Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

Precis: ERCC2 is somatically mutated in patients with urothelial carcinoma who exhibit complete response to cisplatin, and may be a predictive biomarker of clinical benefit from neoadjuvant chemotherapy. See commentary, p. 1118

Discovery of Biomarkers Predictive of GSI Response in Triple-Negative Breast Cancer and Adenoid Cystic Carcinoma

Precis: High levels of activated NOTCH1 and expression of the target gene HES4 are correlated with a robust response to NOTCH pathway inhibition with gamma-secretase inhibitors in NOTCH1-mutant tumors.

A Large-Scale RNAi-Based Mouse Tumorigenesis Screen Identifies New Lung Cancer Tumor Suppressors That Repress FGFR Signaling

Precis: An shRNA-based functional screen identified transcriptionally silenced candidate tumor suppressor genes that are downregulated in human lung squamous cell carcinoma, many of which inhibit FGFR signaling.
Development of siRNA Payloads to Target KRAS-Mutant Cancer ........ 1182

Précis: An RNAi library of potent siRNAs facilitates low-dose, combinatorial gene knockdown of KRAS and RAS pathway effector nodes and inhibits KRAS-mutant colorectal cancer growth.

ATM Regulates 3-Methylpurine-DNA Glycosylase and Promotes Therapeutic Resistance to Alkylating Agents .......... 1198

Précis: ATM can promote temozolomide resistance in pediatric glioblastoma by activating 3-methylpurine-DNA glycosylase (MPG)–mediated base excision repair.

See commentary, p. 1120

The Immune Microenvironment Confers Resistance to MAPK Pathway Inhibitors through Macrophage-Derived TNFα ............ 1214

Précis: TNFα expressed in tumor-associated macrophages promotes MAPK pathway inhibitor resistance in melanoma, which can be overcome by combined treatment with IκB kinase inhibitors.

Active CREB1 Promotes a Malignant TGFβ2 Autocrine Loop in Glioblastoma ................. 1230
L. Rodón, A. González-Juncà, M. del Mar Inda, A. Sala-Hojman, E. Martínez-Sáez, and J. Seoane

Précis: TGFβ activates CREB1- and SMAD3-dependent TGFβ2 transcription and hyperactivation of TGFβ signaling in human glioblastoma cell lines and tumors.

See commentary, p. 1123

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ON THE COVER
Smith, Sanchez-Laorden, and colleagues found that macrophage-derived TNFα was required for BRAFV600E–positive melanoma cell survival and protected these cells from MEK inhibitor (MEKi)–induced cell death via NFKB-dependent upregulation of microphthalmia-associated transcription factor (MITF). MEK/BRAF inhibitor treatment increased tumor-associated macrophage recruitment and TNFα and MITF expression in BRAF-mutant melanomas. Intriguingly, dual treatment with IκB kinase inhibitors (IKKi) and MEKi suppressed both macrophage-derived TNFα expression and MITF expression in melanoma cells and resulted in enhanced inhibition of tumor growth in mice. These findings highlight the role of the immune microenvironment in MAPK inhibitor resistance and suggest that IKKi therapy may improve the efficacy of MAPK pathway inhibitors by preventing TNFα-mediated resistance. For details, please see the article by Smith, Sanchez-Laorden, and colleagues on page 1214.