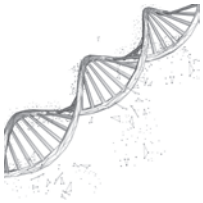
## Epigenetics

**Major Finding:** Deficiency of HUSH complex component MPP8 impaired myeloid leukemia cell growth *in vitro* and *in vivo*.

**Mechanism:** MPP8 suppressed transcription of LINE-1 retrotransposons, protecting leukemia cell genome integrity.

**Impact:** This work identifies the chromatin reader MPP8 as a critical dependency in acute myeloid leukemia.

### MPP8 SILENCES LINE-1 RETROTRANSPOSONS TO PROMOTE ACUTE MYELOID LEUKEMIA



LINE-1 retrotransposons are autonomously mobile transposable elements that can cause disease, including cancer, via insertional mutagenesis. For unknown reasons, evidence of LINE-1 retrotransposition events is common in solid tumors but less so in myeloid cancers. Using a CRISPR–Cas9-based knockout screen targeting epigenetic regulators, Gu, Liu, and colleagues discovered that *MPP8* (also known as *MPHOSPH8*), encoding a chromodomain-containing protein that is a component of the retrotransposon-suppressing human silencing hub (HUSH) complex, was a key dependency of human acute myeloid leukemia (AML) cells *in vitro*. Further, mice xenotransplanted with *MPP8*-deficient AML cells had significantly longer survival and lower leukemia burden than mice xenotransplanted with control AML cells. Additional *in vivo* experiments showed that normal hematopoiesis did not require MPP8, whereas *Mpp8* knockout in a mouse model of *AML1–ETO*- or *MLL–AF9*-driven AML resulted in substantially reduced AML mortality and leukemia burden. Mechanistically, loss of *MPP8* in human AML cells *in vitro* led to reactivation of normally repressed LINE-1 retrotransposons, whereas blocking LINE-1 retrotransposition restored cell growth in *MPP8*-deficient AML cells, both consistent with MPP8's function as the chromatin reader of the HUSH complex. In patient samples, lower LINE-1 expression was associated with poorer prognosis, and the presence of AML driver mutations in genetically engineered mouse models caused LINE-1 downregulation, suggesting that LINE-1 activity may be tumor suppressive in AML and that AML-inducing oncogenic mutations promote LINE-1 silencing. Indeed, CRISPR–Cas9-based activation of endogenous LINE-1 retrotransposons reduced leukemia cell growth *in vitro* and in xenotransplants. Further investigation of the mechanism underlying the dependency of AML cells on MPP8 revealed that HUSH complex–mediated silencing of LINE-1 retrotransposons was essential to prevent DNA damage and the resulting cell-cycle exit, a known sensitivity of myeloid leukemia cells. In summary, this work reveals MPP8 as a core factor promoting AML that acts by suppressing LINE-1 transcription to promote genome stability in leukemia cells. ■

*Gu Z, Liu Y, Zhang Y, Cao H, Lyu J, Wang X, et al. Silencing of LINE-1 retrotransposons is a selective dependency of myeloid leukemia. Nat Genet 2021;53:672–82.*

## Leukemia

**Major Finding:** Loss of ZRSR2, frequently mutated in blood cancer, enhanced hematopoietic stem cell self-renewal.

**Concept:** ZRSR2 loss led to impaired minor intron excision in genes such as *LZTR1*, promoting transformation.

**Impact:** This study shows that minor intron retention via mutation or dysregulated splicing can drive cancer.

### MINOR INTRON SPLICING REGULATES HEMATOPOIETIC STEM CELL SELF-RENEWAL

Mutations in RNA splicing factors are prevalent in myelodysplastic syndromes (MDS), and patients with leukemia often harbor mutations in RNA splicing factor genes, including *SF3B1, SRSF2, U2AF1*, and *ZRSR2*, of which only ZRSR2 functions primarily in the minor spliceosome. Although the major spliceosome is responsible for the removal of more than 99% of introns, the minor spliceosome splices a small but evolutionarily conserved subset of introns. To investigate the role of ZRSR2 and minor intron splicing in the hematopoietic system, Inoue, Polaski, Taylor, and colleagues engineered mice with hematopoietic cell–specific *Zrsr2* deletion and found that loss of *Zrsr2* enhanced self-renewal of hematopoietic stem cells (HSC). RNA-sequencing analyses of bone marrow samples from two independent cohorts of patients with MDS ($n = 18$; $n = 12$) revealed that *ZRSR2*-mutant samples displayed impaired removal of minor introns. ZRSR2 was shown to bind minor intron–containing genes, whereas ZRSR2 loss led to intron retention, specifically of a subset of minor introns harboring branchpoints that were proximal to the 3′ splice site; had sequences similar to that of the minor U12 snRNA consensus sequence; and had a weak or absent polypyrimidine tract. To explore whether *ZRSR2*-mutant disease phenotypes could be attributed to dysregulated splicing of target genes, a CRISPR–Cas9-based knockout screen, encompassing genes that were differently spliced in *ZRSR2*-mutant MDS patient samples, was performed in hematopoietic cell lines. Genetic knockout was designed to mimic the predicted effect of nonsense-mediated decay upon intron retention, and cells were screened for transformation via cytokine-independent enrichment following cytokine depletion. *LZTR1*, a gene encoding a cullin-3 adaptor known to suppress RAS-related GTPases, was a hit in all cell lines, and restoration of LZTR1 in *Zrsr2*-knockout mice decreased HSC self-renewal. In humans, *LZTR1* minor intron retention was observed in diverse disease contexts, including Noonan syndrome, schwannomatosis, and many cancer types. In summary, this work shows the importance of minor intron splicing in HSC self-renewal and reveals minor intron retention as a potential cancer driver. ■

*Inoue D, Polaski JT, Taylor J, Castel P, Chen S, Kobayashi S, et al. Minor intron retention drives clonal hematopoietic disorders and diverse cancer predisposition. Nat Genet 2021;53:707–18.*