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Multifaceted Cooperation Between WNT and PI3K Signaling Axis through the Long Noncoding RNA *SNHG16* and *TCF7* in de novo Acute Lymphoblastic Leukemia Patients

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ABSTRACT

Background: Acute lymphoblastic leukemia is the most prevalent form of acute leukemia in children, arising from the known and unknown factors. This complexity has limited advancements in patient recovery. Recently, lncRNA molecules have emerged as significant but not fully understood players in leukemia research. Studies have indicated that *c-Myc* can stimulate and enhance gene expression through multiple pathways, particularly by activating the PI3K and WNT pathways. The present study investigated the expression levels of lncRNAs involved in the upstream regulation of the PI3K/WNT pathways in patients diagnosed with ALL.

Methods: This case-control cross-sectional study was conducted using RNA from blood samples. The study examined 36 patients with ALL and 36 healthy controls. The expression levels of *SNHG16* and *TCF7* lncRNAs and their target genes were determined using qRT-PCR.

Results: The expression of *Akt, β-catenin* and *c-Myc* genes in the patient group showed a significant increase compared to the control group ($p < 0.05$). The expression levels of *SNHG16* and *TCF7* were significantly elevated in ALL patients compared to the control group ($p < 0.05$). Furthermore, a significant positive correlation was observed between the expression levels of these two lncRNAs in the patient group ($p < 0.05$).

Conclusion: Our findings demonstrate that *SNHG16* and *TCF7* lncRNA may act as crucial regulators of the *Akt* and *β-catenin* in ALL, which in turn influence *c-Myc* expression levels in affected individuals. Further research is needed to better understand the molecular mechanisms underlying ALL, potentially leading to improved treatment and monitoring strategies for patients. ***DOI: 10.61186/ibj.5031***

Keywords: SNHG16 lncRNA, TCF7, Wnt signaling pathway

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List of Abbreviations:
ALL: acute lymphoblastic leukemia; **cDNA:** complementary DNA; **ceRNA:** competing endogenous RNA; **CRC:** colorectal cancer; **IRAK1:** interleukin-1 receptor-associated kinase 1; **IRS1:** insulin receptor substrate 1 ; **lncRNA:** long noncoding RNAs lncRNA; **lncTCF7:** long noncoding RNA TCF7 ; **qRT-PCR:** quantitative real-time PCR; **SNHG16:** small nucleolar RNA host gene 16

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INTRODUCTION

Acute lymphoblastic leukemia is the most common type of leukemia in children, accounting for about 25% of both pediatrics and adult malignancies[1]. Owing to recent research advancements, the five-year survival rate for ALL has increased to 90%[2]. The risk assessment for patients diagnosed with ALL is determined by different factors, including clinical symptoms, patient age, gene expression profiles, white blood cell counts, and initial chemotherapy responses[3]. Even with significant progress and the recognition of prognostic indicators, 20% of ALL patients continue to experience relapses.[4]. Gaining a deeper understanding of the mechanisms underlying the pathogenesis of this disease could lead to the development of tailored therapeutic strategies for ALL patients[5].

Recent findings on the dysregulated molecular functions linked to leukemia have highlighted the significance of lncRNAs[6]. LncRNAs, a class of epigenetic factors, are defined as transcribed RNA molecules exceeding 200 nucleotides in length and lacking coding potential[7]. These molecules play critical roles in multiple biological processes[8]. To date, a relatively small number of lncRNAs have been thoroughly characterized. They have been found to operate through mechanisms such acting as signaling molecules, scaffolds, guides, and decoys[9]. Various genes, including *PI3K/Akt* and *Wnt/β-catenin*, are known to regulate processes such as proliferation, migration, differentiation, and apoptosis in both normal and cancer cells[10]. Studies have pointed out the essential roles of specific lncRNAs in myeloid differentiation and their regulatory influence on key signaling pathways, including the PI3K and WNT[11]. The currently discovered lncRNA, *SNHG16*, has been implicated in the progression of several human malignancies, including colon, cervical, and lung cancers. Notably, elevated levels of *SNHG16* expression correlate with a poor prognosis in lung cancer patients[12]. Research has shown that *SNHG16* facilitates the proliferation and invasion of lung adenocarcinoma cells by sponging let-7a-5p[13]. It has also been indicated that *SNHG16* facilitates the processes of proliferation, migration, and the formation of vessel-like structures in malignancies. Mechanistically, *SNHG16* acts as ceRNAs to sponge miR-20a-5p and miR-101-3p to regulate E2F1 expression, sponge miR-520d-3p to regulate STAT3, or sponge miR-146a-5p and miR-7-5p to regulate IRAK1 and IRS1, and in turs, NF-kB and PI3K/AKT pathways[14]. Several studies have looked into the expression of *SNHG16* lncRNA and its significance in ALL, as in vitro experiments indicate that this lncRNA is found in higher levels in ALL cell lines and may serve as a potential prognostic marker for ALL patients in the future[15].

lnc*TCF7* has been identified as a significant factor in the development and progression of CRC in humans; however, the underlying molecular mechanisms by which this lncRNA operates in CRC remains largely unexplored. The functions and molecular mechanisms of lnc*TCF7* related to the migration and invasion of CRC cells, have been previously elucidated[16]. Of note, lnc*TCF7* exhibited elevated expression levels in CRC cell lines when compared to normal colonic epithelial cells. Furthermore, its knockdown significantly reduced the migration and invasion capabilities of CRC cells[17]. An earlier survey has demonstrated the function of lnc*TCF7* in tumor development and progression by elevating expression, which enhances the invasive potential of non-small cell lung cancer cells. Moreover, lnc*TCF7* has been found to be highly expressed in hepatocellular carcinoma and liver cancer stem cells and contributes to the self-renewal of hepatocellular carcinoma cells[18]. *TCF7* lncRNA is essential for the development of T-cell and the self-renewal of multipotential hematopoietic cells through the activation of Wnt signaling. Notably, *TCF7* expression is significantly elevated in renal cell carcinoma compared to normal tissue, whereas its silencing has been shown to reduce the survival of prostate cancer cells and also impede the development of resistance to androgen deprivation in prostate cancer[19]. Very few studies have been conducted on the expression of *TCF7* lncRNA in ALL, but their results indicate that this lncRNA could be responsible for the pathogenesis of ALL[20].

The activation of PI3K and Wnt axes leads to the activation of *c-Myc*. Given the discrepancies on the pathogenic role of *c-Myc* and its upstream targets in ALL patients, along with the need to propose a plausible mechanism for the pathogenesis of ALL involving lncRNA, we assessed the expression levels of essential components of the PI3K/WNT signaling pathway. Specifically, we focused on *Akt*, *β-catenin*, and *c-Myc* in patients newly diagnosed with ALL[21]. Additionally, we sought to examine the expression of *SNHG16* and *TCF7* lncRNAs and explore potential correlations between these genes relating to this leukemia. Considering the different signaling pathways, particularly the PI3K/Wnt axis and the subsequent activation of *c-Myc* in the pathogenesis of human cancers. Our objective was to investigate the expression of the most significant lncRNA related to PI3K/Wnt pathway. We also aimed to elucidate a potential mechanism underlying the pathogenesis of ALL.

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MATERIALS AND METHODS

Study population

Between May 2023 and July 2024, peripheral blood samples were collected from 36 patients with untreated ALL and 36 healthy control subjects. The control group was matched to the patient group by age and gender. Participants with pre-existing diseases or those who withdraw from the study were excluded. The patient samples were diagnosed at Amirkabir Hospital in Arak (Markazi Province, Iran) utilizing morphological characteristics to identify specific immunophenotypes. Peripheral blood was collected from individuals who had visited for routine physical examinations and showed no signs of hematologic malignancies or significant blood test abnormalities. The mean age of patients at diagnosis was ~9.6 years. Notably, 44% (16 out of 36) of the samples were collected from male patients, while 56% (20 out of 36) were obtained from female patients. The mean age of the control group was ~9.5 years. We selected the male-to-female ratio to match the patients group, minimizing errors related to the age and sex when comparing the case and control groups.

RNA extraction and cDNA synthesis

Peripheral blood mononuclear cells were separated using Ficoll solution (Baharafshan, Iran), taking into account the varying densities of cells and Ficoll solution. Total cellular RNA was isolated and purified from mononuclear cells utilizing the RNase Kit (SinaClone, Iran) in accordance with the manufacturer's protocol. The quality and quantity of the extracted RNA were assessed using a NanoDrop (Thermo Scientific, Wilmington, North Carolina, USA), with an ratio of >1.8 at 280/260 nm. Next, 2 µL of 0.5 µg of RNA was employed for cDNA synthesis in a final volume of 20 µL, using the SinaClone first strand cDNA synthesis kit. The synthesis of cDNA was verified using *GAPDH* primer as a housekeeping gene.

Quantitative real-time PCR

Target genes and lncRNAs (*Akt*, *β-catenin*, *c-Myc*, *SNHG16*, and *TCF7*) were selected for primer design, with *GAPDH* serving as the internal control gene using Gene Runner software (Table 1). The mRNA expression levels of the chosen genes and lncRNAs were measured by qRT-PCR (Roche, LightCycler®96, Germany). Each qRT-PCR reaction consisted of 2 µL of template target cDNA at 100 picogram,, 1 µL of forward and reverse primer, 7.5 µL of Real Plus 2× Master Mix Green-Low ROX (SinaClone), and 4.5 µL of water to reach total volume of 15 µL. The thermal cycling conditions for the 40-cycle RT-PCR were as follows: denaturation at 95 °C for 1 min, annealing at 56-61 °C for 30 s, and extension at 72 °C for 30 s. Primer efficiency was determined by a standard curve based on four consecutive 1:10 dilutions of cDNA sample (1, 0.1, 0.01, and 0.001) for each target gene. Primer efficiency was determined as follows: 95% for *Akt*, 100% for *β-catenin*, 96% for *c-Myc*, 98% for *SNHG16*, and 94% for *TCF7*. All experimental procedures were conducted in triplicate, and the relative quantification of mRNA expression for each sample (fold change ¼ FQ) was calculated using the Livak method ($2^{-\Delta\Delta Ct}$)[22].

Statistical analysis

All statistical analyses were conducted utilizing SPSS software for Windows (version 24.0) and GraphPad Prism 6 software. The gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ formula, where $\Delta\Delta Ct = \Delta Ct$ (Target sample) -ΔCt (Control sample). To assess the normal distribution of gene expression in both ALL patients and the control group, we employed the Shapiro-Wilk and Kolmogorov-Smirnov tests. Based on the normal distribution results, we applied either the student's t-test or the Mann–Whitney U test. Finally, we used Pearson's correlation test to investigate potential correlations between variables with parametric distributions. A *p* values of less than 0.05 were deemed statistically significant.

RESULTS

Characteristics of ALL patients

Table 2 represents the demographic and clinical laboratory data for 36 patients diagnosed with ALL. Gene expression analysis showed that *Akt*, *β-catenin*, and *c-Myc*, along with the lncRNAs *SNHG16* and

Table 1. Nucleotide sequences of the primers used for real-time RT-PCR

Gene	Forward primer (5'-3')	Reverse primer (5'-3')	Size (bp)
GAPDH	GACAGTCAGCCGCATCTTCT	GCGCCCAATACGACCAAATC	104
Akt	TCCTCCTCAAGAATGATGGCA	GTGCGTTCGATGACAGTGGT	181
β-catenin	GTTGAGCACCTGTTTGCCTG	GGCTGTCAGGTTTGATCCCA	169
c-Myc	CCACAGCAAACCTCCTCACAG	GCAGGATAGTCCTTCCGAGTG	105
SNHG16	TGTGAGTTAGCTCCCAGCGA	GAAGCCCAAAGAACGCATGG	99
TCF7	AGGAGTCCTTGGACCTGAGC	AGTGGCTGGCATATAACCAACA	116

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Table 2. Clinical characteristics of de novo ALL patients

No.	Sex	Age (year)	ALL type	Blast (%)	WBC × 10^3	RBC × 10^6	Platelet × 10^3	Hemoglobin (g/dL)	Hematocrit (%)
1	Male	9	B-ALL	22	11500	4.12	110	12.2	36.5
2	Male	12	T-ALL	25	12700	5.15	130	15.1	45.2
3	Female	19	B-ALL	31	14800	3.98	154	10.1	30.2
4	Male	15	B-ALL	24	9100	4.23	98	12.1	36.7
5	Female	8	T-ALL	54	26000	2.94	54	7.1	22.4
6	Male	10	B-ALL	26	12000	3.66	116	10.2	30.5
7	Female	6	B-ALL	41	4800	4.84	124	12.3	35.8
8	Female	4	B-ALL	26	16500	5.31	101	15.4	43.8
9	Female	5	T-ALL	28	17500	4.23	107	12.8	35.7
10	Male	6	B-ALL	31	28000	4.35	78	12.9	37.1
11	Female	8	B-ALL	40	14600	3.78	59	10.7	29.8
12	Male	8	B-ALL	36	22600	4.99	113	13.1	38.4
13	Male	7	B-ALL	38	18700	5.11	154	15.4	45.1
14	Female	6	T-ALL	25	16000	3.96	124	10.4	31.2
15	Male	13	B-ALL	26	10500	4.67	114	12.6	34.8
16	Female	4	B-ALL	46	12400	4.15	76	12.3	35.9
17	Male	8	B-ALL	22	18600	3.78	215	10.6	28.4
18	Female	15	B-ALL	43	19700	2.86	73	7.9	22.4
19	Female	7	B-ALL	57	17300	5.28	157	15.2	45.3
20	Male	13	T-ALL	48	22000	4.21	178	12.4	35.1
21	Female	21	B-ALL	20	10500	3.64	36	10.7	29.7
22	Male	16	B-ALL	36	14300	4.13	69	12.4	34.6
23	Female	12	B-ALL	35	17900	4.86	83	12.9	37.6
24	Male	8	B-ALL	29	13100	5.28	113	15.3	43.2
25	Female	3	T-ALL	35	14500	3.82	97	10.6	31.4
26	Female	13	B-ALL	24	18400	3.73	73	10.7	32.4
27	Female	6	B-ALL	31	28400	5.16	168	14.3	41.8
28	Male	8	B-ALL	25	19500	4.18	105	11.9	34.8
29	Female	9	B-ALL	25	36400	4	74	11.5	34.1
30	Male	4	T-ALL	38	28900	3.82	61	10.1	29.9
31	Female	23	B-ALL	32	20400	3.86	98	10.8	34.1
32	Male	12	B-ALL	36	31500	4.08	63	12.4	37.2
33	Female	11	T-ALL	49	34100	4.16	72	12.9	37.6
34	Female	7	B-ALL	61	46300	3.97	106	11.5	34.1
35	Male	9	T-ALL	36	48700	4.37	162	12.3	37.1
36	Female	6	B-ALL	71	18300	3.46	215	11.3	34.8

TCF7, were significantly upregulated in ALL patients compared to healthy controls (Fig. 1). A diagnostic test evaluation was performed using ROC curve analysis, through which sensitivity, specificity, and AUC values were calculated. An optimal cut-off for relative quantification was also established to distinguish ALL patients from healthy controls. The AUCs for *SNHG16* and *TCF7* lncRNAs in patients and healthy subjects were found to be 0.914 (95% CI: 0.849) and 0.928 (95% CI: 0.862-0.993), respectively, with a p value of < 0.001. The optimal cut-off value for *SNHG16* lncRNA expression was 0.705, with a sensitivity of 92.67% and a specificity of 73.44%. For *TCF7* lncRNA, the optimal cut-off point was determined to be 0.725, with a sensitivity and specificity of 93.44% and 83.31%, respectively (Fig. 2).

Correlation between PI3K/WNT/lncRNAs expression levels in the studied groups

After observing the upregulation of *Akt*, *β-catenin*, and *c-Myc*, *SNHG16*, and *TCF7* in ALL patients compared to healthy individuals, a statistical correlation analysis was conducted to assess potential relationships among the expression levels of these genes. Significant correlations were found between various genes and lncRNAs, including *Akt* and *c-Myc* (r = 0.456; Fig. 3A),

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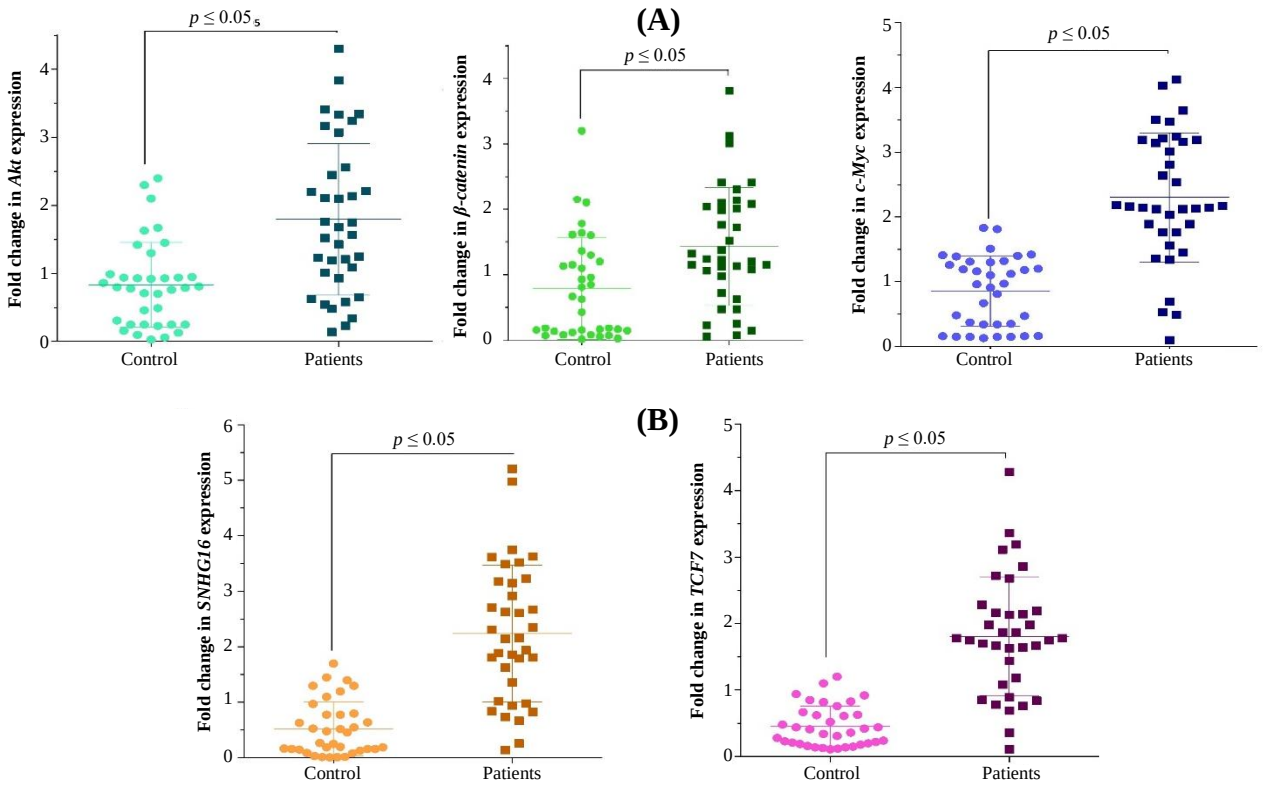

Fig. 1. Expression levels of (A) *Akt*, *β-catenin*, and *c-Myc* genes and (B) lncRNAs *SNHG16* and *TCF7*.

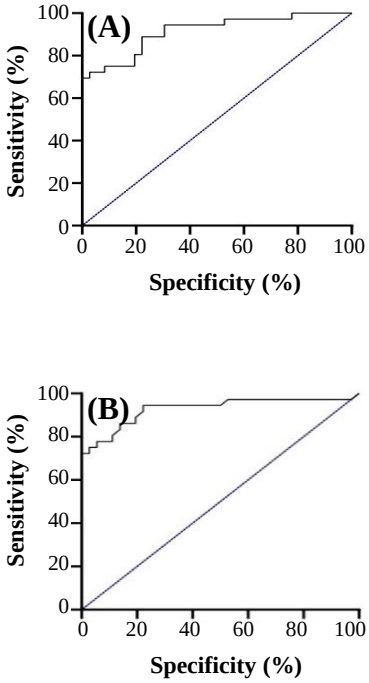

Fig. 2. ROC analysis for lncRNAs (A) *SNHG16* (AUC: 0.914; 95% CI: 0.849-0.979; $p < 0.001$) and (B) *TCF7* (AUC: 0.928; 95% CI: 0.862-0.993; $p < 0.001$).

Akt and *SNHG16* (r = 0.653; Fig. 3B), *β-catenin* and *TCF7* (r = 0.727; Fig. 3C), and *c-Myc* and *SNHG16* (r = 0.486; Fig. 3D), all with a *p* value of <0.01. However, the relationships between the following genes and lncRNAs were observed to be non-significant: *Akt* and *β-catenin* (r = 0.044; Fig. 3E), *c-Myc* and *β-catenin* (r = 0.143; Fig. 3F), *Akt* and *TCF7* (r = 0.103; Fig. 3G), *β-catenin* and *SNHG16* (r = 0.070; Fig. 3H), *c-Myc* and *TCF7* (r = 0.110; Fig. 3I), and *SNHG16* and *TCF7* (r = -0.030; Fig. 3I), with a *p* value of >0.05. These results highlight the possible role of lncRNAs and genes in the pathogenesis of ALL.

DISCUSSION

Despite significant therapeutic advancements for ALL patients in recent years, overall survival rates are low, highlighting the need for identifying new biomarkers that can better elucidate the pathogenesis of the disease[23]. Growing attention is being directed toward exploring the association between these biomarkers and the progression or prognosis of ALL. Genetic and molecular studies have demonstrated that dysregulated expression of lncRNA is a common feature in various cancers[24]. Several lncRNAs have emerged as

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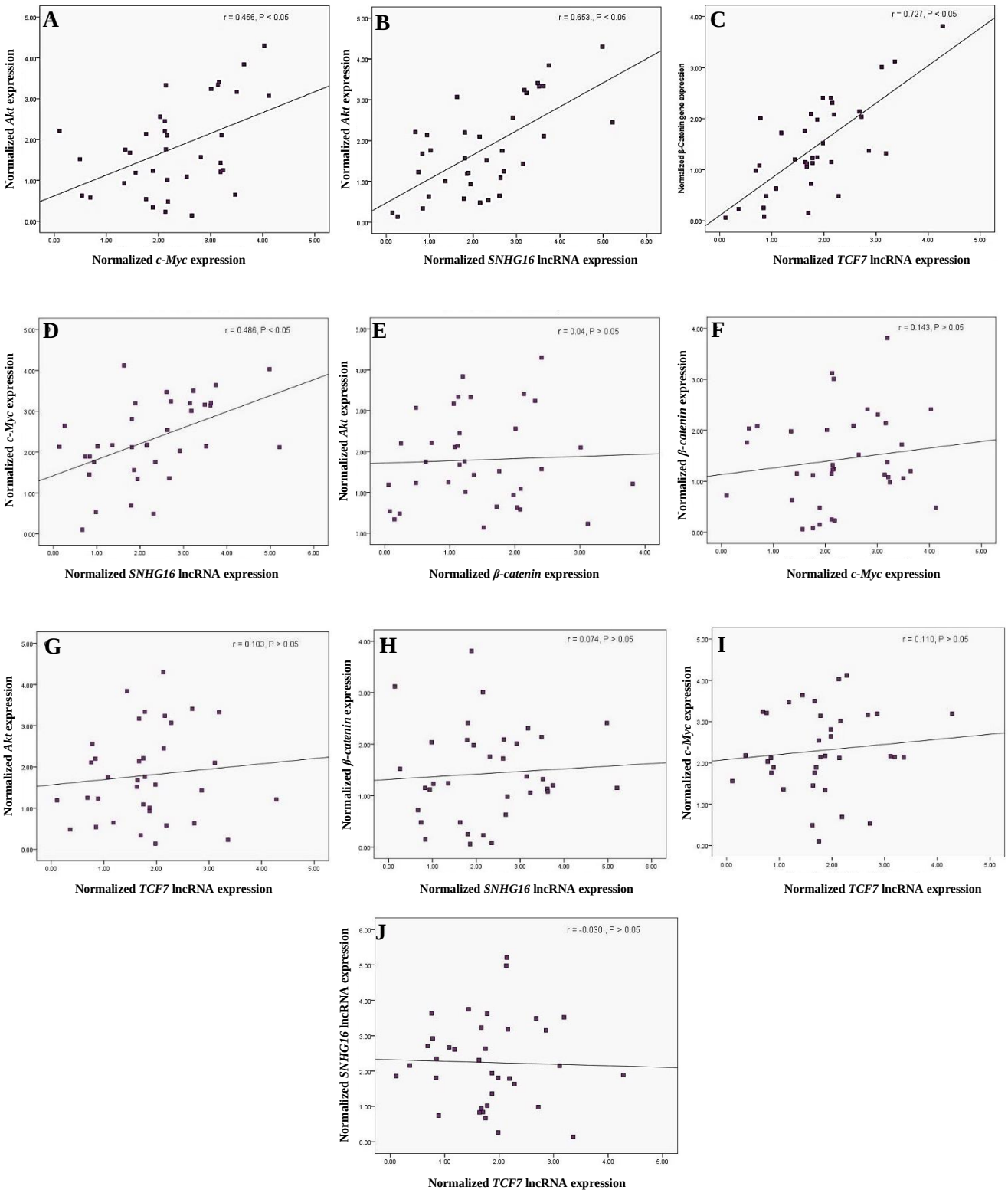

Fig. 3. Correlation analysis between the expression levels of *Akt*, *β-catenin*, *c-Myc*, *SNHG16*, and *TCF7* in leukemic samples. Normal distribution of data was achieved by $\log_{10}$ transformation. The correlation between genes and lncRNAs was assessed in 36 ALL patients. Values are represented as mean ± standard deviation of three independent experiments.

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promising candidates for the detection and prediction of hematological malignancies[25]. However, a substantial knowledge gap still exists regarding the expression patterns of specific lncRNAs in ALL patients and their potential correlations with various clinicopathological classifications[26].

Studies in genetics and molecular biology have demonstrated a dysregulated expression or activity of the oncogene *c-Myc* in cases diagnosed with ALL[27]. This finding has prompted further investigation into the relationship between *c-Myc* and the pathogenesis and prognosis of the disease. Mutation analysis in ALL patients has revealed that, unlike in certain malignant hematopoietic disorders such as multiple myeloma and non-Hodgkin lymphoma—where *c-Myc* acts as a prognostic indicator and a pathogenic driver—mutations in the *c-Myc* gene are more prominent. However, these mutations do not appear to be crucial for the onset of ALL[28]. In the current research, we observed increased expression levels of *c-Myc* in ALL patient samples; however, no significant correlation was found between gene expression and variables such as age, gender, or the percentage of blast cells. Notably, evidence from additional studies suggests that elevated *c-Myc* expression in neoplastic lymphoid cells may play a pivotal role in driving disease progression and developing drug resistance in ALL patients[29]. Furthermore, the inhibition of *c-Myc* in acute leukemia cells has been shown to significantly decrease cell survival and enhance the efficacy of chemotherapeutic drugs[30].

Molecular mediators significantly influences the regulation of *c-Myc* activity in malignant cells. Among them, the PI3K and WNT signaling pathways are recognized as key modulators of *c-Myc* oncogene function[31]. In addition to *c-Myc* regulation, the integrative activity of the PI3K and WNT pathways in different intracellular processes has received considerable attention due to their oncogenic potential[32]. Recent investigations have highlighted the dysregulation of these pathways, particularly the overexpression of *Akt*, a key downstream effector of the PI3K/Akt pathway. This dysregulation has led to the exploration of PI3K/*Akt* inhibitors as potential therapeutic strategies for cancer[33]. Therefore, the PI3K/*Akt* signaling axis has become the focus of investigation across multiple malignancies, including ALL.

Evidence has revealed that different subtypes of ALL, particularly those characterized by the BCR-ABL translocation, exhibit significantly elevated levels of over-activated *Akt* and WNT signaling pathways[34]. Additional research has shown that ALL cell lines are more susceptible to the antileukemic effects of PI3K and WNT inhibitors compared to other cell lines derived from ALL[35]. In contrast, in our current investigation, both B-ALL and T-ALL patients displayed higher expression levels of *Akt* and *β-catenin* compared to their healthy counterparts. This finding aligns with the observed increase in *c-Myc* expression levels in these patients, underscoring the potential role of the PI3K/WNT/c-Myc signaling axis in the pathogenesis of ALL. Genomic analyses have displayed that the interaction between PI3K/WNT signaling pathways and oncogene *c-Myc* depends on the involvement of the lncRNAs *SNHG16* and *TCF7*[35,36]. This insight has attracted growing interest in evaluating the relationship between these factors and the development or prognosis of ALL, particularly following genetic and molecular studies that have identified deviations in lncRNA expression across different cancer types[13]. Specific lncRNAs, especially *SNHG16* and *TCF7*, have emerged as potential biomarkers for the detection and prediction of malignancies[37].

In this study, we found increased expression levels of *SNHG16* and *TCF7* in ALL patient samples. However, we did not find a significant correlation between their expression and variations in age or gender. Additionally, ALL patients exhibited higher expression levels of *Akt*, *β-catenin*, and *c-Myc* compared to healthy individuals. This upregulation was associated with the elevated expression levels of *SNHG16* and *TCF7* in the patient cohort. These observations emphasize the potential involvement of the PI3K//WNT/c-Myc signaling pathway, activated by *SNHG16* and *TCF7*, in the pathogenesis of ALL.

Several molecular factors have been implicated in the activation of the PI3K/*Akt* signaling pathway in malignant cells, with *SNHG16* serving as a particularly influential lncRNA that modulates *Akt* activity[38]. Research has shown that *SNHG16* can regulate *Akt* expression, thereby promoting cellular proliferation. Recently, increased levels of *SNHG16* have been observed in various human malignancies, indicating its oncogenic role across different cancer types[39]. For instance, the overexpression of *SNHG16* has been linked to increased invasiveness in bladder cancer, whereas its lower expression levels have been correlated with unfavorable outcomes in CRC[15]. This study primarily examined the roles of *SNHG16* and *TCF7* in regulating the biological functions of ALL cells, potentially through the modulation of Akt/β-catenin signaling pathway and its downstream effector, *c-Myc*. Our findings corroborate that ALL patients with elevated levels of *SNHG16* and *TCF7* expression also exhibit increased expression levels of *Akt*[40]. Moreover, we noted a rise in *SNHG16* expression among ALL patients compared to the control subjects. While the

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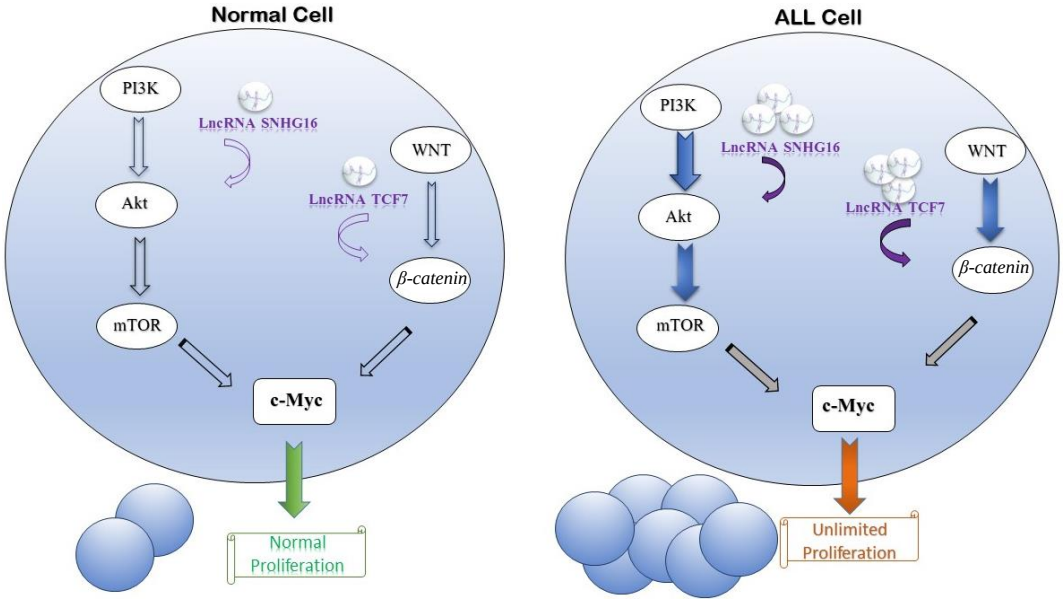

Fig. 4. Schematic illustration showing the probable role of PI3K/WNT/c-Myc axis in ALL cells. The excessive overexpression of *SNHG16* leads to an over-activation of the PI3K signaling pathway, and the subsequent upregulation of *TCF7* may be linked to the activation of the WNT axis in ALL cells. Finally, *c-Myc* may be crucial in providing ALL cells with the opportunity to proliferate.

exact mechanisms by which *SNHG16* and *TCF7* contribute to the pathogenesis of ALL are poorly understood, this study provides new insights suggesting that these lncRNAs may act a critical role in regulating the relationship between *SNHG16* and *TCF7* in modulating *Akt*/*β-catenin* expression levels.

CONCLUSION

Our findings indicate that components of the PI3K/WNT/*c-Myc* signaling axis could serve as promising targets for innovative therapeutic strategies in ALL. The interaction between *SNHG16*/*Akt* and *TCF7*/*β-catenin* appears to be critical for the upregulation of *c-Myc* expression levels in the pathogenesis of ALL. However, the precise role of this intriguing pathway in hematological cancers, especially in ALL, requires further in-depth research (Fig. 4).

DECLARATIONS

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Ethical approval
All the experimental procedures in this study were approved by the Research Ethics Committee at Arak University of Medical Sciences, Arak, Iran (ethical code: IR.ARAKMU.REC.1402.148).

Consent to participate
All the subjects voluntarily agree to participate in this research. Written informed consents were provided by all the subjects participated in the study.

Consent for publication
All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions
MKH: investigation and writing original draft; AL: supervision, review, and editing; MS: supervision, project administration, methodology, validation, writing –review, and editing.

Data availability
All relevant data can be found within the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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