RESEARCH ARTICLE

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Expression and Alteration Value of Long Noncoding RNA AB073614 and FER1L4 in Patients with Acute Myeloid Leukemia (AML)

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Abstract

Background: Numerous studies have probed the deregulation of the long noncoding RNA AB073614 and FER1L4, which have been discovered in a variety of cancers. However, the precise expression pattern of these lncRNAs and their clinical implications in acute myeloid leukemia (AML) remain elusive. Considering the involvement of the PI3K axis in AML pathogenesis, an investigation into the expression of AB073614 and FER1L4 targets of this pathway has been proposed, aiming to elucidate a potential mechanism underlying AML development. **Methods:** The expression levels of lncRNA AB073614 and FER1L4 were assessed in 30 newly diagnosed AML patients and 12 healthy individuals using quantitative reverse transcription–polymerase chain reaction techniques. A statistical analysis was conducted to determine the association of AB073614 and FER1L4 expression levels with clinicopathological features. **Results:** A significant upregulation of AB073614 was observed in AML patients compared to the control group ($p < 0.05$). Moreover, a notable increase in AB073614 expression levels coincided with a significant reduction in FER1L4 expression levels in AML samples ($p < 0.05$). The diagnostic value of these lncRNAs was validated using the receiver operating characteristic (ROC) curve and area under the curve (AUC) calculations. Sensitivity values of AB073614 and FER1L4 gene expression were 96.7% and 100%, respectively, using cut-off relative quantification of 1.045 and 0.770. Additionally, specificity values were observed to be 100%. **Conclusions:** The present study indicates that AB073614 and FER1L4 might serve as prognosis biomarkers in AML patients. However, further detailed examinations in this field are warranted. It is proposed that the likely mechanism of imbalanced PI3K and PTEN activity, triggered by the deregulation of AB073614 and FER1L4, may have a crucial role in AML pathogenesis. Any component of this pathway could potentially serve as a new target for more insightful treatment approaches.

Keywords: AB073614- FER1L4- AML- PI3K/Akt- PTEN

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Introduction

Acute myeloid leukemia (AML) is characterized by rapid progression and the accumulation of abnormal myeloblast cells in the bone marrow, resulting in disruption to the production of normal blood cells (Kantarjian et al., 2021). AML, the most common type of leukemia in adults, is notorious for its heterogeneous genetic characteristics. Numerous molecules and signaling pathways contribute significantly to the molecular pathogenesis of this malignancy (Sheikhi et al., 2017; Giannopoulos, 2019; Stanchina et al., 2020). Currently, targeted therapies are crucial for cancer patients, although strides continue to be made to enhance the efficacy of these treatments and minimize their side effects (Yang and Wang, 2018; Cucchi et al., 2021). Continued efforts are being made to identify unique biomarkers not only to predict prognosis but also for therapeutic interventions (Ye et al., 2019; Yu et al., 2020). Long noncoding RNAs (LncRNAs), typically shorter than protein-coding genes and primarily transcribed by RNA polymerase II, are a diverse class of noncoding RNAs (ncRNAs) longer than 200 nucleotides without defined open-reading frames (Jiang et al., 2019).

LncRNAs have emerged as pivotal modulators of gene expression, demonstrating cell-specific expression patterns and engaging significantly in various biological processes, including imprinting, epigenetic regulation, differentiation, apoptosis, and cell cycle progression (Koch, 2017; Peng et al., 2017). Multiple studies suggest that lncRNAs could serve as promising targets

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for therapy in human cancer, as well as diagnostic and prognostic markers in specific cancers. Recent research has revealed some lncRNAs play critical roles in myeloid differentiation and regulate vital signaling pathways such as the PI3K axis in AML (Do and Kim, 2018).

LncRNA AB073614 is postulated to exert its effects by targeting the PI3/AKT-mediated signaling pathway. It has been observed that AB073614 expression is upregulated in ovarian cancer and glioblastoma, acting as a functional oncogene in the development of these cancers (Wang et al., 2017). Moreover, the reduction of AB073614 expression substantially inhibited cell proliferation and invasion, induced G1 phase cell cycle arrest, and markedly increased apoptosis rates of ovarian cancer cells (Cheng et al., 2015). A decrease in AB073614 curtailed U251 glioma cell proliferation, migration, and epithelial-mesenchymal transition. Nevertheless, the precise role of lncRNA AB073614 in the pathogenesis and progression of AML remains a contentious issue (Li et al., 2016; Liao et al., 2019).

LncRNA Fer-1-like protein 4 (FER1L4), initially identified in gastric cancer, is implicated in tumorigenesis through inhibition of the PI3K/AKT pathway in cancer cells such as osteosarcoma, hepatocellular carcinoma, and colon cancer. It plays critical roles in numerous processes, including cell growth, apoptosis, migration, and invasion (Liu et al., 2014; Fei et al., 2018; Huang et al., 2020).

Considering the uncertainties regarding the pathogenic value of AB073614 via the PI3K axis and its downstream targets in AML patients, alongside the important role of FER1L4 in adjusting the PI3K pathway, a study was conducted. This study aimed not only to assess the expression levels of the novel lncRNAs AB073614 and FER1L4 in newly diagnosed AML patients but also to investigate any potential correlation between the aforementioned lncRNAs in this leukemia. The goal was to examine the expression of AB073614 and FER1L4 targets of the PI3K pathway to propose a probable mechanism underlying AML pathogenesis.

Materials and Methods

Patients and controls samples

Peripheral blood samples were gathered from 30 newly diagnosed AML patients, who had not undergone previous treatment, and 20 healthy controls. Written informed consent was procured from each participant, aged between 17–74. The research protocol received approval from the Research Ethics Committee at the Arak University of Medical Sciences (ID number: IR.ARAKMU.REC.1399.194) in adherence to the Helsinki Declaration. Table 1 provides a summary of the clinicopathological features of the de-novo AML patients.

Patients were diagnosed based on morphological characteristics and specific immunophenotypes, following the French-American-British (FAB) classification that categorizes AML subtypes based on cellular morphological features. Of the examined samples, 80% were classified as non-M3 AML and 20% as AML-M3. The median age at diagnosis was approximately 53 years. It is worth mentioning that 64% of the patients (19 out of 30) were male, and 36% (11 out of 30) were female. In the control group, the median age was also around 53 years, with 60% male (12 out of 20) and 40% female (8 out of 20).

RNA Extraction and Preparation of cDNA

Total RNA was extracted from the buffy coat layer of patients' and healthy controls' peripheral blood using RNX Plus (Trizol) reagent (Sinaclon), per the manufacturer's instructions. RNA quantity was measured using a NanoDrop spectrophotometer (Optical Density (OD) 260/280 nm ratio > 1.8). The stability of the extracted RNA was evaluated by running 1 µL of RNA on 1.5% agarose gel to identify ribosomal RNA (rRNA) bands corresponding to 28s and 18s subunits. A total of 1000 ng of total RNA was reversed-transcribed to cDNA using a cDNA synthesis kit (Sinaclon). The synthesized cDNA was stored at -20°C for subsequent use.

Quantitative Real-Time PCR

Target lncRNA-specific primers (AB073614 and FER1L4) were utilized, along with GAPDH as a reference gene, using GeneRunner software (details in Table 2). Changes in lncRNAs expression levels were detected using SYBR green-based real-time quantitative polymerase chain reaction (qRT-PCR) (Roche, LightCycler® 96, Germany). A 15 µL reaction containing 2 µL cDNA, 1 µL Sense and antisense primers, 7.5 µL of master Mix (Sinaclon, Iran), and 4.5 µL water was amplified in a thermal cycler. Primer specificity was ensured through melting curve analysis. For each target lncRNA, primer efficiency was verified using a serial dilution (fivefold dilutions) of cDNA samples. All tests were conducted in triplicate, and changes in mRNA expression were calculated using the Livak method (2-ΔΔCT) (Livak and Schmittgen, 2001).

Statistical Analysis

Statistical analyses were executed using SPSS software (version 20.0), and graphs were generated with the GraphPad Prism 6 software. The normality of all continuous variables was tested with the Kolmogorov-Smirnov test. Independent student t or Mann-Whitney U tests were employed for comparisons between patients and the control group. The potential correlation between indicated lncRNAs was evaluated using Pearson's correlation test. A probability level of less than 0.05 was deemed statistically significant.

Results

AB073614 and FER1L4 expression in AML patients and healthy subjects

Results demonstrated that the upsurge in AB073614 transcript level in AML patients was accompanied by a reduction in FER1L4 lncRNA expression (Fig.1). The expression level of both AB073614 and FER1L4 was found to vary between AML patients and healthy individuals. However, the research findings suggested no significant relationship between expression changes and age, sex, or type of malignancy (data not shown).

Table 1. Clinicopathological Characteristics of De Novo Acute Myeloid Leukemia Patients

Patient	FAB Class	Age	RBC × 10^6	WBC × 10^3	Plt × 10^3	Blast (%)
1	AML-M2	47	4.12	4.5	156	36
2	AML-M3	61	3.15	20.4	74	53
3	AML-M2	52	3.94	11.7	191	29
4	AML-M1	59	2.91	6.3	123	24
5	AML-M0	26	3.96	5.8	125	27
6	AML-M3	74	5.25	14.3	65	39
7	AML-M4	48	4.38	36.2	43	46
8	AML-M3	66	4.12	18.4	36	34
9	AML-M5	62	3.84	12.1	79	33
10	AML-M2	17	2.73	10.2	101	47
11	AML-M1	43	4.87	9.8	174	29
12	AML-M5	31	3.41	13.6	15	71
13	AML-M2	69	5.36	4.9	76	53
14	AML-M6	55	2.52	2.6	99	43
15	AML-M2	51	3.61	9.4	121	61
16	AML-M3	46	4.08	11.5	35	57
17	AML-M7	52	4.98	2.9	142	32
18	AML-M2	37	2.76	7.6	101	27
19	AML-M3	48	3.63	10.7	68	23
20	AML-M2	67	4.37	25.5	79	34
21	AML-M3	41	5.02	21.3	31	43
22	AML-M1	36	4.78	6.7	99	51
23	AML-M2	55	5.12	5.9	57	47
24	AML-M4	62	3.46	12.1	63	28
25	AML-M4	71	3.86	14.9	98	32
26	AML-M3	48	4.05	10.8	76	36
27	AML-M5	65	4.82	9.7	105	28
28	AML-M2	49	3.92	10.8	156	27
29	AML-M0	53	3.84	12.3	106	47
30	AML-M1	50	4.31	4.9	84	31

AB073614 and FER1L4 expression as a potential diagnostic marker of AML patients

Diagnostic test evaluation was conducted based on sensitivity and specificity through the Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) calculation. The optimal cut-off for relative quantification differentiating AML patients from controls was determined. The AUC for AB073614 transcript level in patients and healthy subjects was 0.980 (95% CI, 0.9389–1.000; $p < 0.001$) (Figure 2A). Furthermore, the optimal cut-off value was set at 1.045, with sensitivity and specificity levels identified as 96.7% and 100%, respectively. For a discriminative capacity of FER1L4 expression, the cut-off point was set at 0.770, and the AUC was 1 (95% CI, 1–1; $p < 0.001$), boasting 100% sensitivity and specificity (Figure 2A).

Correlation between AB073614 and FER1L4 expression levels in studied groups

Statistical correlation analysis was used to assess if a significant correlation exists between the expression levels of the lncRNAs in the patient group. Results indicated a significant positive correlation between the lncRNA expression levels of AB073614 and FER1L4 ($r = -0.57$, $P < 0.05$) (Figure 2B), underlining the noticeable role of this pathway in the pathogenesis of AML.

Table 2. Nucleotide Sequences of the Primers Used for Real-Time RT-PCR

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')	Product size
GAPDH	GACAGTCAGCCGCATCTTCT	GCGCCCAATACGACCAAATC	104
AB073614	ATTTCTGCTCCTGGGTCTTAC	AGTGGCTTGTCTGTTAGAGTC	124
FER1L4	CAGCCTCCACTCAGCATCTTG	TGTCTCCTCCATCTCTCCTTCC	152

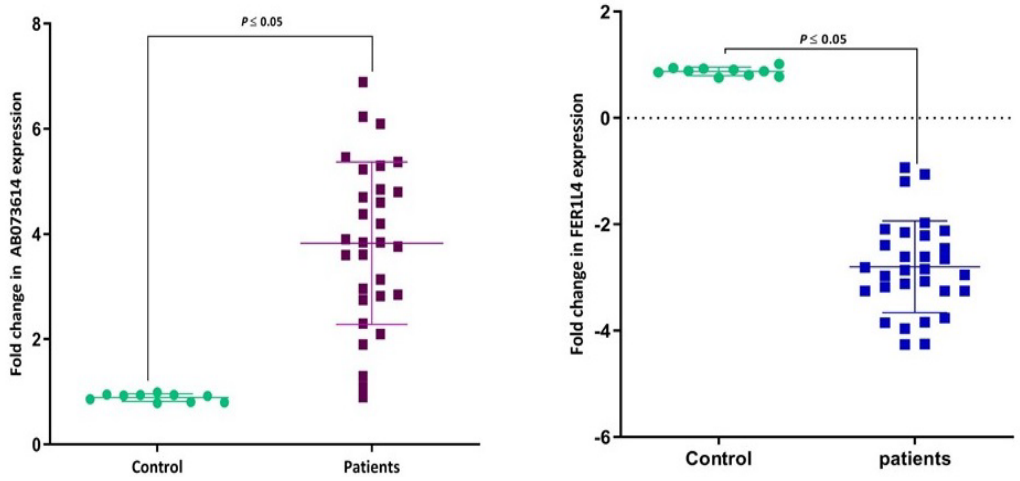

Figure 1. The lncRNA Expression Level of FER1L4 Significantly Decreased. values are given as mean ± standard deviation of three independent experiments.

Discussion

The prevention and timely diagnosis of various cancers, including acute myeloid leukemia (AML), are important aspects of human health, requiring continuous exploration in this field (Voso et al., 2019). It is increasingly recognized that several long noncoding RNAs (lncRNAs) play a fundamental role in regulating gene expression during the development of blood cells. Dysregulated expression of these lncRNAs can disrupt

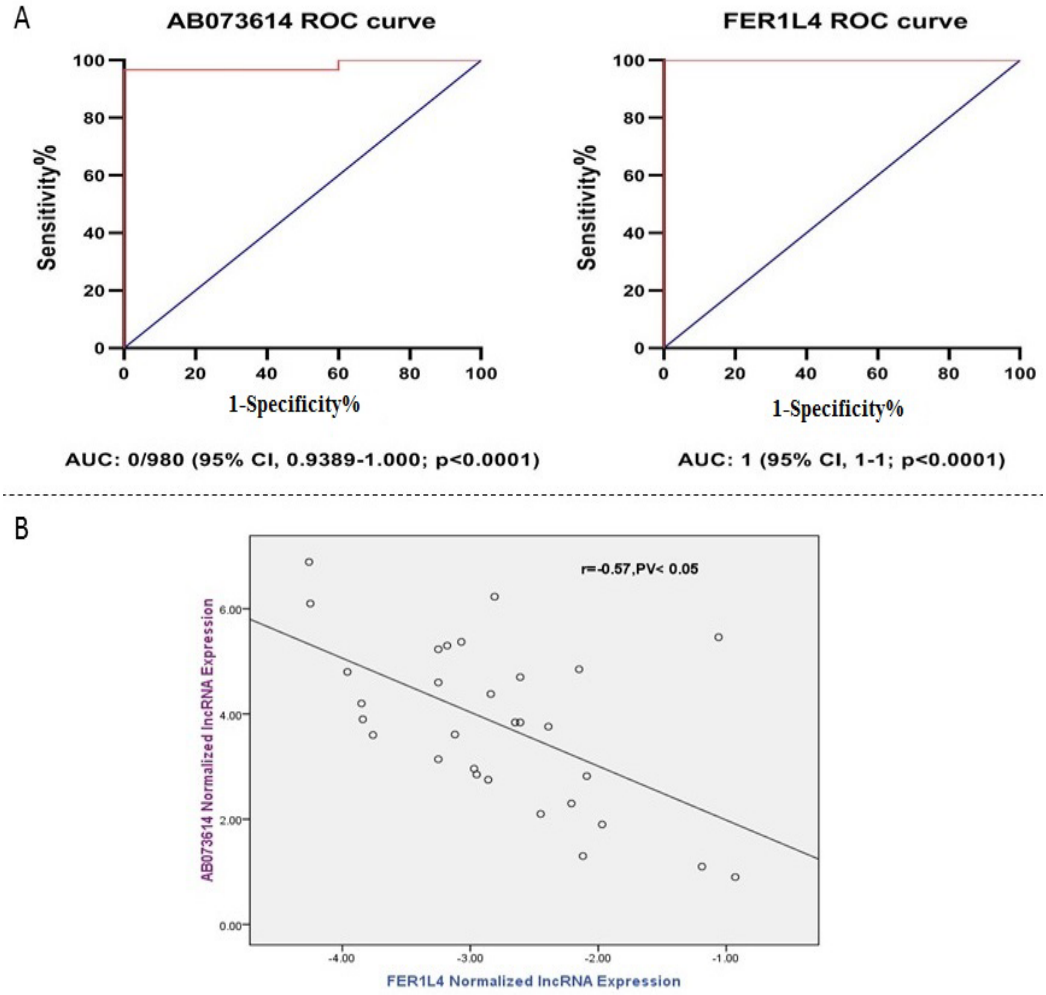

Figure 2. A, Area under the curve (AUC) of receiver operating characteristic (ROC) for lncRNA AB073614 and FER1L4 have been shown. 95% confidence interval (CI), sensitivity, specificity and the P-values are also shown. B, Correlation between the expression level of AB073614 and FER1L4 in leukemic samples. Values are given as mean ± standard deviation of three independent experiments.

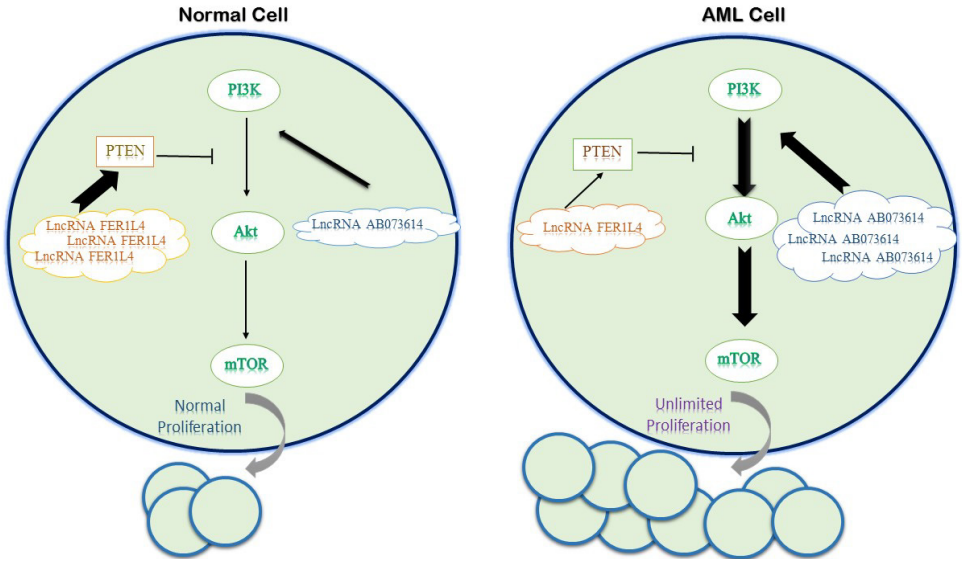

Figure 3. Schematic Illustration Proposed for the Probable Role of PI3K Axis in AML Cells. Through aberrant over-expression of AB073614 activation, subsequently leads to over activation PI3K signaling pathway in AML cells. Upon FER1L4 downregulation, and this defective loop may be responsible for providing a chance for AML cells to proliferate more strongly.

blood cell differentiation and promote uncontrolled proliferation, contributing to the development of leukemia, such as AML (Dieter et al., 2020; Gao et al., 2020). Some of these lncRNAs have shown promise as diagnostic and prognostic tools for hematologic cancers, particularly AML, and have garnered significant attention in the field (Gourvest et al., 2019). However, information regarding the expression of specific lncRNAs in AML patients and their correlation with clinicopathological classification remains limited (Wang et al., 2018).

Therefore, this study aimed to assess the expression of lncRNAs AB073614 and FER1L4 in newly diagnosed AML patients and investigate their association with clinical features. LncRNA AB073614 is a recently characterized transcript that was initially identified as a cDNA clone in Homo sapiens primary hepatoblastoma (clone: HMFN1050) (Tripathi et al., 2018). The exact biological functions of lncRNA AB073614 are still unclear. Recent studies have demonstrated that lncRNA AB073614 is upregulated in glioma tissue and ovarian cancer, and its overexpression is associated with poor prognosis and an increased risk of progression in these cancers (Li et al., 2017; Wang et al., 2019).

In this study, we examined the levels of lncRNA AB073614 in 30 AML patients and adjacent normal individuals using qRT-PCR. Our aim was to explore the impact of AB073614 transcription levels on the clinicopathological features and prognosis of these patients. We observed higher expression levels of AB073614 in patients with newly diagnosed AML compared to healthy individuals. ROC analysis revealed that AB073614 expression levels could serve as a favorable biomarker for distinguishing AML patients from healthy individuals. Additionally, we found a significant correlation between the upregulation of AB073614 and higher white blood cell (WBC) count and blast count in AML patients, indicative of a more aggressive clinicopathological profile.

The role of lncRNA AB073614 has been described in the context of ovarian and glioma malignancies, where its knockdown significantly inhibited tumorigenesis and metastasis (Guo et al., 2019). Knockdown of lncRNA AB073614 suppressed the proliferation and invasiveness of ovarian cancer cells, increased their rate of apoptosis, and induced G1-phase cell cycle arrest, potentially through modulation of the AKT-mediated signaling pathway (Mishra et al., 2021). The critical role of the PI3K/AKT pathway in colorectal cancer cells induced by lncRNA AB073614 was demonstrated in studies using both a PI3K/AKT signaling pathway agonist and inhibitor. Similarly, the knockdown of AB073614 was shown to inhibit the propagation, migration, and epithelial-mesenchymal transition process in U251 glioma cells (Liao et al., 2019).

In the past decade, significant attention has been directed toward the dysregulation of long noncoding RNAs (lncRNAs) in various diseases, particularly malignancies, where they can function as central regulators in both physiological and pathological processes (Wu et al., 2020). Some lncRNAs have been identified to be dysregulated in different tissues, and the expression levels of certain lncRNAs have been proposed as potential indicators of cancer development and prognosis (Herman et al., 2022). FER1L4 is a lncRNA that has primarily been associated with gastrointestinal malignancies, where it is believed to act as a tumor suppressor (Mou et al., 2022).

In this study, we examined the association between the expression levels of lncRNAs FER1L4 and AB073614 with AML patients and their prognosis, compared to normal individuals, for the first time. Our data revealed downregulated levels of FER1L4 expression in AML patients, consistent with the findings of Ye et al. (Ye et al., 2019). Additionally, we statistically analyzed the correlation between FER1L4 and clinical features and prognosis in AML patients to explore whether FER1L4

could serve as a prognostic marker for AML. Previous studies have shown that lncRNA FER1L4 can inhibit cell growth by modulating PTEN expression (Li et al., 2018). In endometrial carcinoma, lncRNA FER1L4 was found to impair cell proliferation and affect the cell cycle by targeting PTEN (Kong and Ren, 2018). In glioblastoma, lncRNA FER1L4 was upregulated and appeared to regulate tumor progression in glioma cells. PTEN is a key tumor suppressor gene with therapeutic implications for cancer prognosis. It negatively regulates the PI3K/Akt/mTOR axis through its lipid phosphatase activity (Ding et al., 2017; Sadek et al., 2020). While FER1L4 has the potential to enhance PTEN expression levels in tumor cells, the restoration of FER1L4 expression in cancer cells with initially low levels may not only induce PTEN expression but also inhibit the levels of phosphorylated Akt (You et al., 2020). The decrease in FER1L4 expression levels also positively correlates with low levels of PTEN expression in cancers, consistent with findings in colon cancer (Yue et al., 2015). Although the regulatory mechanism between FER1L4 and PTEN has been explored in other cancer types, this study primarily focuses on the role of FER1L4 in regulating the biological activity of AML cells, possibly through its influence on PTEN and subsequent Akt signaling pathways.

It is important to note that the PI3K/Akt axis serves as a key regulator of cell proliferation and apoptosis, and PTEN can modulate the overexpression of pro-apoptotic pathways through Akt-dependent mechanisms. In line with this, our results indicated that AML patients with overexpression of AB073614 exhibited a reduction in FER1L4 expression compared to the control group. The specific roles of lncRNA AB073614 and FER1L4 in AML mechanisms have not been fully elucidated, and this study suggests, for the first time, that these lncRNAs may act as missing links in the regulation of the PI3K/PTEN axis (Figure 3) within AML cells.

In conclusion, our research provides evidence of the upregulation of AB073614 and downregulation of FER1L4 in AML patients, with these altered expression levels being closely associated with specific clinical factors in AML. Our findings suggest that AB073614 and FER1L4 may have significant roles in the pathogenesis of AML, and any component of this pathway could serve as a potential target for intervention in novel treatment strategies. However, the precise molecular mechanisms by which these lncRNAs contribute to AML pathology require further investigation.

Author Contribution Statement

Conception and design: Mohammad sayyadi, development of methodology: Mohammad sayyadi, Ali ganji, Mahmood Khosravi, Acquisition of data: Ghasem Mosayebi, Milad Gholami, Ali Ghazavi, Nafiseh Keshavarzian, Aanalysis and interpretation of data: Mohammad sayyadi, Ali ganji, Writing, review and/or revision of the manuscript: Mohammad sayyadi..

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Ethical approval

The research protocol was approved by the Research Ethics Committee at the Arak University of Medical Sciences (ID number: IR.ARAKMU.REC.1399.194), and all patients and controls signed an informed consent document in accordance with the statement of Helsinki.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Cheng Z, Guo J, Chen L, et al (2015). A long noncoding RNA AB073614 promotes tumorigenesis and predicts poor prognosis in ovarian cancer. *Oncotarget*, **6**, 25381.

Cucchi DG, Polak TB, Ossenkoppele GJ, et al (2021). Two decades of targeted therapies in acute myeloid leukemia. *Leukemia*, **35**, 651-60.

Dieter C, Lourenco ED, Lemos NE (2020). Association of long non-coding RNA and leukemia: a systematic review. *Gene*, **735**, 144405.

Ding F, Tang H, Nie D, et al (2017). Long non-coding RNA Fer-1-like family member 4 is overexpressed in human glioblastoma and regulates the tumorigenicity of glioma cells. *Oncol Lett*, **14**, 2379-84.

Do H, Kim W (2018). Roles of oncogenic long non-coding RNAs in cancer development. *Genom Inform*, **16**.

Fei D, Zhang X, Liu J, et al (2018). Long noncoding RNA FER1L4 suppresses tumorigenesis by regulating the expression of PTEN targeting miR-18a-5p in osteosarcoma. *Cell Physiol Biochem*, **51**, 1364-75.

Gao J, Wang F, Wu P, et al (2020). Aberrant LncRNA expression in leukemia. *J Cancer*, **11**, 4284.

Giannopoulos K (2019). Targeting immune signaling checkpoints in acute myeloid leukemia. *J Clin Med*, **8**, 236.

Gourvest M, Brousset P, Bousquet M (2019). Long noncoding RNAs in acute myeloid leukemia: functional characterization and clinical relevance. *Cancers*, **11**, 1638.

Guo L, Qin C, Zou H, et al (2019). LncRNA AB073614 promotes the proliferation and inhibits apoptosis of cervical cancer cells by repressing RBM5. *Eur Rev Med Pharmaco*, **23**, 2374-9.

Herman AB, Tsitsipatis D, Gorospe M (2022). Integrated lncRNA function upon genomic and epigenomic regulation. *Mol CelL*, **82**, 2252-66.

Huang Y, Han Y, Guo R, et al (2020). Long non-coding RNA FER1L4 promotes osteogenic differentiation of human periodontal ligament stromal cells via miR-874-3p and vascular endothelial growth factor A. *Stem Cell Res Ther*, **11**, 1-12.

Jiang MC, Ni JJ, Cui WY, et al (2019). Emerging roles of lncRNA in cancer and therapeutic opportunities. *Am J Cancer Res*,

9, 1354.
Kantarjian H, Kadia T, DiNardo C, et al (2021). Acute myeloid leukemia: current progress and future directions. *Blood Cancer J*, **11**, 1-25.
Koch L (2017). Screening for lncRNA function. *Nat Rev Genet*, **18**, 70.
Kong Y, Ren Z (2018). Overexpression of LncRNA FER1L4 in endometrial carcinoma is associated with favorable survival outcome. *Eur Rev Med Pharmaco*, **22**, 8113-8.
Li J, Wang Y, Song Y (2016). Knockdown of long noncoding RNA AB073614 inhibits glioma cell proliferation and migration via affecting epithelial-mesenchymal transition. *Eur Rev Med Pharmaco*, **20**, 3997-4002.
Li W, Zhang T, Guo L, et al (2018). Regulation of PTEN expression by noncoding RNAs. *J Exp Clin Canc Res*, **37**, 1-12.
Li Y, Zhu G, Zeng W, et al (2017). Long noncoding RNA AB073614 promotes the malignance of glioma by activating Wnt/β-catenin signaling through downregulating SOX7. *Oncotarget*, **8**, 65577.
Liao L, Kuang H, Xue J, et al (2019). Up-regulated long noncoding RNA AB073614 modulates the tumor cell proliferation, invasion and migration in human colorectal cancer. *Int J Clin Exp Patho*, **12**, 2849.
Liu Z, Shao Y, Tan L, et al (2014). Clinical significance of the low expression of FER1L4 in gastric cancer patients. *Tumor Biol*, **35**, 9613-7.
Livak KJ, Schmittgen TD (2001). Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta CT}$ method. *Methods*, 25, 402-8.
Mishra R, Patel H, Alanazi S, et al (2021). PI3K inhibitors in cancer: clinical implications and adverse effects. *Int J Mol Sci*, **22**, 3464.
Mou J, Wang B, Liu Y, et al (2022). FER1L4: A Long Non-coding RNA with Multiple Roles in the Occurrence and Development of Tumors. *Curr Pharm Des*, **28**, 1334-41.
Peng WX, Koirala P, Mo YY (2017). LncRNA-mediated regulation of cell signaling in cancer. *Oncogene*, **36**, 5661-7.
Sadek NA, Abd-eltawab SM, Assem NM, et al (2020). Prognostic value of absolute lymphocyte count, lymphocyte percentage, serum albumin, aberrant expression of CD7, CD19 and the tumor suppressors (PTEN and p53) in patients with acute myeloid leukemia. *Asian Pac J Cancer Biol*, **5**, 131-40.
Sheikhi M, Zaker F, Javadi G, et al (2017). Surveying Mutation of FLT3 Genes in Children with Acute Leukemia. *Asian Pac J Cancer Care*, **2**, 7.
Stanchina M, Soong D, Zheng-Lin B, et al (2020). Advances in acute myeloid leukemia: recently approved therapies and drugs in development. *Cancers*, **12**, 3225.
Tripathi MK, Doxtater K, Keramatnia F, et al (2018). Role of lncRNAs in ovarian cancer: defining new biomarkers for therapeutic purposes. *Drug Discov Today*, **23**, 1635-43.
Voso MT, Ottone T, Lavorgna S, et al (2019). MRD in AML: the role of new techniques. *Front Oncol*, **9**, 655.
Wang F, Tian X, Zhou J, et al (2018). A three-lncRNA signature for prognosis prediction of acute myeloid leukemia in patients. *Mol Med Rep*, **18**, 1473-84.
Wang Jy, Lu Aq, Chen Lj (2019). LncRNAs in ovarian cancer. *Clin Chim Acta*, **490**, 17-27.
Wang Y, Kuang H, Xue J, et al (2017). LncRNA AB073614 regulates proliferation and metastasis of colorectal cancer cells via the PI3K/AKT signaling pathway. *Biomed Pharmacother*, **93**, 1230-7.
Wu P, Mo Y, Peng M, et al (2020). Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. *Mol Cancer*, **19**, 1-14.
Yang X, Wang J (2018). Precision therapy for acute myeloid leukemia. *J Hematol Oncol*, **11**, 1-11.
Ye F, Tian L, Zhou Q, et al (2019). LncRNA FER1L4 induces apoptosis and suppresses EMT and the activation of PI3K/AKT pathway in osteosarcoma cells via inhibiting miR-18a-5p to promote SOCS5. *Gene*, **721**, 144093.
You Z, Ge A, Pang D, et al (2020). Long noncoding RNA FER1L4 acts as an oncogenic driver in human pan-cancer. *J Cell Physiol*, **235**, 1795-807.
Yu J, Jiang PY, Sun H, et al (2020). Advances in targeted therapy for acute myeloid leukemia. *Biomark Res*, **8**, 1-11.
Yue B, Sun B, Liu C, et al (2015). Long non-coding RNA Fer-1-like protein 4 suppresses oncogenesis and exhibits prognostic value by associating with miR-106a-5p in colon cancer. *Cancer Sci*, **106**, 1323-32.