Antiangiogenic Therapies: Going beyond Their Limits .......................... 31
L. Moserle, G. Jiménez-Valerio, and O. Casanovas

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 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.

**Research Articles**

**A Novel AKT1 Mutant Amplifies an Adaptive Melanoma Response to BRAF Inhibition**


**Précis:** BRAF inhibition induces an AKT-dependent early adaptive response that shapes selection of PI3K-AKT-amplifying late-resistance mutations and modulates sensitivity to AKT blockade.

**See commentary, p. 27**

**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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