Heterogeneity Underlies the Emergence of EGFR\textsuperscript{T790M} Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor ..........................713

Précis: Baseline intratumor heterogeneity for the EGFR\textsuperscript{T790M} mutation is associated with outgrowth of resistant EGFR\textsuperscript{T790M} wild-type subclones and predicts clinical response to the EGFR\textsuperscript{T790M}-specific inhibitor rociletinib.

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Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma .................723

Précis: Germline inactivating mutations in CDKN2B were identified in patients with inherited renal cell carcinoma and predicted to impair its tumor suppressive activity.

INPP4B Is a Tumor Suppressor in the Context of PTEN Deficiency ..........697
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INPP4B Is a PtdIns(3,4,5)P\textsubscript{3} Phosphatase That Can Act as a Tumor Suppressor .................730
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Précis: Loss of INPP4B in mice promotes enhanced AKT2 activation and P(3,4,5)P\textsubscript{3} accumulation to induce metastatic thyroid tumors in the context of PTEN deficiency.

See commentary, p. 697
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**In Vivo Role of INPP4B in Tumor and Metastasis Suppression through Regulation of PI3K–AKT Signaling at Endosomes**


**Précis:** Loss of INPP4B drives localized activation of PI3K–AKT2 in early endosomes and cooperates with PTEN inactivation to promote aggressive and metastatic thyroid tumor formation.

See commentary, p. 697
See article, p. 730

**Targeting Translation Initiation Bypasses Signaling Crosstalk Mechanisms That Maintain High MYC Levels in Colorectal Cancer**


**Précis:** Silvestrol, an eIF4A inhibitor, circumvents feedback mechanisms that maintain MYC translation downstream of dual PI3K/mTOR inhibition to reduce MYC expression and inhibit colorectal cancer growth.

See commentary, p. 701

**ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors**


**Précis:** The identification of a role of ARID1A in the DNA damage response suggests a potential therapeutic vulnerability of ARID1A-mutant cancers.

Shen and colleagues identified ARID1A, a subunit of SWI/SNF chromatin remodeling complexes, as a binding partner of ATR, a key regulator of the DNA damage response. ARID1A is recruited to DNA double-strand breaks (DSB) in an ATR-dependent manner and promotes efficient DSB end resection, which is necessary for activation of ATR and subsequent initiation and maintenance of the G2/M checkpoint. ARID1A loss impaired homologous recombination and single-strand annealing DSB repair mechanisms and, similar to loss of BRCA1 or BRCA2, conferred sensitivity to DSB-inducing PARP inhibitors. Given that inactivating mutations in ARID1A are among the most frequent genetic events in human cancers, these findings suggest that PARP inhibitors may be effective in a broader spectrum of cancers than previously appreciated. For details, please see the article by Shen and colleagues on page 752.