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**Highlighted research articles**

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

## NEWS IN BRIEF

**Important news stories affecting the community**

6. **Q&A: Mitchell Zeller on the FDA and Tobacco**

10. **The Science of Tobacco Addiction and Cessation**

## NEWS IN DEPTH

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22. **miR-30c-2-3p and miR-30a-3p: New Pieces of the Jigsaw Puzzle in HIF2α Regulation**
   
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27. **Towards a Unified Model of RAF Inhibitor Resistance**
   
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## RESEARCH BRIEFS

**Antiangiogenic Therapies: Going beyond Their Limits**

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**


**Restricted Expression of miR-30c-2-3p and miR-30a-3p in Clear Cell Renal Cell Carcinomas Enhances HIF2α Activity**


**MAP Kinase Pathway Alterations in BRAF-Mutant Melanoma Patients with Acquired Resistance to Combined RAF/MEK Inhibition**


## ONLINE

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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 \( \text{KRAS} \)- 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.

**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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- NCI Issues Omics Checklist for Tests
- Obinutuzumab Breaks through to FDA Approval
- ICR Expands CanSAR Drug Discovery Platform
- ASCO Forges Ahead with CancerLinQ
- HPV Vaccine Works against Nine Viral Types
- Ibrutinib Approved for Mantle Cell Lymphoma

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