Original Research Article | J Adv Med Biomed Res. 2025; 33(159): 310-318

Category: Medical Biology

Peer Reviewed | Open Access

Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

EZH2 Gene Expression and *SOCS1* Gene Methylation in Acute Myeloid Leukemia: Unraveling Epigenetic Interactions and Clinical Implications

Farahnaz Saadat Gholami[1], Akbar Safipour Afshar[1], Sajjad Sadeghi Zarghari[2], Arefeh Mazhari[3], Payam Siyadat[4], Maryam Sheikhi[3], Amirali Ayatollahi[3], Yasamin Ayatollahi[3], Hossein Ayatollahi[3]*

1. *Department of Biology, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*
2. *Department of Hematology and Blood Banking, Mashhad University of Medical Sciences, Mashhad. Iran*
3. *Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad. Iran*
4. *Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran*

Article Info

10.30699/jambr.33.159.310

Received: 2025/04/25;
Accepted: 2025/09/09;
Published Online: 29 Sept 2025;

Use your device to scan and read the article online

***Corresponding author:**
Hossein Ayatollahi,
Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad. Iran

Email: ayatollahih@mums.ac.ir

ABSTRACT

Background & Objective: Acute myeloid leukemia (AML) is a diverse blood cancer that predominantly affects adults. In addition to genetic mutations, epigenetic processes, including DNA methylation and histone modifications are key factors in leukemogenesis. This study investigated the relationship between the *Suppressor of Cytokine Signaling 1 (SOCS1)* gene methylation and the *Enhancer of Zeste Homolog 2 (EZH2)* gene expression in patients with AML.

Materials & Methods: This cross-sectional study included 85 AML patients admitted to Ghaem Hospital (Mashhad, Iran) between April 2017 and March 2023. Patients were diagnosed based on the World Health Organization (WHO) guidelines and the French-American-British (FAB) classification. The *EZH2* expression level and *SOCS1* methylation patterns were analyzed. The associations between these epigenetic alterations, demographic characteristics, and clinical outcomes were assessed.

Results: Our findings indicated a significant inverse relationship between *EZH2* expression and *SOCS1* gene methylation. Furthermore, *EZH2* overexpression and *SOCS1* hypomethylation were associated with reduced overall survival.

Conclusion: This study suggests that *EZH2* and *SOCS1* may jointly influence AML progression and patient outcomes through epigenetic changes—their prognostic relevance and therapeutic potential merit further research in larger studies.

Keywords: *EZH2, SOCS1, Epigenetics, Methylation,* Acute Myeloid Leukemia

1. Introduction

Acute myeloid leukemia (AML) represents the most frequent form of leukemia in adults and arises from a variety of genetic alterations (1). In addition to genetic mutations, abnormal epigenetic changes, including DNA methylation, histone alterations, and non-coding RNA interactions, contribute significantly to the initiation and progression of AML (2, 3). These epigenetic changes alter gene expression and modulate hematopoietic progenitor cells (*HPCs*) functions (4). Recent research also highlights that mutations in epigenetic regulators can initiate pre-leukemic states and contribute to the early stages of AML (5).

DNA methylation serves as a pivotal epigenetic regulator that modulates gene expression. It is catalyzed by DNA methyltransferases (DNMTs) that methylate the 5′ carbon of cytosine in CpG dinucleotides, resulting in the formation of 5-methylcytosine (6). CpG sites are primarily located in CpG islands (CGIs) near gene promoters **(7)**. Studies show that increased CGI methylation is often linked to gene silencing, while hypomethylation is associated with gene activation **(8)**. Abnormal methylation, such as that of the *Suppressor of Cytokine Signaling 1 (SOCS1)* gene, contributes to the uncontrolled proliferation of myeloid cells and promotes cancer development **(9)**.

SOCS1, a member of the *SOCS* protein family, negatively regulates the *JAK-STAT* signaling pathway, which is essential for the function of *HPCs* **(8, 9)**. Aberrant methylation of *SOCS1* disrupts this regulation, resulting in sustained *STAT* activation and contributing to leukemogenesis **(9, 10)**.

Histone modifications are epigenetic processes that influence gene expression by changing chromatin structure **(5)**. Chemical changes, like methylation on N-terminal tails of histones modulate transcriptional activity, by either enhancing or repressing genes through the formation of open (euchromatin) or closed (heterochromatin) chromatin states **(11, 12)**. *Enhancer of Zeste Homolog 2 (EZH2)* serves as the catalytic subunit of the *Polycomb Repressive Complex 2 (PRC2)*, mediating tri-methylation of histone H3 at lysine 27 (H3K27me3) and inducing gene silencing through chromatin remodeling **(13)**.

EZH2 activity regulates important cellular processes, such as the cell cycle, DNA repair, autophagy, and apoptosis. During hematopoiesis, *EZH2* functions in regulating the balance between hematopoietic stem cell differentiation and self-renewal **(14, 15)**. Given its broad influence on cellular functions, both *EZH2* overexpression and loss of function have been implicated in the pathogenesis of hematologic and non-hematologic malignancies **(16, 17)**.

Understanding the impact of epigenetic mechanisms on cancer initiation and progression enhances our understanding of the molecular underpinnings of these diseases. This insight also paves the way for developing personalized therapeutic strategies for patients. The present study aimed to explore *SOCS1* gene methylation patterns, *EZH2* expression status, and their association in AML.

2. Materials and Methods

2.1 Data Collection and Sample Preparation

This cross-sectional study analyzed bone marrow or peripheral blood samples from 85 AML patients admitted to the cancer molecular pathology research center at Ghaem Hospital (Mashhad, Iran) between April 2024 and February 2025. The inclusion criteria required a confirmed diagnosis of AML based on the French-American-British (FAB) and World Health Organization (WHO) guidelines, which included assessments of blood cell counts, peripheral blood smears, cellular immunophenotypes, and clinical symptoms. The diagnosis was confirmed by both a pathologist and a hematologist. All patients were newly diagnosed and had not received any treatment at the time of sample collection. Demographic, laboratory, and clinical data were extracted from medical records. Additional methodological details are presented in the supplementary section.

2.2 RNA Isolation and cDNA Synthesis

Bone marrow samples were used to isolate total RNA with the RNeasy Kit (AddBio, Korea, Cat. No. 10119) following the manufacturer's guidelines. RNA purity and concentration were determined by measuring absorbance ratios at 260/280 nm using a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). Samples that did not meet quality standards or had low RNA yield were excluded. For cDNA synthesis, 2.5 µl of RNA was combined with 5 µl of 2x reaction buffer, 1 µl of dNTPs and oligo dT/random primers, and 0.5 µl of Moloney Murine Leukemia Virus (MMLV) reverse transcriptase, according to the kit instructions (AddBio, Korea, Cat. No. 22701).

2.3 Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR) for *EZH2* Expression

Quantitative real-time PCR was performed to measure *EZH2* expression, utilizing SYBR Green Master Mix (AddBio, Korea, Cat. No. 70205) on an ABI StepOne platform (Applied Biosystems, USA). The reaction mixture was prepared in a microtube by combining 2 µl of cDNA template, 4 µl of SYBR Green Master Mix, 0.2 µl of each primer, and 3.8 µl of distilled water (DW), resulting in a total volume of 10 µl. PCR cycling conditions initiated with 8 minutes at 94 °C, followed by 38 cycles of 94 °C for 12 seconds and 64 °C for 58 seconds. Melt curve analysis was done at 58 °C and 94 °C for 10 seconds each. *Glyceraldehyde 3-phosphate dehydrogenase* (*GAPDH*) was employed as the internal control. The primers used were as follows: for *EZH2*, forward 5′-TTGTTGGCGGAAGCGTGTAAAATC-3′ and reverse 5′-TCCCTAGTCCCGCGCAATGAGC-3′; for GAPDH, forward 5′-TGAACGGGAAGCTCACTGG-3′ and reverse 5′-TCCACCACCCTGTTGCTGTA-3′. Relative expression of *EZH2* was determined utilizing the 2^ (-ΔΔct) method.

2.4 DNA Extraction and Methylation-specific PCR (MSP) for *SOCS1* Gene

DNA was extracted from BM samples using the *FavorPrep Blood Genomic DNA Extraction Mini Kit* (FABGK 000, 4 Preps) following the manufacturer's protocol. The isolated DNA was treated with the EpiTect Bisulfite Kit (QIAGEN, USA), which converts unmethylated cytosines into uracil, leaving methylated cytosines intact. The resulting DNA was then resuspended in elution buffer and either subjected to immediate evaluation or preserved at −80 °C for subsequent procedures. Methylation-specific PCR (MSP) was utilized to determine the methylation profile of the *SOCS1* promoter, a sensitive method for detecting both methylated and unmethylated DNA in experimental cell cultures and clinical specimens **(10, 18)**. Real-time PCR was carried out using primer pairs designed to specifically amplify methylated (M) or unmethylated (U) sequences. This procedure enabled the classification of bisulfite-modified DNA into fully methylated (MM) or partially methylated (MU) categories, providing a precise assessment of the *SOCS1* methylation.

2.5 Statistical Analyses

SPSS software (IBM, version 21) was employed for statistical analysis. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test to assess normality. Non-normally distributed data were compared between groups using the Mann–Whitney U test. Associations between categorical variables were explored using Pearson's Chi-square test or Fisher's exact test, depending on the data characteristics. The prognostic relevance of *EZH2* expression and *SOCS1* methylation was assessed by Kaplan-Meier survival analysis, with differences evaluated using the log-rank test. A P value less than 0.05 (two-tailed) was considered indicative of statistical significance.

3. Result

3.1 *EZH2* Expression Level

In this study, 85 AML patients with an average age of 38.5 years were analyzed. Patients were classified into two groups based on *EZH2* gene expression. Among them, 43 patients (50.58%; 18 men and 25 women) exhibited *EZH2* overexpression, while 42 patients (49.42%; 20 men and 22 women) exhibited *EZH2* underexpression.

3.2 The Correlation Between *EZH2* Expression and Patients' Clinical Characteristics

As shown in Table 1, a comparison of demographic, hematologic, and molecular indices between patients with *EZH2* overexpression and underexpression revealed a significant association between elevated *EZH2* expression and higher white blood cell count ($P = 0.04$).

3.3 *SOCS1* Methylation Status and Its Correlation with Patients' Clinical Characteristics

A total of 33 patients (38.82%; 18 men and 15 women) exhibited hypermethylation, while 52 patients (61.18%; 20 men and 32 women) showed hypomethylation of the *SOCS1* gene. No significant differences in demographic, hematologic, or molecular indices were found between the two groups (Table 2).

3.4 The Relationship Between *EZH2* Expression and *SOCS1* Methylation Status

As indicated in Table 3, the current study found a significant inverse relationship between *EZH2* expression and *SOCS1* methylation ($P < 0.0001$, $r = -0.37$).

3.5 Survival Analysis

Survival analysis, shown in Figure 1, revealed that both *EZH2* overexpression and *SOCS1* hypomethylation showed a relationship with poorer overall survival (OS) ($P = 0.008$ and $P < 0.0001$, respectively). In addition, Cox regression analyses, both univariate and multivariate, were performed to assess how additional clinical parameters influenced prognosis in AML cases. In univariate Cox Regression analysis, PLT counts, SOSC1 methylation, and *EZH2* gene expression were as adverse prognostic factors and Multivariate Cox Regression analysis showed that PLT counts and *SOCS1* methylation were as poor prognostic factors for OS in AML patients (as shown in Table 4).

Table 1. Differences of demographic data, laboratory, and molecular findings between AML patients with high and low expression of *EZH2*.

Parameter	Overexpression *EZH2*	Under Expression *EZH2*	P-value
Sex (female/male)	25/18	22/20	0.59
Age (years) (mean±SD)	21.08±41.66	19.32±36.09	0.20
Hb (g/dl) (Mean Rank)	44.91	41.05	0.47
WBC ($\times 10^9$/L) (Mean Rank)	37.57	48.56	0.04
PLT ($\times 10^9$/L) (Mean Rank)	44.73	41.23	0.51
t (15;17) (+/-)	0/43	1/41	0.30
FLT3-ITD (+/-)	7/36	13/29	0.11
FLT3-TKD (+/-)	4/39	4/38	>0.99
NPM1 (+/-)	4/39	7/35	0.31

Hb: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; FLT3: Fms-related tyrosine kinase-3; ITD: Internal tandem duplication; NPM1: Nucleophosmin.

Table 2. Comparison of demographic data, laboratory, and molecular findings between AML patients with *SOCS1* hyper and hypomethylation.

Parameter	Overexpression *EZH2*	Under Expression *EZH2*	P-value
Sex (female/male)	15/18	32/20	0.14
Age (years) (mean±SD)	17.22±39.69	22.18±38.41	0.77
Hb (g/dl) (Mean Rank)	42.94	43.03	0.98
WBC ($\times 10^9$/L) (Mean Rank)	46.74	40.63	0.26
PLT ($\times 10^9$/L) (Mean Rank)	40.29	44.72	0.42
t (15;17) (+/-)	1/32	0/52	0.38
FLT3-ITD (+/-)	8/25	12/40	0.90
FLT3-TKD (+/-)	3/30	5/47	>0.99
NPM1 (+/-)	4/29	7/45	>0.99

Hb: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; FLT3: Fms-related tyrosine kinase-3; ITD: Internal tandem duplication; NPM1: Nucleophosmin.

Table 3. The relationship between *EZH2* expression and *SOCS1* methylation.

	P-value	R
gene expression *EZH2*	>0.0001	-0.37
methylation *SOCS1*	>0.0001	-0.37

Table 4. Multivariate assessment of factors associated with OS in AML.

Variables	P-value	OS HR	CI
Plt counts	0.01	1.002	1.000-1.004
SOCS1 methylation	0.002	0.440	0.259-0.746
EZH2 gene expression	0.19	1.385	2.256

AML: Acute myeloid leukemia; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; PLT: Platelet

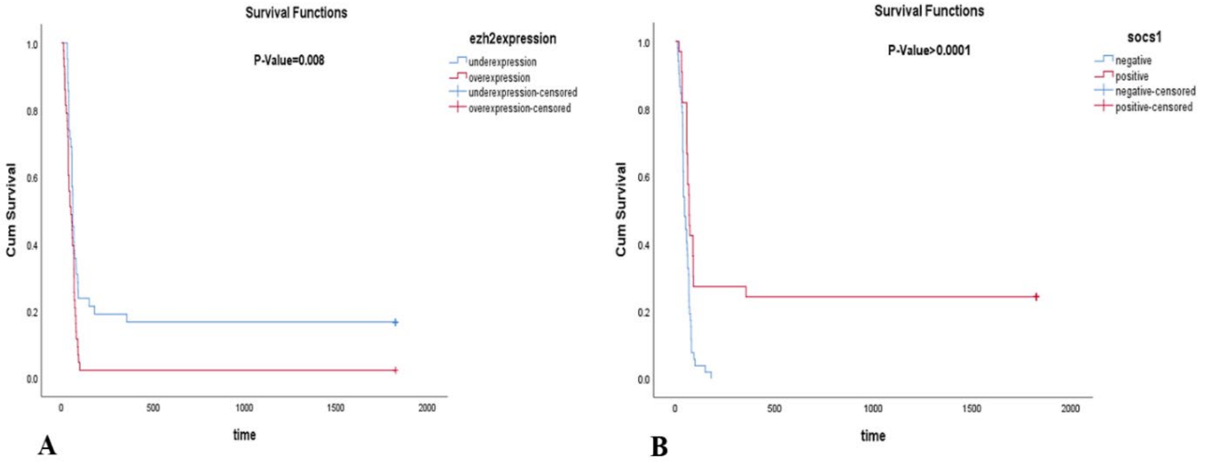

Figure 1. Kaplan–Meier survival graph in AML patients based on *EZH2* expression and *SOCS1* methylation. *(A)* Patients with *EZH2* overexpression (Red line) show significantly reduced overall survival compared to those with underexpression (Blue line) (P = 0.008); *(B)* Patients with *SOCS1* hypomethylation (Blue line) have poorer survival than those with methylation (Red line) (P = 0.0001). Censored cases are shown as tick marks on the curves. (**Designed by Authors, 2025**).

4. Discussions

The pathogenesis of AML is strongly shaped by epigenetic changes, including both DNA methylation and histone modifications, reflecting the disease's heterogeneity **(19)**. We analyzed *SOCS1* promoter methylation and *EZH2* expression in AML patients to clarify their clinical significance. Our findings showed that 50.58% of AML patients exhibited *EZH2* overexpression, while 49.42% had reduced expression. *EZH2* expression was assessed exclusively in AML patients in our study. Several studies, however, have compared *EZH2* expression between AML patients and healthy controls. For instance, Zhu et al **(20)** and Xu et al **(21)** reported elevated *EZH2* expression in AML patients relative to healthy individuals, whereas Hamed et al **(15)** and Chu et al **(22)** indicated *EZH2* downregulation in AML, reflecting the heterogeneity of its expression level across studies.

From a prognostic viewpoint, our findings showed that higher *EZH2* expression was significantly linked to reduced overall survival, indicating its potential role in disease progression. This is consistent with Zhu et al **(20)** who reported poorer outcomes and extramedullary infiltration in patients with elevated *EZH2*. They also found that silencing *EZH2* reduced proliferation and migration while increasing apoptosis **(20)**. Stomper et al **(23)** also showed the association between *EZH2* dysregulation and worse outcomes. In contrast, Chu et al **(22)** observed no clear link to survival, and Hamed et al **(15)** found that low *EZH2* expression correlated with higher mortality. Additionally, Göllner et al **(24)** identified *EZH2* loss as a factor contributing to treatment resistance **(24)**. These mixed results emphasize the context-dependent role of *EZH2* and the need for further subtype- and treatment-specific research **(25)**.

In our cohort, *EZH2* expression showed no significant correlation with common genetic alterations such as *FLT3-ITD* (20 cases), *FLT3-TKD* (8 cases), and *NPM1* (11 cases). However, Stomper et al **(23)** reported frequent *EZH2* mutations co-occurring with *CEBPA* (67%), *ASXL1* (50%), *TET2*, and *RAD21* mutations (33% each) **(23)**. Furthermore, Wang et al **(26)** suggest that dysregulation of *TET2* and *EZH2* may promote leukemogenesis and disease progression **(26)**.

Regarding *SOCS1*, 38.82% of AML patients exhibited promoter methylation, consistent with the 48% prevalence reported by Zhang et al **(9)** in newly diagnosed cases **(9)**. In contrast, Hou et al **(27)** observed a higher frequency, ranging from 60% to 72% **(27)**. Notably, Zhang et al. also found *SOCS1* methylation in 80% of relapsed or refractory patients, suggesting a potential correlation with disease progression. Their study further demonstrated that methylation of *SOCS1* suppresses its expression and is associated with elevated levels of *JAK2*, *STAT3*, and *STAT5*, indicating activation of the *JAK/STAT* signaling pathway **(9)**. These findings are supported by Park et al **(28)** who showed that *SOCS1* silencing through methylation promotes *STAT* phosphorylation and tumor progression in breast cancer **(28)**. However, Hou et al **(27)** found no clear association between *SOCS1* methylation and expression **(27)**.

In the current study, *SOCS1* hypomethylation was associated with reduced overall survival, indicating its potential as a poor prognostic marker. Hou et al **(27)** also linked higher *SOCS1* expression to adverse outcomes **(27)**. In contrast, Enoch Tin et al **(29)** reported that lower *SOCS1* expression in primary AML cells correlated with better survival and enhanced T-cell activity, suggesting a role in immune evasion **(29)**. These findings underscore the complex and context-dependent nature of *SOCS1* regulation in AML. Further studies assessing both methylation and expression in parallel are needed to clarify its prognostic significance.

Importantly, we observed an inverse association between *EZH2* expression and *SOCS1* promoter methylation in AML samples. Although this relationship has not been previously explored in AML, prior research shows that *EZH2* regulates *SOCS* family members through different mechanisms depending on the context. For example, Bao et al **(30)** reported that *EZH2* inhibition increases *SOCS1* expression in IL-4–stimulated M2 macrophages via changes *in STAT* signaling. Similarly, regulation of another family member, *SOCS3*, has been linked to *EZH2* in hepatocellular carcinoma **(31)** and autoimmune inflammation **(32)**. These findings suggest that *EZH2's* impact on *SOCS* genes may differ by context. Our results provide initial evidence of this relationship in AML and suggest further studies are needed.

Clinically, *EZH2* and *SOCS1* are promising therapeutic targets in AML **(33)**. Huang et al **(34)** showed that *Tanshinone I* directly binds *EZH2* and fosters AML cell differentiation and apoptosis **(34)**. Similarly, Sbirkov et al **(35)** demonstrated that *HKMTI-1-005*, a competitive EZH2 inhibitor, promotes AML cell differentiation **(35)**. Recently published, Velez et al **(36)** and Wang et al **(37)** reported that the *PROTAC* degraders *MS177* and *MS8847* effectively reduce *EZH2* levels, suppress colony formation, halt the cell cycle, and trigger apoptosis in AML cell lines and animal models. Regarding *SOCS1*, Enoch Tin et al. found that *SOCS1* helps AML cells evade allogeneic T cell–mediated killing via the *SOCS1–JAK1–STAT1* pathway by downregulating IFNγ-induced *ICAM-1* expression. Notably, lower *SOCS1* expression in primary AML cells exhibited a relationship with better overall survival and enhanced T cell activity, supporting its potential as a target to boost T cell–based immunotherapies **(29)**. Together, these findings highlight the therapeutic value of targeting *EZH2* and *SOCS1*, especially in strategies combining epigenetic modulation with immunotherapy in AML.

5. Conclusion

This study demonstrates that both *EZH2* overexpression and *SOCS1* hypomethylation are associated with reduced overall survival in AML, supporting their potential as markers influencing disease outcome. Additionally, we identified an inverse correlation between *EZH2* expression and *SOCS1* promoter methylation, suggesting a possible interaction that may contribute to disease biology. While these findings are compelling, the precise association between *SOCS1* methylation and its expression level, as well as the regulatory influence of *EZH2* on *SOCS1* activity, remains unclear and warrants further investigation. Considering the growing interest in *EZH2* and *SOCS1* as therapeutic targets—particularly in the context of epigenetic modulation and immune evasion—our findings provide a basis for future investigations into their combined role in AML progression and treatment response. Validation in larger, genetically diverse cohorts is warranted.

6. Declarations

6.1 Acknowledgments

This work was extracted from the Master of Science (MSc.) student thesis. We would like to thank our colleagues from Ghaem hospital, Mashad, Iran.

6.2 Ethical Considerations

The current study received approval from the Ethics Committee of MUMS (Ethics code: IR.MUMS.MEDICAL.REC.1403.036), with informed consent obtained from all participants.

6.3 Authors' Contributions

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

6.4 Conflict of Interest

All authors declare any conflicts of interests in the study.

6.5 Fund or Financial Support

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors did not use any form of artificial intelligence in the preparation of this manuscript.

References

1. Shimony S, Stahl M, Stone RM. Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(3):502-26. [DOI:10.1002/ajh.26822] [PMID]
2. Schrezenmeier J, Huntly BJP. Epigenetic dysregulation in acute myeloid leukemia.

Semin Hematol. 2025;S0037-1963(25):00028-9. [DOI:10.1053/j.seminhematol.2025.06.003] [PMID]

3. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet. 2016; 17(8):487-500. [DOI:10.1038/nrg.2016.59] [PMID]
4. Meng Y, Nerlov C. Epigenetic regulation of hematopoietic stem cell fate. Trends Cell Biol. 2025;35(3):217-29. [PMID] [PMCID] [DOI:10.1016/j.tcb.2024.08.005]
5. Eriksson A, Lennartsson A, Lehmann S. Epigenetic aberrations in acute myeloid leukemia: Early key events during leukemogenesis. Exp Hematol. 2015;43(8): 609-24. [DOI:10.1016/j.exphem.2015.05.009] [PMID]
6. Davletgildeeva AT, Kuznetsov NA. The Role of DNMT Methyltransferases and TET Dioxygenases in the Maintenance of the DNA Methylation Level. Biomolecules. 2024;14(9): 1117. [DOI:10.3390/biom14091117] [PMID] [PMCID]
7. Zhang X, Blumenthal RM, Cheng X. Keep Fingers on the CpG Islands. Epigenomes. 2024; 8(2):23. [DOI:10.3390/epigenomes8020023] [PMID] [PMCID]
8. Dong Y, Liao H, Huang F, Bao Y, Guo W, Tan Z. Machine learning approaches reveal methylation signatures associated with pediatric acute myeloid leukemia recurrence. Sci Rep. 2025;15(1):15815. [PMCID] [DOI:10.1038/s41598-025-99258-4] [PMID]
9. Zhang XH, Yang L, Liu XJ, Zhan Y, Pan YX, Wang XZ, et al. Association between methylation of tumor suppressor gene SOCS1 and acute myeloid leukemia. Oncol Rep. 2018; 40(2):1008-16. [DOI:10.3892/or.2018.6508] [PMID]
10. Beaurivage C, Champagne A, Tobelaim WS, Pomerleau V, Menendez A, Saucier C. SOCS1 in cancer: An oncogene and a tumor suppressor. Cytokine. 2016;82:87-94. [DOI:10.1016/j.cyto.2016.01.005] [PMID]
11. Ludwig CH, Bintu L, Klein A, Treutlein B. Mapping chromatin modifications at the single cell level. Development. 2019;146(12): dev170217. [DOI:10.1242/dev.170217] [PMID] [PMCID]
12. Kouzarides T. Chromatin modifications and their function. Cell. 2007;128(4):693-705. [DOI:10.1016/j.cell.2007.02.005] [PMID]
13. Bouligny IM, Maher KR, Grant S. Secondary-Type Mutations in Acute Myeloid Leukemia: Updates from ELN 2022. Cancers (Basel). 2023;15(13):3292. [PMID] [PMCID] [DOI:10.3390/cancers15133292]
14. Duan R, Du W, Guo W. EZH2: a novel target for cancer treatment. J Hematol Oncol. 2020; 13(1):104. [PMID] [PMCID] [DOI:10.1186/s13045-020-00937-8]
15. Hamed NAM, El Ghandour A, Abo Elwafa RA, Rezk MR, Ghallab O. Expression of Enhancer of Zeste Homolog 2 (EZH2) Gene in Acute Myeloid Leukemia. Asian Pac J Cancer Prev. 2023;24(1):81-5. [PMID] [PMCID] [DOI:10.31557/APJCP.2023.24.1.81]
16. Kim KH, Roberts CW. Targeting EZH2 in cancer. Nat Med. 2016;22(2):128-34. [DOI:10.1038/nm.4036] [PMID] [PMCID]
17. Liu Y, Yang Q. The roles of EZH2 in cancer and its inhibitors. Med Oncol. 2023;40(6):167. [DOI:10.1007/s12032-023-02025-6][PMID] [PMCID]
18. Chen CY, Tsay W, Tang JL, Shen HL, Lin SW, Huang SY, et al. SOCS1 methylation in patients with newly diagnosed acute myeloid leukemia. Genes Chromosomes Cancer. 2003; 37(3):300-5. [DOI:10.1002/gcc.10222][PMID]
19. Kühn MWM, Pemmaraju N, Heidel FH. The evolving landscape of epigenetic target molecules and therapies in myeloid cancers: focus on acute myeloid leukemia and myeloproliferative neoplasms. Leukemia. 2025;39(8):1824-37. [PMID] [PMCID] [DOI:10.1038/s41375-025-02639-x]
20. Zhu Q, Zhang L, Li X, Chen F, Jiang L, Yu G, et al. Higher EZH2 expression is associated with extramedullary infiltration in acute myeloid leukemia. Tumour Biol. 2016;37(8): 11409-20. [DOI:10.1007/s13277-016-4983-4] [PMID]
21. Xu F, Li X, Wu L, Zhang Q, Yang R, Yang Y, et al. Overexpression of the EZH2, RING1 and BMI1 genes is common in myelodysplastic syndromes: relation to adverse epigenetic alteration and poor prognostic scoring. Ann Hematol. 2011;90(6):643-53. [DOI:10.1007/s00277-010-1128-5] [PMID]
22. Chu MQ, Zhang TJ, Xu ZJ, Gu Y, Ma JC, Zhang W, et al. EZH2 dysregulation: Potential biomarkers predicting prognosis and guiding treatment choice in acute myeloid leukaemia. J Cell Mol Med. 2020;24(2):1640-9. [DOI:10.1111/jcmm.14855] [PMID] [PMCID]
23. Stomper J, Meier R, Ma T, Pfeifer D, Ihorst G, Blagitko-Dorfs N, et al. Integrative study of EZH2 mutational status, copy number, protein expression and H3K27 trimethylation in AML/MDS patients. Clin Epigenetics. 2021; 13(1):77. [DOI:10.1186/s13148-021-01052-2]

[DOI:10.1186/s13148-021-01087-5][PMID] [PMCID]

24. Göllner S, Oellerich T, Agrawal-Singh S, Schenk T, Klein HU, Rohde C, et al. Loss of the histone methyltransferase EZH2 induces resistance to multiple drugs in acute myeloid leukemia. Nat Med. 2017;23(1):69-78. [DOI:10.1038/nm.4247] [PMID] [PMCID]
25. Bouligny IM, Maher KR, Grant S. Mechanisms of myeloid leukemogenesis: Current perspectives and therapeutic objectives. Blood Rev. 2023;57:100996. [PMID] [PMCID] [DOI:10.1016/j.blre.2022.100996]
26. Wang J, He N, Wang R, Tian T, Han F, Zhong C, et al. Analysis of TET2 and EZH2 gene functions in chromosome instability in acute myeloid leukemia. Sci Rep. 2020;10(1):2706. [DOI:10.1038/s41598-020-59365-w][PMID] [PMCID]
27. Hou HA, Lu JW, Lin TY, Tsai CH, Chou WC, Lin CC, et al. Clinico-biological significance of suppressor of cytokine signaling 1 expression in acute myeloid leukemia. Blood Cancer J. 2017;7(7):e588. [DOI:10.1038/bcj.2017.67] [PMID] [PMCID]
28. Park Y, Shon SK, Kim A, Kim KI, Yang Y, Cho DH, et al. SOCS1 induced by NDRG2 expression negatively regulates STAT3 activation in breast cancer cells. Biochem Biophys Res Commun. 2007;363(2):361-7. [DOI:10.1016/j.bbrc.2015.04.039] [DOI:10.1016/j.bbrc.2007.08.195]
29. Tin E, Rutella S, Khatri I, Na Y, Yan Y, MacLean N, et al. SOCS1 Protects Acute Myeloid Leukemia against Allogeneic T Cell-Mediated Cytotoxicity. Blood Cancer Discov. 2025;6(3):217-32. [PMID] [DOI:10.1158/2643-3230.BCD-24-0140]
30. Bao X, Liu X, Liu N, Zhuang S, Yang Q, Ren H, et al. Inhibition of EZH2 prevents acute respiratory distress syndrome (ARDS)-associated pulmonary fibrosis by regulating the macrophage polarization phenotype. Respir Res. 2021;22(1):194. [PMID] [PMCID] [DOI:10.1186/s12931-021-01785-x]
31. Wei L, Liu Q, Huang Y, Liu Z, Zhao R, Li B, et al. Knockdown of CTCF reduces the binding of EZH2 and affects the methylation of the SOCS3 promoter in hepatocellular carcinoma. Int J Biochem Cell Biol. 2020;120:105685. [DOI:10.1016/j.biocel.2020.105685] [PMID]
32. Zhang X, Wang Y, Yuan J, Li N, Pei S, Xu J, et al. Macrophage/microglial Ezh2 facilitates autoimmune inflammation through inhibition of Socs3. J Exp Med. 2018;215(5):1365-82. [DOI:10.1084/jem.20171417] [PMID] [PMCID]
33. Fang J, Zhang J, Zhu L, Xin X, Hu H. The epigenetic role of EZH2 in acute myeloid leukemia. Peer J. 2024;12:e18656. [DOI:10.7717/peerj.18656] [PMID] [PMCID]
34. Huang Y, Yu SH, Zhen WX, Cheng T, Wang D, Lin JB, et al. Tanshinone I, a new EZH2 inhibitor restricts normal and malignant hematopoiesis through upregulation of MMP9 and ABCG2. Theranostics. 2021;11(14):6891-904. [DOI:10.7150/thno.53170] [PMID] [PMCID]
35. Sbirkov Y, Schenk T, Kwok C, Stengel S, Brown R, Brown G, et al. Dual inhibition of EZH2 and G9A/GLP histone methyltransferases by HKMTI-1-005 promotes differentiation of acute myeloid leukemia cells. Front Cell Dev Biol. 2023;11:1076458. [DOI:10.3389/fcell.2023.1076458] [PMID] [PMCID]
36. Velez J, Dale B, Park KS, Kaniskan H, Yu X, Jin J. Discovery of a novel, highly potent EZH2 PROTAC degrader for targeting non-canonical oncogenic functions of EZH2. Eur J Med Chem. 2024;267:116154. [PMCID] [DOI:10.1016/j.ejmech.2024.116154] [PMID]
37. Wang J, Yu X, Gong W, Liu X, Park KS, Ma A, et al. EZH2 noncanonically binds cMyc and p300 through a cryptic transactivation domain to mediate gene activation and promote oncogenesis. Nat Cell Biol. 2022;24(3):384-99. [DOI:10.1038/s41556-022-00850-x] [PMID] [PMCID

How to Cite This Article:

Gholami F S, Safipour Afshar A, Sadeghi Zarghari S, Mazhari A, Siyadat P, Sheikhi M, et al. *EZH2* Gene Expression and *SOCS1* Gene Methylation in Acute Myeloid Leukemia: Unraveling Epigenetic Interactions and Clinical Implications. J Adv Med Biomed Res. 2025;33(159):310-8.