 27