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Ectopic Humanized Mesenchymal Niche in Mice Enables Robust Engraftment of Myelodysplastic Stem Cells ..................... 135
Précis: Human bone marrow stromal niche engineering in mice supports long-term engraftment of primary patient MDS cells with preserved disease characteristics.

A Therapeutic Strategy for Preferential Targeting of TET2-Mutant and TET Dioxygenase-Deficient Cells in Myeloid Neoplasms .................. 146
Précis: 2HG accumulation from IDH1/2 mutation induces synthetic lethality in TET2-mutant cells by reducing TET activity below essentially required. A new TET inhibitor mimics 2HG and selectively restricts clonal evolution of TET2-mutant cells in vitro and in vivo.

TFEB Links MYC Signaling to Epigenetic Control of Myeloid Differentiation and Acute Myeloid Leukemia .................. 162
Précis: MYC directly inhibits expression of TFEB, which serves as a tumor suppressor in AML via promoting myeloid differentiation and cell death. TFEB induces IDH1/2 expression to establish myeloid epigenetic programs, and it is a druggable target in AML.

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RESEARCH BRIEFS

Patterns of Resistance Differ in Patients with Acute Myeloid Leukemia Treated with Type I versus Type II FLT3 Inhibitors ............ 125
Précis: Genetic patterns underlying resistance to FLT3-targeted therapies in AML reveal distinct drivers associated with relapse on type 1 versus type 2 inhibitors and link mutation emergence with clinical outcomes.
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TET dioxygenases initiate DNA demethylation and are commonly inactivated in myeloid neoplasms by somatic mutations or metabolically by 2-hydroxyglutarate (2HG) product of mutant IDH1/2 enzymes. In this issue, the team of Jha, Maciejewski, and colleagues shows that minimal TET activity is essential for neoplastic cell survival and underlies synthetic lethality of TET and IDH mutations. To prove the concept and harness it for therapy, the authors develop TETi76 as a mimic of 2HG. TETi76 inhibits TET activity and mimics synthetic lethality of IDH mutation in TET-deficient cells while sparing normal hematopoiesis. TETi76 selectively restricts clonal expansion of TET2-mutant cancer cells in mouse xenografts. For details, please see the article on page 146.