ARID1A Mutations in Cancer: Another Epigenetic Tumor Suppressor? 35
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Opposing Effects of Androgen Deprivation and Targeted Therapy on Prostate Cancer Prevention 44

Précis: Antiandrogen therapies promote prostate cancer progression, whereas blockade of PI3K and MAPK signaling suppresses tumor growth in the context of PTEN deficiency.

Genotype-Selective Combination Therapies for Melanoma Identified by High-Throughput Drug Screening 52

Précis: A systematic screening approach was used to characterize inhibitor combinations that are effective in melanomas driven by specific oncogenic mutations.

Loss of 53BP1 Causes PARP Inhibitor Resistance in Brca1-Mutated Mouse Mammary Tumors 68

Précis: PARP inhibitor resistance can arise in vivo through partial restoration of homologous recombination caused by 53BP1 inactivation.
The mTORC1 Inhibitor Everolimus Prevents and Treats Eμ-Myc Lymphoma by Restoring Oncogene-Induced Senescence .................. 82
Précis: mTORC1-dependent bypass of MYC-induced senescence is required for the initiation and maintenance of Eμ-Myc B-cell lymphoma.

Targeting C4-Demethylating Genes in the Cholesterol Pathway Sensitizes Cancer Cells to EGF Receptor Inhibitors via Increased EGF Receptor Degradation ... 96
Précis: Sterol biosynthesis genes regulate EGFR endocytosis and signaling, and inhibition of these genes increases the efficacy of anti-EGFR therapies.

Oncogenic and Wild-type Ras Play Divergent Roles in the Regulation of Mitogen-Activated Protein Kinase Signaling ...................... 112
A. Young, D. Lou, and F. McCormick
See commentary, p. 24
Précis: Wild-type RAS isoforms regulate growth factor signaling in the context of oncogenic RAS and are required for optimal growth of cells harboring RAS mutations.

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Young and colleagues show that oncogenic and wild-type RAS isoforms have nonredundant, independent roles in cancer cells. Oncogenic RAS isoforms desensitize cells to receptor tyrosine kinase (RTK) stimulation and promote basal mitogen-activated protein kinase (MAPK) signaling, whereas wild-type RAS isoforms are required for RTK-dependent activation of MAPK signaling and optimal growth of cancer cells expressing oncogenic RAS. Depletion of oncogenic RAS sensitizes cells to wild-type isoform-mediated growth factor signaling, uncovering a potential resistance mechanism employed by RAS-mutant cells. Combined inhibition of RAS and RTK signaling effectively blocks growth of cells expressing oncogenic RAS and may therefore be a potential approach to circumvent resistance. For details, please see the article by Young and colleagues on page 112.
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