
Précis: Baseline intratumor heterogeneity for the \( \text{EGFR} \) \( \text{EGFR}^{T790M} \) mutation is associated with outgrowth of resistant \( \text{EGFR}^{T790–} \) wild-type subclones and predicts clinical response to the \( \text{EGFR}^{T790M} \)-specific inhibitor rociletinib.

See commentary, p. 694


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

See article, p. 723

INPP4B Is a Tumor Suppressor in the Context of \( \text{PTEN} \) Deficiency. T.-T.T. Vo and D.A. Fruman

See article, p. 730

Targeting \( \text{MYC} \) Translation in Colorectal Cancer. A. Castell and L.-G. Larsson

See article, p. 740

APOBEC Enzymes: Mutagenic Fuel for Cancer Evolution and Heterogeneity. C. Swanton, N. McGranahan, G.J. Starrett, and R.S. Harris

See article, p. 768
**RESEARCH ARTICLES**

**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

**ARID1A Deficiency Impairs the DNA DamageCheckpoint 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.

**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

**ON THE COVER**

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