In Focus

Compensatory Pathways in Oncogenic Kinase Signaling and Resistance to Targeted Therapies: Six Degrees of Separation ....... 876
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REVIEW

Cancer Cell Metabolism: One Hallmark, Many Faces ....... 881
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RESEARCH BRIEF

Comparative Genomic Analysis of Esophageal Adenocarcinoma and Squamous Cell Carcinoma ....... 899

Précis: Exomic sequencing of esophageal cancer subtypes identified geographic disparities and differences in mutation frequencies, particularly of NOTCH genes.

RESEARCH ARTICLES

VEGF/Neuropilin-2 Regulation of Bmi-1 and Consequent Repression of IGF-IR Define a Novel Mechanism of Aggressive Prostate Cancer ....... 906

HER2 Amplification: A Potential Mechanism of Acquired Resistance to EGFR Inhibition in EGFR-Mutant Lung Cancers That Lack the Second-Site EGFR<sup>T790M</sup> Mutation .......................... 922


Précis: Increased HER2 expression confers resistance to EGFR tyrosine kinase inhibitors in non–small cell lung cancers with EGFR mutations.

Reactivation of ERK Signaling Causes Resistance to EGFR Kinase Inhibitors .......................... 934


Précis: Acquired resistance to EGFR inhibitors can occur through aberrant activation of ERK signaling via MAPK1 amplification or downregulation of ERK negative regulators.

Correction


Harbinski and colleagues performed a high-throughput screen of the human secretome to identify proteins capable of rescuing growth of receptor tyrosine kinase (RTK)–addicted cells following RTK inhibition and observed numerous potential ligand-mediated resistance mechanisms. Multiple human epidermal growth factor (HER) and fibroblast growth factor (FGF) ligands could rescue growth of hepatocyte growth factor (HGF) receptor (MET)–addicted cancer cells following MET inhibition, and FGF–addicted cell lines treated with FGF inhibitors could be rescued by HER ligands or HGF. Combination therapy modalities targeting the broad compensatory relationship between MET, FGF, and HER ligands may thus have improved clinical efficacy. For details, please see the article by Harbinski and colleagues on page 948.