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

**Précis:** 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**

**Précis:** 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**

**Précis:** 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.
ON THE COVER

Smith, Sanchez-Laorden, and colleagues found that macrophage-derived TNFα was required for BRAF V600E-positive melanoma cell survival and protected these cells from MEK inhibitor (MEKi)-induced cell death via NFκB-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.