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

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


\textit{See commentary, p. 27}

\section*{Research Articles}

\subsection*{A Novel AKT1 Mutant Amplifies an Adaptive Melanoma Response to BRAF Inhibition}


\textit{See commentary, p. 27}

\subsection*{The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma}


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

\textit{See commentary, p. 27}

\subsection*{Defective Stromal Remodeling and Neutrophil Extracellular Traps in Lymphoid Tissues Favor the Transition from Autoimmunity to Lymphoma}


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

\textit{See commentary, p. 27}