### In Focus

**A Tale of Metabolites: The Cross-Talk between Chromatin and Energy Metabolism**

B. Martinez-Pastor, C. Cosentino, and R. Mostoslavsky

---

### Review

**Molecular Dissection of Microsatellite Instable Colorectal Cancer**

E. Vilar and J. Tabernero

---

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


**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

---

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


**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

---

### Research Articles

**Two Drugs Deemed Breakthrough Therapies**

---

**Q&A: Powel Brown on Cancer Prevention Research**

---

**In The Spotlight**

G34, Another Connection between MYCN and a Pediatric Tumor

M. Huang and W.A. Weiss

See article, p. 512

---

**Déjà Vu: EGF Receptors Drive Resistance to BRAF Inhibitors**

M.R. Girotti and R. Marais

See article, p. 520

---

**Two Is Better Than One: Combining IGF1R and MEK Blockade as a Promising Novel Treatment Strategy Against KRAS-Mutant Lung Cancer**

R. Chen and E.A. Sweet-Cordero

See article, p. 548

---

**Discovering What Makes STAT Signaling TYK in T-ALL**

L. Fontan and A. Melnick

See article, p. 564
De-Repression of PDGFRβ Transcription 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

TYK2–STAT1–BCL2 Pathway Dependence in T-cell Acute Lymphoblastic Leukemia. 564
Précis: Activation of tyrosine kinase 2 (TYK2) by mutation or autocrine interleukin-10 signaling promotes T-ALL cell survival through activation of STAT1 and upregulation of BCL2.
See commentary, p. 494

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.

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.