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RESEARCH BRIEFS

mTOR Inhibition Specifically Sensitizes Colorectal Cancers with KRAS or BRAF Mutations to BCL-2/BCL-XL Inhibition by Suppressing MCL-1 ............ 42
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. See commentary, p. 19

Restricted Expression of miR-30c-2-3p and miR-30a-3p in Clear Cell Renal Cell Carcinomas Enhances HIF2α Activity ............ 53
Précis: Repression of specific miRNAs antagonizes the tumor-suppressive activity of HIF1α in ccRCC tumors by augmenting expression of the oncoprotein HIF2α. See commentary, p. 22

MAP Kinase Pathway Alterations in BRAF-Mutant Melanoma Patients with Acquired Resistance to Combined RAF/MEK Inhibition ........... 61
Précis: Whole-exome and transcriptome sequencing of dabrafenib- and trametinib-resistant melanomas identifies putative mechanisms of acquired resistance to combined RAF/MEK inhibition. See commentary, p. 27
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 \( \text{KRAS} \)- and \( \text{BRAF} \)-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 \( \text{KRAS} \)-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in \( \text{KRAS} \)-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with \( \text{KRAS} \)- and \( \text{BRAF} \)-mutant colorectal cancer.

For details, please see the article by Faber and colleagues on page 42.

**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

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**ON THE COVER**

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 \( \text{KRAS} \)- and \( \text{BRAF} \)-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 \( \text{KRAS} \)-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in \( \text{KRAS} \)-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with \( \text{KRAS} \)- and \( \text{BRAF} \)-mutant colorectal cancer. For details, please see the article by Faber and colleagues on page 42.