A Tale of Metabolites: The Cross-Talk between Chromatin and Energy Metabolism
B. Martinez-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

In Focus

In The Spotlight
G34, Another Connection between MYCN and a Pediatric Tumor
M. Huang and W.A. Weiss

Déjà Vu: EGF Receptors Drive Resistance to BRAF Inhibitors
M.R. Girotti and R. Marais

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

Discovering What Makes STAT Signaling TYK in T-ALL
L. Fontan and A. Melnick

Q&A: Powel Brown on Cancer Prevention Research
Two Drugs Deemed Breakthrough Therapies

Selected highlights of recent articles of exceptional significance from the cancer literature

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De-Repression of PDGFRβ Transcription Promotes Acquired Resistance to EGFR Tyrosine Kinase Inhibitors in Glioblastoma Patients


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

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


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


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.