A Tale of Metabolites: The Cross-Talk between Chromatin and Energy Metabolism
B. Martínez-Pastor, C. Cosentino, and R. Mostoslavsky

Molecular Dissection of Microsatellite Instable Colorectal Cancer
E. Vilar and J. Tabernero

Histone H3.3 Mutations Drive Pediatric Glioblastoma through Upregulation of MYCN

Relief of Feedback Inhibition of HER3 Transcription by RAF and MEK Inhibitors Attenuates Their Antitumor Effects in BRAF-Mutant Thyroid Carcinomas

Précis: Histone variant H3.3 glycine-34 mutations induce differential genome-wide histone H3 lysine 36 trimethylation and lead to upregulation of MYCN in the developing forebrain.
See commentary, p. 484

Précis: Lineage-specific HER3 upregulation and ligand-dependent HER2/HER3 activation confer resistance to MAPK pathway inhibitors in BRAF-mutant thyroid cancer cells.
See commentary, p. 487
De-Repression of PDGFRβ Transcripton Promotes Acquired Resistance to EGFR Tyrosine Kinase Inhibitors in Glioblastoma Patients .................. 534
Précis: Transcriptional derepression of PDGFRβ in response to EGFR inhibition renders EGFR-mutant glioblastomas dependent on PDGFRβ for survival.

Coordinate Direct Input of Both KRAS and IGF1 Receptor to Activation of PI3 Kinase in KRAS-Mutant Lung Cancer .......... 548
M. Molina-Arcas, D.C. Hancock, C. Sheridan, M.S. Kumar, and J. Downward
Précis: KRAS-mutant NSCLC cells are selectively sensitive to inhibition of IGF1R, which is required for KRAS-mediated activation of PI3K signaling.
See commentary, p. 491

Bone Marrow–Derived Gr1+ Cells Can Generate a Metastasis-Resistant Microenvironment Via Induced Secretion of Thrombospondin-1 .......... 578
Précis: Metastasis-incompetent tumors systemically reprogram bone marrow–derived myeloid cells in the premetastatic niche to produce TSP-1 to suppress metastatic outgrowth.

ON THE COVER
Montero-Conde and colleagues show that BRAF-mutant thyroid cancer cells are resistant to RAF and MAP/ERK (MEK) inhibitors. Reactivation of RAS signaling in these cells was associated with de-repression of HER3 transcription due to decreased binding of C-terminal binding protein 1 and 2 (CTBP1/CTBP2) to the HER3 promoter. RAF/MEK inhibition also triggered increased HER3 phosphorylation and activation of HER2/HER3 heterodimers specifically in BRAF-mutant thyroid cancer cells. This effect was dependent on autocrine production of the HER3 ligand neuregulin 1 in thyroid cancer cells, identifying a lineage-specific mechanism of MAPK inhibitor resistance. Treatment with lapatinib sensitized thyroid cancer cells to RAF/MEK blockade and inhibited the growth of murine thyroid tumors, suggesting that this combination may overcome resistance in patients with thyroid cancer. For details, please see the article by Montero-Conde and colleagues on page 520.