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RNA methylation as a leukemia stem cell vulnerability

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In this issue of Haematologica, Zhou et al. report that the RNA 5-methylcytosine (m^5C) methyltransferase NSUN2 is selectively required for leukemia stem cell (LSC) maintenance while being largely dispensable for normal hematopoiesis(1). Using complementary human and murine acute myeloid leukemia (AML) models, the authors demonstrate that NSUN2 sustains leukemic stemness through an m^5C-dependent regulatory axis involving FOSB and BCL2L1. These findings identify RNA cytosine methylation as a context-specific vulnerability in AML and highlight the growing importance of epitranscriptomic regulation in hematologic malignancies.

AML is organized as a cellular hierarchy in which a rare population of leukemia stem cells drives disease propagation and relapse(2). While conventional therapies often eliminate bulk leukemic blasts, LSC frequently survive treatment and regenerate the disease. Identifying molecular dependencies that distinguish LSC from normal hematopoietic stem cells (HSC) therefore remains a major therapeutic goal. Because these populations share many transcriptional and epigenetic features, however, defining selective vulnerabilities has proven challenging.

Over the past decade, studies of chromatin regulators and DNA methylation pathways have revealed critical epigenetic dependencies in AML. More recently, RNA modifications have emerged as an additional regulatory layer shaping gene expression(3). Chemical modifications on RNA can influence RNA stability, translation, and cellular stress responses, thereby controlling gene expression programs essential for stem cell function. Among these modifications, N^6-methyladenosine (m^6A) has been most extensively studied in leukemia. Components of the m^6A machinery, including METTL3, FTO, and ALKBH5, have been shown to regulate leukemic proliferation and leukemia stem cell self-renewal, establishing RNA modifications as functional drivers of leukemogenesis(4-6).

The study by Zhou et al. extends this paradigm by focusing on RNA cytosine methylation. NSUN2 catalyzes m^5C modification across multiple RNA species, including tRNA and mRNA, and has been implicated in RNA stability and translational control. Through inducible knockout models, the authors demonstrate that NSUN2 is required for leukemia maintenance across multiple AML contexts. Deletion of Nsun2 markedly reduces LSC frequency and impairs leukemic propagation, whereas normal hematopoietic stem and progenitor cells show minimal dependence on NSUN2. This differential requirement between malignant and normal stem cells suggests a potential therapeutic window.

Mechanistically, the authors provide evidence that NSUN2 promotes m^5C modification within the 3’ untranslated region of FOSB mRNA, enhancing its expression and sustaining downstream BCL2L1-mediated survival signaling. Although further work will be needed to fully define NSUN2 RNA targets and the dynamics of m^5C deposition, this NSUN2–FOSB–BCL2L1 axis illustrates how RNA modifications can stabilize oncogenic programs at the post-transcriptional level.

The broader significance of this work lies in the expanding landscape of RNA modifications in leukemia biology. In addition to m^6A and m^5C, RNA editing mediated by ADAR enzymes and alterations in ribosomal RNA modifications have also been implicated in malignant hematopoiesis(7, 8). For example, changes in ribosomal RNA 2'-O-methylation can influence ribosome function and translational control, further linking RNA chemical diversity to leukemic transformation. Together, these findings suggest that multiple layers of RNA modification contribute to regulatory networks sustaining leukemia stem cells.

Why leukemia stem cells may be particularly dependent on RNA modification pathways remains an open question. Leukemic cells may experience heightened proliferative and metabolic stress, increasing reliance on mechanisms that stabilize RNA and optimize translation. Alternatively, normal hematopoietic stem cells may possess compensatory pathways that buffer against disruption of individual RNA modifiers. Clarifying these differences will be important for determining whether RNA methylation dependencies are broadly shared across AML subtypes or restricted to specific genetic contexts.

The work by Zhou et al. highlights the expanding role of RNA modifications in leukemia biology. As the field of epitranscriptomics continues to evolve, defining context-specific dependencies such as NSUN2 may provide new insights into leukemia stem cell regulation and potential therapeutic strategies.

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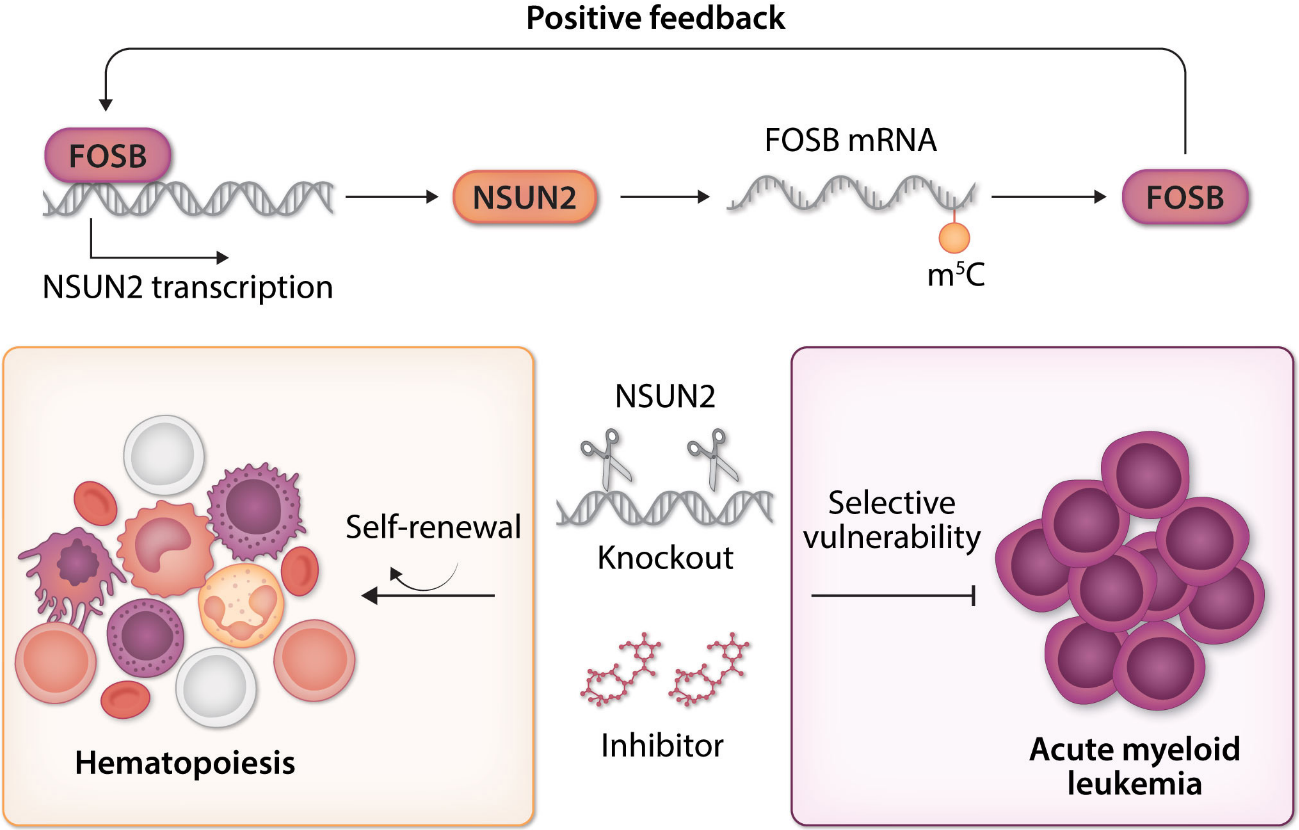
Table 1. RNA modifications implicated in AML

RNA modification	**Key enzymes**	**Functional relevance in AML**
m^{6}A (N6-methyladenosine)	METTL3, METTL14, FTO, ALKBH5	Controls leukemic proliferation and LSC maintenance
m^{5}C (5-methylcytosine)	NSUN2, DNMT2	Supports leukemia stem cell survival and RNA stability
A-to-I RNA editing	ADAR1	Promotes leukemic cell survival and immune signaling regulation
rRNA 2′-O-methylation	Fibrillarin (FBL)	Alters ribosome function and translational control in leukemia

Figure 1. A selective epitranscriptomic vulnerability in leukemia stem cells. The study by Zhou et al. identifies NSUN2-mediated m^5C methylation as a selective vulnerability in leukemia stem cells. NSUN2 deposits m^5C on the 3′ untranslated region of *FOSB* mRNA to increase its stability and expression, while FOSB transcriptionally activates *NSUN2*, forming a positive feedback loop that sustains leukemic stemness but is largely dispensable for normal hematopoiesis.


Positive feedback
FOSB
NSUN2 transcription
NSUN2
FOSB mRNA
m5C
FOSB
Hematopoiesis
Self-renewal
NSUN2
Knockout
Inhibitor
Selective vulnerability
Acute myeloid leukemia