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In The Spotlight

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Hitting Gliomas When They Are Down: Exploiting IDH-Mutant Metabolic Vulnerabilities ... 1629
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Mini Review

Precision Prevention and Cancer Interception: The New Challenges of Liquid Biopsy ............ 1635

Research Brief

Epigenetic Suppression of Transgenic T-cell Receptor Expression via Gamma-Retroviral Vector Methylation in Adoptive Cell Transfer Therapy ......... 1645
Précis: In patients treated with T-cell receptor adoptive cell therapy, engineered T cells retained the transgenic DNA, but the DNA was subject to DNA methylation-based epigenetic silencing, which may be a cause of treatment resistance or relapse.

Research Articles

An In Vivo Kras Allelic Series Reveals Distinct Phenotypes of Common Oncogenic Variants ............ 1654
Précis: In vivo, organ-specific expression of oncogenic mutant Kras produced different phenotypes depending on the specific mutation; for example, unlike other Kras variants studied, KrasG12R expression in the pancreas was not highly oncogenic.
See commentary, p. 1626

Poly(ADP-ribose) Glycohydrolase Inhibition Sequesters NAD+ to Potentiate the Metabolic Lethality of Alkylating Chemotherapy in IDH-Mutant Tumor Cells ...... 1672
Précis: IDH mutations seen in some cancers lead to low basal NAD+ levels that are further decreased by alkylating drugs, and adding a poly(ADP-ribose) glycohydrolase inhibitor to block NAD+ pool restoration synergized with alkylators in these tumors.
See commentary, p. 1629
Exploiting the Therapeutic Interaction of WNT Pathway Activation and Asparaginase for Colorectal Cancer Therapy ......... 1690

Précis: Mutations that activate the WNT pathway upstream of GSK3, which occur in 10% to 15% of colorectal cancers, caused colorectal cancer cell lines, organoids, and tumors grown in vivo to be sensitive to asparaginase.

See commentary, p. 1632

Identification of BBOX1 as a Therapeutic Target in Triple-Negative Breast Cancer .......... 1706

Précis: BBOX1 stabilized the endoplasmic reticulum (ER) calcium channel IP3R3, and loss or inhibition of BBOX1 in triple-negative breast cancer cells caused growth defects in vitro and in vivo due to faulty transport of calcium from the ER.

Disabled Homolog 2 Controls Prometastatic Activity of Tumor-Associated Macrophages .......... 1758

Précis: DAB2-expressing tumor-associated macrophages at the perilesional region promoted extracellular matrix remodeling to enhance tumor-cell invasiveness and metastasis, and DAB2 expression correlated with poor prognosis.

PRMT5 Inhibition Modulates E2F1 Methylation and Gene-Regulatory Networks Leading to Therapeutic Efficacy in JAK2V617F-Mutant MPN .......... 1742

Précis: A small-molecule inhibitor of the protein arginine methyltransferase PRMT5 was effective in mouse models of the myeloproliferative neoplasms polycythemia vera and myelofibrosis and synergized with JAK1/2 inhibition.

ON THE COVER
Many mutations that activate KRAS by raising the abundance of GTP-bound (active) protein are recognized to be oncogenic. However, Zafra and colleagues found that the effects of individual KRAS-activating mutations depended strongly on the specific amino acid–residue change and where the mutant allele was expressed. For example, KrasG12C or KrasG12D expression in the pancreas caused rapid tumorigenesis, whereas KrasG13D expression caused slower pancreatic tumorigenesis, and KrasG12R expression caused almost no pancreatic tumorigenesis even after one year. Mutation type also affected drug sensitivity, with KrasG12D-expressing pancreatic organoids exhibiting sensitivity to EGFR inhibition and KrasG12C-expressing pancreatic organoids being sensitive to KRA5G12C-specific inhibitors only in the context of EGFR suppression. For more information, see the article by Zafra and colleagues on page 1654.