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# Deciphering the role of Mmrn1 in hematopoiesis and acute myeloid leukemia: the critical need to explore niche interactions and molecular subtyping. Comment on: "Mmrn1 expression defines a novel subset of hematopoietic stem cells and leukemia stem cells with great self-renewal potential"

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# Deciphering the role of Mmrn1 in hematopoiesis and acute myeloid leukemia: the critical need to explore niche interactions and molecular subtyping. Comment on: "Mmrn1 expression defines a novel subset of hematopoietic stem cells and leukemia stem cells with great self-renewal potential"

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**Authors' contributions**

Conception and design: Q.S. Manuscript Writing: Q.S. Manuscript revision: Q.S. Research supervision: Q.S. All authors contributed to the article and approved the submitted version.

**Disclosure**

The author declare no conflict of interest.

**To the Editor,**

We read with great interest the recent article by Chen et al.[1] published in *Haematologica*. The authors elegantly demonstrate that Multimerin 1 (Mmrn1) defines a novel, highly quiescent, and self-renewing subset of normal hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs). By employing comprehensive *in vivo* and *in vitro* models, the study convincingly illustrates that Mmrn1-high LSCs possess robust leukemogenic potential and that targeting Mmrn1 may offer a promising strategy to delay acute myeloid leukemia (AML) progression. While this study marks a significant step forward in deciphering the functional heterogeneity of stem cells, we believe that integrating investigations into bone marrow (BM) niche interactions and the extensive molecular subtyping of AML will be vital for translating these preclinical findings into clinical applications.

First, the interplay between LSCs and the BM microenvironment is widely recognized as a central driver of therapeutic resistance and disease relapse[2]. As an EMILIN family protein containing an EGF-like domain, Mmrn1 is functionally implicated in extracellular matrix (ECM) assembly, cellular adhesion, and signal transduction. However, the current study primarily focuses on the intracellular transcriptomic shifts, cell cycle regulation, and self-renewal capacities of Mmrn1-high LSCs. We hypothesize that Mmrn1 might not merely act as an autocrine or paracrine secreted factor, but could actively mediate physical interactions between LSCs and the protective BM niche. Recent literature underscores that LSCs hijack normal endosteal and perivascular niches—using specific adhesion molecules to interact with mesenchymal stromal cells and endothelial cells—thereby evading the cytotoxic effects of chemotherapy[3]. Specifically, interactions mediated by the extracellular matrix can induce profound metabolic reprogramming and quiescence in leukemic blasts, fortifying them against

targeted therapies. It would be highly informative for future studies to explore whether Mmrn1 interacts with specific integrins or stromal cell surface receptors within the BM microenvironment to tether LSCs to these sanctuaries. If Mmrn1 indeed functions as a physical anchor for LSCs in the niche, combination therapies pairing Mmrn1 inhibition with standard induction chemotherapy could effectively mobilize LSCs into the peripheral circulation, rendering them highly susceptible to conventional cytotoxicity.

Second, the clinical translation of Mmrn1 as a robust biomarker necessitates a deeper contextualization within the profound genetic heterogeneity of AML. Chen et al. highlight through database analyses that MMRN1 is upregulated in non-M3 AML and that its overexpression tightly correlates with a poor clinical prognosis. Furthermore, they successfully utilize an MLL-AF9 murine model to validate the aggressive nature of Mmrn1-high LSCs *in vivo*. While compelling, classifying AML broadly into "M3" and "non-M3" subtypes oversimplifies the genomic diversity of the disease. Modern AML risk stratification heavily relies on specific mutational profiles, such as *FLT3-ITD*, *NPM1*, *CEBPA*, or *IDH1/2* mutations, which critically dictate both the hierarchical evolution of the leukemia and patient outcomes [4]. Distinct mutation orders and clonal evolution patterns create unique phenotypic vulnerabilities across different AML patients[4].

Therefore, it is crucial to determine whether elevated MMRN1 expression independently drives pathogenesis or if it strongly co-segregates with specific, high-risk driver mutations. Multi-omic integration frameworks have recently proven essential in uncovering molecularly silent variance and bridging transcriptomic data with established risk classifications to refine prognostic accuracy[5]. We suggest that expanding validation cohorts to include patient-derived xenograft (PDX) models representing a broader spectrum of molecular subgroups will clarify

whether Mmrn1's function is universal across AML or restricted to specific genomic landscapes. Elucidating the precise mutational backgrounds in which MMRN1 is most active is essential to identify which patient subpopulations would genuinely benefit from targeted therapies. For instance, evaluating MMRN1 expression across varying mutational burdens could yield predictive biomarkers for future combination regimens.

In conclusion, we highly commend Chen et al. for their meticulous contribution to our understanding of stem cell heterogeneity in normal and malignant hematopoiesis. Expanding future research efforts to encompass Mmrn1-mediated LSC-niche interactions and high-resolution molecular subtyping will not only solidify its biological significance but also accelerate its seamless integration into the precision oncology paradigm. We eagerly anticipate future studies that will address these complex but highly translational dimensions.

**References**

1. Chen N, Yang L, Chen F, et al. Mmrn1 expression defines a novel subset of hematopoietic stem cells and leukemia stem cells with great self-renewal potential. Haematologica. 2026;111(6):2032-2046.

2. Choi HS, Kim BS, Yoon S, et al. Leukemic stem cells and hematological malignancies. Int J Mol Sci. 2024;25(12):6639.

3. Xinyi Y, Vladimirovich RI, Beeraka NM, et al. Emerging insights into epigenetics and hematopoietic stem cell trafficking in age-related hematological malignancies. Stem Cell Res Ther. 2024;15(1):401.

4. Schwede M, Jahn K, Kuipers J, et al. Mutation order in acute myeloid leukemia identifies uncommon patterns of evolution and illuminates phenotypic heterogeneity. Leukemia. 2024;38(7):1501-1510.

5. Karakaslar EO, Severens JF, Sánchez-López E, et al. A transcriptomic based deconvolution framework for assessing differentiation stages and drug responses of AML. NPJ Precis Oncol. 2024;8(1):105.