ELSEVIER

Blood 142 (2023) 4134

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

SUMO E3 Ligase ZMIZ1 Drives Leukemogenesis Via Transcriptional Deregulation in Acute Myeloid Leukemia

Fu Ziyu, PhD[1], *Yun Tan, PhD*[1], *Xiaoguang Xu, PhD*[1], *Jie Xu*[2], *Sai-Juan Chen, MD PhD*[1]

[1] Shanghai Institute of Hematology, National Research Center for Translational Medicine, State Key Laboratory of Medical Genomics, Ruijin Hospital Affiliated to Shanghai Jiao Tong University (SJTU) School of Medicine, Shanghai, China
[2] Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Transcriptional deregulation is one of the hallmarks of acute myeloid leukemia (AML), which causes the aberrant expression of genes essential for hematopoiesis, proliferation, stemness et, al. Emerging evidence has demonstrated that transcription is regulated by post-translational modification of transcription factors, such as SUMOylation, and the recruitment of co-regulators, such as epigenetic regulators.

Here, we conducted a CRISPR-Cas9 screen using sgRNAs targeting epigenetic regulators and a SUMO E3 ligase to explore essential regulators for hematopoiesis and leukemogenesis. Intriguingly, sgRNAs targeting ZMIZ1 was identified to be significantly decreased in proliferated leukemia cells and enriched in differentiated ones. ZMIZ1 (also known as ZIMP10 or RAI17) is a SUMO E3 ligase and transcriptional co-regulator of the Protein Inhibitor of Activated STAT (PIAS)-like family. Moreover, we found ZMIZ1 was highly expressed in AML and related to unfavorable outcomes, suggesting a potential diagnostic and prognostic target for AML.

Next, we analyzed the function of ZMIZ1 in AML using both in vivo and in vitro approaches. We knocked down the expression of ZMIZ1 in MOLM-13, THP1, OCI-AML3, HL60, and NB4 cells and found that knockdown of ZMIZ1 suppressed cell viability and induced apoptosis in all five cell lines. Meanwhile, knockdown of ZMIZ1 enhanced the sensitivity to chemotherapy (such as Ara-C). Additionally, knockdown of ZMIZ1 induced cell differentiation in NB4 cells. Moreover, we established conditional knockout mouse models (Zmiz1 $^{flox/flox}$Mx1-Cre), in which Zmiz1 was deleted with the Mx1-Cre transgene. We isolated the bone marrow of these mice and transfected it with the MLL-AF9 fusion gene, followed by transplantation into recipient mice. The conditional knockout was induced after two weeks of transfection. We found that inactivation of Zmiz1 significantly prolonged survival and relieved the leukemic burden.

To examine the regulatory function of ZMIZ1 in AML, we conducted ChIP-seq analysis in MOLM-13, THP1, OCI-AML3, HL60, and NB4 cells using antibodies against ZMIZ1. The binding peaks of ZMIZ1 differ in AML cell lines, as fewer than 30% of binding sites were overlapped between different cells. However, the binding motifs for ZMIZ1 showed a similar pattern. Motifs bound by MYB, CENPE, and RUNX1 were enriched in all five cell lines. To test the regulatory effects of ZMIZ1 on these transcription factors, we conducted luciferase reporter assays and found that ZMIZ1 enhanced the transcriptional activity of MYB.

Taken together, our study suggests an essential function of ZMIZ1 in leukemogenesis, presumably via SUMOylating essential transcription factors, and sheds new light on AML targeting therapy probably by targeting ZMIZ1.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-187978