CANCER DISCOVERY CONTENTS

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RESEARCH BRIEF
Clinical Acquired Resistance to RAF Inhibitor Combinations in BRAF-Mutant Colorectal Cancer through MAPK Pathway Alterations ...................... 358

Précis: Genetic alterations that drive sustained MAPK signaling in patients with BRAF-mutant colorectal cancer confer acquired resistance to RAF/EGFR and RAF/MEK inhibition but retain sensitivity to ERK inhibitors.
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A Large-Scale Analysis of Genetic Variants within Putative miRNA Binding Sites in Prostate Cancer ....................... 368

Précis: A large association study identified 22 SNPs in predicted microRNA binding sites (miRSNP) that are linked to prostate cancer risk, including miRSNPs in KLK3 and VAMP8 that are differentially regulated by specific miRNAs.
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The Genetics of Splicing in Neuroblastoma .............. 380

Précis: An integrative genomic analysis of differential alternative splicing patterns across the genome identified recurrently mutated intrinsic splicing motifs and genes potentially relevant to neuroblastoma and glioblastoma development.

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A Genetic Platform to Model Sarcomagenesis from Primary Adult Mesenchymal Stem Cells .......... 396
Précis: Hypoxic culture of Trp53-null bone marrow mesenchymal stem cells provides a platform to identify genetic drivers of undifferentiated sarcoma and reveals a critical role for the LRF–DLK1–SOX9 pathway in sarcomagenesis.

Atg7 Overcomes Senescence and Promotes Growth of Braf\(^{V600E}\)-Driven Melanoma .......... 410
X. Xie, J.Y. Koh, S. Price, E. White, and J.M. Mehnert
Précis: Deletion of the essential autophagy gene Atg7 in Braf\(^{V600E}\), Pten-null melanoma increases oxidative stress and senescence and suppresses tumor growth, establishing that autophagy supports the growth of these tumors.

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First Selective Small Molecule Inhibitor of FGFR4 for the Treatment of Hepatocellular Carcinomas with an Activated FGFR4 Signaling Pathway ................. 424
Précis: HCC cells with FGF19 gene amplification or overexpression and an intact FGFR4 signaling pathway are sensitive to potent and selective FGFR4 inhibition by the small molecule BLU9931 in vitro and in xenograft models.

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FGFR-Mediated Reactivation of MAPK Signaling Attenuates Antitumor Effects of Imatinib in Gastrointestinal Stromal Tumors ......................... 438
F. Li, H. Huynh, X. Li, D.A. Ruddy, Y. Wang, R. Ong, P. Chow, S. Qiu, A. Tam, D.P. Rakiec, R. Schlegel, J.E. Monahan, and A. Huang
Précis: Long-term imatinib treatment leads to downregulation of Sprouty proteins and FGFR-driven reactivation of the MAPK–ERK pathway in KIT-mutant GIST cells, which can be repressed by FGFR inhibition.

Deregulated control of alternative splicing has been implicated in many cancers. To map the genetic regulation of splicing in neuroblastoma, Chen and colleagues integrated genome and transcriptome data from a mouse model of neuroblastoma. Characterization of splicing quantitative trait loci (sQTL) highlighted genes that regulate alternative splicing and strain-specific splicing of genes that correlated with patient survival. In addition, the authors identified unique intronic splicing motifs in genes that were recurrently mutated in human neuroblastoma and glioblastoma. Mutation of these motifs resulted in functional changes in alternative splicing, and altered expression of the corresponding genes correlated with patient outcome in neuroblastoma. These results identify splicing factors and intronic splicing motifs that modulate alternative splicing across cancers and highlight candidate genes potentially involved in neuroblastoma. For details, please see the article by Chen and colleagues on page 380.