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Précis: Genotoxic therapy-induced persistent damage to non-hematopoietic tissues promotes myeloid leukemia development by conferring advantage to p53-deficient preleukemic clones and driving acquisition of additional lesions in DNA damage response genes.

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Précis: Differential regulation of MIR300 targets by TUG1 IncRNA promotes CML leukemic progenitor survival while retaining cell cycle arrest, and blocking MIR300–TUG1 interaction eliminates quiescent leukemic stem cells.

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The Genomic Landscape of HIV-Associated Plasmablastic Lymphoma

Monosomic Loss of MIR15A/MIR16-1 Is a Driver of Multiple Myeloma Proliferation and Disease Progression
Précis: MIR15A/MIR16-1 deletion promotes multiple myeloma (MM) initiation and progression in mice, identifying it as a key tumor suppressor gene associated with human chromosome 13 loss in MM.

See commentary, p. 16

Targeting MEF2D-fusion Oncogenic Transcriptional Circuitries in B-cell Precursor Acute Lymphoblastic Leukemia


Précis: MEF2D fusion protein reprograms B-ALL transcriptional circuits, establishing self-reinforcing regulatory network dependent on pre-BCR and SREBF1, which can be exploited to therapeutically target a fusion-driven leukemia.

See commentary, p. 18

Mutational Landscape and Patterns of Clonal Evolution in Relapsed Pediatric Acute Lymphoblastic Leukemia


Précis: The landscape of mutations and clonal evolution trajectories in pediatric ALL reveal relapse-fated, drug-resistant subclones present at diagnosis and expanded by therapy.

See commentary, p. 21

Genomic Characterization of HIV-Associated Plasmablastic Lymphoma Identifies Pervasive Mutations in the JAK–STAT Pathway


Précis: Jak-STAT, Ras, Notch pathway genes and CD44 are frequently mutated in HIV-associated PBL, and together with transcriptomic features distinguish the disease from closely related B-cell cancers.

See commentary, p. 23

ON THE COVER The labs of John Dick, Roland Kuiper, Charles Mullighan join forces to characterize mechanisms of relapse in a large cohort of pediatric ALL through the power of high-resolution genomics. They report that in most cases, relapse-associated mutations can be traced to a subclone already present at diagnosis. Taken from treatment-naïve patients, these subclones display drug resistance in mouse xenografts. The relapse-fated subclones carry genomic alterations known to drive resistance, and expand in patients following therapy. Clones persisting through serial relapses display hypermutation suggestive of increased immunogenicity. Genomic patterns revealed in this analysis may help identifying personalized therapies least prone to relapse. For details, please see the article by Waanders and colleagues on page 96 and a joint publication in the April issue of Cancer Discovery.