
**Research Brieﬁng:**

- **Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline POLE Defi ciency Treated with Checkpoint Blockade Immunotherapy**
  - **Precis:** Immune checkpoint blockade induced an immunologic and clinical response in a patient with germline POLE defi ciency and a hypermutated glioblastoma.
  - See commentary, p. 1210

- **Chronic Myelogenous Leukemia–Initiating Cells Require Polycomb Group Protein EZH2**
  - **Precis:** CML leukemic stem cells are dependent on EZH2 expression and can be targeted by EZH2 inhibition to potentially eradicate leukemic stem cells in patients with CML.
  - See related article, p. 1248

- **Epigenetic Reprogramming Sensitizes CML Stem Cells to Combined EZH2 and Tyrosine Kinase Inhibition**
  - **Precis:** EZH2 inhibition sensitizes CML stem cells to tyrosine kinase inhibition in vitro and in vivo via reduced H3K27me3 and altered EZH2 target gene expression, which results in enhanced apoptosis.
  - See related article, p. 1237

**News in Brief:**

- **When Drug Trials Are Halted**
  - A. Snyder and J.D. Wolchok
  - See article, p. 1230

**Research Watch:**

- **TERT Promoter Mutations Enhance Telomerase Activation by Long-Range Chromatin Interactions**
  - J. Min and J.W. Shay
  - See article, p. 1276

**In The Spotlight:**

- **Successful Treatment of a Patient with Glioblastoma and a Germline POLE Mutation: Where Next?**
  - A. Snyder and J.D. Wolchok
  - See article, p. 1230

- **TERT Promoter Mutations Enhance Telomerase Activation by Long-Range Chromatin Interactions**
  - J. Min and J.W. Shay
  - See article, p. 1276

- **Emergence of the Noncoding Cancer Genome: A Target of Genetic and Epigenetic Alterations**
  - S. Zhou, A.E. Treloar, and M. Lupien
  - See related article, p. 1237

**Hot Topics:**

- **When Drug Trials Are Halted**
  - A. Snyder and J.D. Wolchok
  - See article, p. 1230

- **TERT Promoter Mutations Enhance Telomerase Activation by Long-Range Chromatin Interactions**
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- **Emergence of the Noncoding Cancer Genome: A Target of Genetic and Epigenetic Alterations**
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  - See related article, p. 1237
Biallelic Alteration and Dysregulation of the Hippo Pathway in Mucinous Tubular and Spindle Cell Carcinoma of the Kidney ........................................ 1258

Precis: In-depth genetic characterization identifies Hippo pathway activation in mucinous tubular and spindle cell carcinoma of the kidney.

A Recurrent ERCC3 Truncating Mutation Confers Moderate Risk for Breast Cancer ................. 1267

Precis: A protein-truncating mutation in the nucleotide excision repair gene ERCC3 results in hypomorphic DNA repair function and is associated with increased breast cancer risk in individuals of Ashkenazi Jewish ancestry.

RESEARCH ARTICLE
Long-Range Chromatin Interactions Drive Mutant TERT Promoter Activation .......................... 1276
S.C. Akınçılар, E. Khattar, P.L.S. Boon, B. Unal, M.J. Fullwood, and V. Tergaonkar

Precis: Cancer-specific mutations in the TERT promoter that permit binding of GABPA facilitate long-range chromatin interactions and TERT expression.

See commentary, p. 1212

ON THE COVER
Tyrosine kinase inhibitors (TKI) successfully target BCR-ABL1 in chronic myelogenous leukemia (CML), but the cure rate is low due in part to the resistance of leukemic stem cells (LSC) to TKIs. In two related studies, Xie and colleagues and Scott, Korfi, and colleagues discovered a dependence of CML LSCs on EZH2 that might be targeted to eradicate LSCs. CML LSCs exhibited upregulation of EZH2 and deregulation of polycomb repressive complex 2 target genes, and suppression of EZH2 reduced colony-forming ability and induced apoptosis in LSCs alone and in combination with TKIs. In vivo, genetic inactivation or pharmacologic inhibition of EZH2 reduced the LSC population and prolonged survival. These studies indicate that EZH2 inhibition may eliminate CML LSCs and support further clinical investigation of EZH2 inhibitors in combination with TKIs in patients with CML. For details, please see the article by Xie and colleagues on page 1237 and the article by Scott, Korfi, and colleagues on page 1248.