A Coding Single-Nucleotide Polymorphism in Lysine Demethylase KDM4A Associates with Increased Sensitivity to mTOR Inhibitors


Précis: A germline coding SNP in the chromatin-modifying enzyme gene KDM4A increases its protein turnover and enhances mTOR inhibitor sensitivity, suggesting this SNP as a potential candidate biomarker in NSCLC.

See commentary, p. 228
See article, p. 255

Lysine Demethylase KDM4A Associates with Translation Machinery and Regulates Protein Synthesis

C. Van Rechem, J.C. Black, M. Boukhali, M.J. Aryee, S. Gräslund, W. Haas, C.H. Benes, and J.R. Whetstine

Précis: Cytoplasmic KDM4A modulates protein synthesis via interaction with the translation initiation complex, and inhibition of KDM4A/KDM5A enhances mTOR inhibitor sensitivity.

See commentary, p. 228
See article, p. 245

Ligand-Independent EPHA2 Signaling Drives the Adoption of a Targeted Therapy–Mediated Metastatic Melanoma Phenotype


Précis: Chronic BRAF inhibition leads to AKT–EPHA2-induced melanoma cell invasion and is associated with metastatic spread in patients treated with BRAF inhibitors.

See article, p. 274
**MARCH 2015**

**CANCER DISCOVERY**

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### EPHA2 Is a Mediator of Vemurafenib Resistance and a Novel Therapeutic Target in Melanoma


**Précis:** EPHA2 upregulation confers BRAF inhibitor resistance in melanoma, which can be overcome by treatment with small-molecule inhibitors targeting EPHA2.

See article, p. 264

### PRMT5 Is Required for Lymphomagenesis Triggered by Multiple Oncogenic Drivers


**Précis:** PRMT5 cooperates with oncogenic drivers such as cyclin D1 to promote lymphomagenesis via p53 methylation, which alters p53 chromatin occupancy and inhibits proapoptotic p53 target genes.

See commentary, p. 234

### Combined Inhibition of MAP Kinase and KIT Signaling Synergistically Destabilizes ETV1 and Suppresses GIST Tumor Growth


**Précis:** Targeted destabilization of the lineage-specific transcription factor ETV1 via dual KIT/MEK inhibition disrupts an ETV1-KIT positive feedback loop and potently inhibits GIST tumor growth.

See commentary, p. 231

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### Correction

**Correction: Comprehensive Genomic Profiling of Pancreatic Acinar Cell Carcinomas Identifies Recurrent RAF Fusions and Frequent Inactivation of DNA Repair Genes**

Chromatin-modifying enzymes such as lysine (K)-specific demethylases (KDM) have been implicated in tumorigenesis. Van Rechem and colleagues identified a nonsynonymous coding SNP in KDM4A, which increased its protein turnover and was associated with worse outcome in non–small cell lung cancer. Reduced KDM4A expression or homozygosity for this SNP increased the sensitivity of lung cancer cells to mTOR inhibitors. In a second article, Van Rechem and colleagues found that KDM4A regulated protein synthesis by interacting with and modulating the distribution of translation initiation factors in polysome fractions. In addition, KDM4A depletion or treatment with a JmjC demethylase inhibitor enhanced the suppressive effects of mTOR inhibition on translation initiation. Together, these studies implicate KDM4A as a potential therapeutic target and a possible biomarker for mTOR inhibitor therapy. For details, please see the articles by Van Rechem and colleagues on pages 245 and 255. Cover photo by Johnathan R. Whetstine, of the sculpture Dancing Peptides by Mara Haseltine.

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**ON THE COVER**

Chromatin-modifying enzymes such as lysine (K)-specific demethylases (KDM) have been implicated in tumorigenesis. Van Rechem and colleagues identified a nonsynonymous coding SNP in KDM4A, which increased its protein turnover and was associated with worse outcome in non–small cell lung cancer. Reduced KDM4A expression or homozygosity for this SNP increased the sensitivity of lung cancer cells to mTOR inhibitors. In a second article, Van Rechem and colleagues found that KDM4A regulated protein synthesis by interacting with and modulating the distribution of translation initiation factors in polysome fractions. In addition, KDM4A depletion or treatment with a JmjC demethylase inhibitor enhanced the suppressive effects of mTOR inhibition on translation initiation. Together, these studies implicate KDM4A as a potential therapeutic target and a possible biomarker for mTOR inhibitor therapy. For details, please see the articles by Van Rechem and colleagues on pages 245 and 255. Cover photo by Johnathan R. Whetstine, of the sculpture Dancing Peptides by Mara Haseltine.