Précis: Coamplification of EGFR and ERBB2 is associated with afatinib response in patients with trastuzumab-refractory esophagogastric cancer, whereas selection for MET amplification or loss of EGFR amplification is associated with resistance. See commentary, p. 166

BRCA Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma

Précis: Analysis of cfDNA from 112 patients with high-grade ovarian carcinoma showed that BRCA reversion mutations may be associated with reduced clinical benefit from the PARP inhibitor rucaparib.

PPT1 Promotes Tumor Growth and Is the Molecular Target of Chloroquine Derivatives in Cancer

Précis: Chloroquine derivatives exert their antiautophagic and antitumor effects by binding palmitoyl-protein thioesterase 1 (PPT1) and inhibiting its enzymatic activity.

Précis: A CRISPR/Cas9 screen identifies a synthetic lethal relationship between RB1 and AURKB loss in SCLC cells.

See commentary, p. 169

Aurora A Kinase Inhibition Is Synthetic Lethal with Loss of the RB1 Tumor Suppressor Gene ................. 248


Précis: A screen of cell-cycle inhibitors reveals that RB1-mutant cancer cells are selectively dependent on Aurora kinase A.

See commentary, p. 169

EIF1AX and RAS Mutations Cooperate to Drive Thyroid Tumorigenesis through ATF4 and c-MYC ............. 264


Précis: The EIF1AX-A113sp1 mutation results in an alternatively spliced transcript that cooperates with RAS mutations to stabilize MYC, activate mTOR, and promote tumorigenesis.

AC icon indicates AuthorChoice

For more information please visit http://www.aacrjournals.org

IL1-Induced JAK/STAT Signaling Is Antagonized by TGFβ to Shape CAF Heterogeneity in Pancreatic Ductal Adenocarcinoma ................. 282

G. Biffi, T.E. Oni, B. Spielman, Y. Hao, E. Elyada, Y. Park, J. Preall, and D.A. Tuveson

Précis: TGFβ antagonizes IL1-driven JAK/STAT activation, which induces an inflammatory pancreatic ductal adenocarcinoma cancer-associated fibroblast (CAF) phenotype, to promote CAF heterogeneity.

See commentary, p. 173

Corrections

Correction: Drug-Resistant Brain Metastases: A Role for Pharmacology, Tumor Evolution, and Too-Late Therapy .......... 302

T. Stricker and C.L. Arteaga

Correction: An Acquired HER2T798I Gatekeeper Mutation Induces Resistance to Neratinib in a Patient with HER2 Mutant–Driven Breast Cancer .......... 303


Correction: Neoadjuvant Trials in ER+ Breast Cancer: A Tool for Acceleration of Drug Development and Discovery ...... 304

A.L. Guerrero-Zotano and C.L. Arteaga

Aurora kinase A (AURKA) and Aurora kinase B (AURKB) were found to be synthetic lethal with RB1 loss using a “gene–gene” interaction CRISPR/Cas9-based screening approach initiated by Oser and colleagues and a “gene–drug” interaction approach involving a screen of cell-cycle inhibitors performed by Gong, Du, Parsons, and colleagues. Both an AURKB-specific inhibitor, AZD2811, and the developed AURKA-specific inhibitor, LY3295668, specifically eliminated RB1-mutant but not RB1–wild-type cells and had in vivo efficacy against RB1-mutant tumors. Mechanistic studies suggested that RB1 and AURKA or AURKB have partially redundant roles in mitosis, explaining their synthetic lethal interaction. These findings suggest a potential therapeutic vulnerability caused by RB1 loss and a possible way forward for treatment of RB1-mutant tumors. For details, please see the article by Oser and colleagues on page 230 and the article by Gong, Du, Parsons, and colleagues on page 248.

ON THE COVER

Aurora kinase A (AURKA) and Aurora kinase B (AURKB) were found to be synthetic lethal with RB1 loss using a “gene–gene” interaction CRISPR/Cas9-based screening approach initiated by Oser and colleagues and a “gene–drug” interaction approach involving a screen of cell-cycle inhibitors performed by Gong, Du, Parsons, and colleagues. Both an AURKB-specific inhibitor, AZD2811, and the developed AURKA-specific inhibitor, LY3295668, specifically eliminated RB1-mutant but not RB1–wild-type cells and had in vivo efficacy against RB1-mutant tumors. Mechanistic studies suggested that RB1 and AURKA or AURKB have partially redundant roles in mitosis, explaining their synthetic lethal interaction. These findings suggest a potential therapeutic vulnerability caused by RB1 loss and a possible way forward for treatment of RB1-mutant tumors. For details, please see the article by Oser and colleagues on page 230 and the article by Gong, Du, Parsons, and colleagues on page 248.