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Précis: mTORC inhibitors decrease MCL-1 translation and cooperate with BCL-2/BCL-XL inhibitors to induce apoptosis and growth arrest in KRAS- and BRAF-mutant colorectal cancer.

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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


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

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