Heterogeneity Underlies the Emergence of EGFR T790 Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor


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

See commentary, p. 694

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


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

T.-T.T. Vo and D.A. Fruman

Précis: Loss of INPP4B in mice promotes enhanced AKT2 activation and PI(3,4,5)P3 accumulation to induce metastatic thyroid tumors in the context of PTEN deficiency.

See commentary, p. 697

See article, p. 740

Targeting MYC Translation in Colorectal Cancer

A. Castell and L.-G. Larsson

See article, p. 768

APOBEC Enzymes: Mutagenic Fuel for Cancer Evolution and Heterogeneity

C. Swanton, N. McGranahan, G.J. Starrett, and R.S. Harris

Précis: Loss of INPP4B in mice promotes enhanced AKT2 activation and PI(3,4,5)P3 accumulation to induce metastatic thyroid tumors in the context of PTEN deficiency.

See commentary, p. 697

See article, p. 740

In The Spotlight

Shades of T790M: Intratumor Heterogeneity in EGFR-Mutant Lung Cancer

E. Ichihara and C.M. Lovly

See article, p. 713

INPP4B Is a Tumor Suppressor in the Context of PTEN Deficiency

T.-T.T. Vo and D.A. Fruman

See article, p. 730

See article, p. 740

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See commentary, p. 697

See article, p. 740
**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

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**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.

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**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.
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