Triple Combination Trial Shows Promise against *IDH*-Mutated Myeloid Cancers

IDH-mutated AML is sensitive to azacytidine combinations with venetoclax or ivosidenib. Lachowiez et al. tested triple combination of these agents, as well as oral doublet of ivodesinib with venetoclax, in a phase 1b clinical trial of 31 patients with *IDH1*-mutated myeloid cancers. The double as well as triple combination demonstrated durable efficacy without reaching dose-limiting toxicity, comparing favorably to historical controls. Mutant *IDH1* allele clearance occurred in the majority of cases within 5 cycles of therapy. Survival benefit was higher in patients with additional mutations affecting DNA methylation. Single-cell multiomic analyses reveal complex clonal dynamics underscoring potential mechanisms of response and relapse. If safety and efficacy of these findings is reproduced in the expansion phase of the trial, these regimens could be broadly applicable to high-risk *IDH*-mutated patients. ■

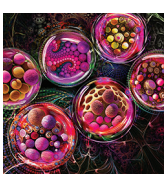
See article, p. 276.

eIF5A Hypusination Is Essential for Development and Maintenance of MYC-Driven Lymphoma

The polyamine-hypusine axis augments the functions of eIF5A in translation, yet the role of hypusinated eIF5A (eIF5A^{Hyp}) in tumorigenesis is unclear. Here Nakanishi et al. show eIF5A overexpression is a hallmark of many human cancers, including MYC-driven lymphoma, and that eIF5A^{Hyp} is essential for malignant conversion during lymphoma development and for maintenance of lymphoma in genetic mouse models. Expression, ribosome profiling, and proteomic analyses established the hypusine circuit is necessary for efficient translation of regulatory factors controlling cell cycle transit and DNA replication, including E2F transcription factors and DNA polymerase-δ1. This study suggests the hypusine circuit as a therapeutic target for many human cancer types. ■

See article, p. 294.

AML Patient-Derived iPSCs Closely Resemble Primary AML PDXs



Kotini, Carcamo, Cruz-Rodriguez et al. report the generation of a compendium of induced pluripotent stem cell (iPSC) lines from patients with acute myeloid leukemia (AML), capturing all main AML genetic groups. While in the iPSC state, the reprogrammed cells (iPSC-AML) show both similarities and differences to the primary samples. Remarkably, xenotransplantation of iPSC-AML cells selects for leukemia-initiating cells that are almost identical immunophenotypically to those of the patient-matched primary cells. iPSCs capturing clones and subclones from the same patient allow the characterization of the contribution of specific mutations to the leukemic phenotype. This comprehensive collection of iPSC lines offers unprecedented tools for dissecting mechanisms of human AML oncogenesis and testing new therapies *in vivo*. ■

See article, p. 318.

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